ANESTHETIC RISK AND COMPLICATIONS IN VETERINARY MEDICINE

EDITED BY: Karine Portier and Keila K. Ida

PUBLISHED IN: Frontiers in Veterinary Science

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88963-983-0
DOI 10.3389/978-2-88963-983-0

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

ANESTHETIC RISK AND COMPLICATIONS IN VETERINARY MEDICINE

Topic Editors:
Karine Portier, Université de Lyon, France
Keila K. Ida, Texas A&M University, United States

Citation: Portier, K., Ida, K. K., eds. (2020). Anesthetic Risk and Complications in Veterinary Medicine. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88963-983-0

Table of Contents

frontiers in Veterinary Science

EDITORIAL
published: 15 July 2020
doi: 10.3389/fvets.2020.00397

Editorial: Anesthetic Risk and Complications in Veterinary Medicine

Karine Portier[1,2] *and Keila K. Ida*[3]*

[1] Université de Lyon, VetAgro Sup, GREAT, Marcy l'Etoile, France, [2] Université de Lyon, CarMeN Laboratory, INSERM, INRA, INSA Lyon, Université Claude Bernard Lyon 1, Bron, France, [3] Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, United States

Keywords: death, morbidity and mortality, anesthesia, animals, safety

Editorial on the Research Topic

Anesthetic Risk and Complications in Veterinary Medicine

Veterinary practitioners have obligations to inform owners of the potential risks their animal might encounter during a surgery. A third of veterinarians believe that the majority of their clients are particularly concerned about their animal being anesthetized. The lack of a clear definition of anesthesia-related mortality and morbidity makes it difficult to specify the real anesthetic risk to the animals' owners. The timing a complication occurs, intra- or postoperatively, can also impose uncertainty in defining whether incidents are associated with the anesthetic procedure.

Large veterinary multicenter studies defined anesthesia-related death as those occurring within 48 h (small animals) or 7 days (horses) of termination of the procedure, where anesthesia could not be excluded as being one of the contributory factors. Based on this definition, the authors identified an overall 0.17% anesthetic-related risk of death in dogs, 0.24% in cats, and 1.9% in horses. Such high rates compared with human patients warned clinicians and researchers on the need of improvements. Since then, several efforts have been made to increase the safety of animals undergoing anesthesia. This Research Topic was part of these efforts by creating an opportunity for the contribution of 35 researchers through 12 publications on the subject. They share, among others, the challenges found on the attempts to prevent the occurrence of deaths and complications. They also describe clinical complications and the successful management that was applied.

Since 2002, when it was announced that horses have a high mortality rate associated with anesthesia, new equipment was developed to improve safety in this animal species. In 2008, Tafonius, the large animal anesthesia machine, was released with integrated monitoring and ventilator systems. The emerging technology allowed, among other features, to control the fresh gas flow into the breathing system either by a manually- or computer-driven flowmeter. The convenience of having a machine adjusting the flow of different gases to pre-determined concentrations is an attractive feature and its accuracy was, therefore, tested by Raillard et al.. In this original article, the authors describe that the prediction of the isoflurane fraction course in the breathing system was challenging when using the computer-driven flowmeter. This was especially true at low inspired fractions of oxygen. The discrepancies between flows set on the controlled-driven flowmeter and actual lower delivered flows should be taken into consideration. Insufficient concentrations of inhalant anesthetics might lead to serious safety concerns, including both awaking of horses during anesthesia or unwarranted high concentrations of anesthetics that might result in cardiovascular and respiratory complications.

An excessive delivery of inhalant anesthetics can significantly decrease the systemic vascular resistance and cause relative hypovolemia. This is of particular concern in equine patients since 20–50% of all anesthesia-related deaths in this animal species are associated with cardiovascular complications. The exact mechanisms are explained by Noel-Morgan and Muir who also

Edited and reviewed by:
Andrea Tipold,
University of Veterinary Medicine Hannover, Germany

***Correspondence:**
Keila K. Ida
kida@cvm.tamu.edu

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *23 April 2020*
Accepted: *03 June 2020*
Published: *15 July 2020*

Citation:
Portier K and Ida KK (2020) Editorial: Anesthetic Risk and Complications in Veterinary Medicine. Front. Vet. Sci. 7:397. doi: 10.3389/fvets.2020.00397

provide further considerations on the monitoring and treatment of anesthesia-associated relative hypovolemia. Such perspective is especially important in life-threatening situations, which become evident in three of the clinical cases reported in the present Research Topic. Tong et al. describe the management of recurrent hyperkalemia during general anesthesia in a dog. Marolf et al. describe the development of an advanced atrio-ventricular block unresponsive to antimuscarinic drugs in an anesthetized foal. Conde-Ruiz and Junot share the case of a horse suffering a cardiac arrest at the arrival of the recovery room. In all three cases, the authors discuss the potential causes, the preventive measures and the successful treatments applied. They demonstrate how the close monitoring proved to be decisive for early recognition and prompt management of the cardiovascular complications, which were crucial for the good outcome.

A less close monitoring may be responsible for the increased risk of anesthetic-related morbidity and mortality associated with the recovery period. In dogs, cats, and rabbits, nearly 50% of the postoperative deaths occur within 3 h of the end of anesthesia. In horses, Laurenza et al. found that 92% of complications occur during recovery and most of them are associated with neuromuscular and respiratory causes. The pathogenesis of certain conditions is still unclear, which makes it difficult not only to provide adequate care but also to prevent complications in future cases. This was the key point of discussion in the case reported by Mirra et al.. The authors describe an unusual presentation of a potential post-anesthetic neuropathy in the non-dependent limb of a horse. In another case report, Dupont et al. discuss the role of hypoxemia as the potential cause of the delayed recovery from anesthesia in a draft horse. In both occasions, despite of the unknown mechanisms for the clinical alterations, the horses were successfully managed. In some situations, it is possible to anticipate the development of potential postoperative complications and apply preventive measures. This was addressed in the case report by Ida et al. who shared the ventilatory management that prevented respiratory complications during recovery from anesthesia of two ponies with tracheal collapse.

Preventive measures may play an important role to avoid further complications. The reduction of mortality and morbidity risks has been suggested with the use of safety checklists. The implementation of checklists may have some challenges that are revealed in the original research from Menoud et al.. The authors describe numerous methods used to create and implement a safety checklist in a veterinary university teaching hospital. Morbidity and mortality conferences also seem to have an impact on patient care. In the mini review by Pang et al. the authors illustrate the measurable improvements in patient care generated by these conferences, which may also represent a powerful educational tool.

Another preventive tool is the ASA PS classification, which ability to identify animals at a greater risk of anesthesia-related death was put in question in the systemic review by Portier and Ida. The authors assessed a total of 258,298 dogs, cats, rabbits, and pigs. The results show evidences to justify the use of the ASA PS as a prognostic tool to identify the odds of death related to anesthesia in these animal species. In fact, Laurenza et al. identified that a high ASA PS score represents, among other factors, a major risk for mortality and complications in horses. In this original research article, the authors describe a 1.4% overall mortality associated with anesthesia on horses in a French university teaching hospital. It corresponds to a reduction from the 1.9% anesthesia-related equine deaths announced in 2002. Now, 18 years later, the effects of several efforts to improve case management and decrease the morbidity and mortality seem to have had a positive impact.

We believe that this Research Topic adds to the clinical practice of veterinary doctors, contributing to reduce the anesthetic risk and complications in animals. We also expect that this Research Topic motivates readers to share their experience with anesthetic complications and to produce further studies in this field. This, combined with the implementation of expert recommendations, could contribute to the continuing improvement of the quality of anesthesia and, therefore, to decrease the complications and the mortality rate of veterinary patients undergoing anesthesia.

AUTHOR CONTRIBUTIONS

KP and KI co-edited the Research Topic and wrote this editorial. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We warmly thank contributors who have advanced and expanded the field of knowledge on anesthetic risks and complications.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

CASE REPORT
published: 07 February 2018
doi: 10.3389/fvets.2018.00012

Suspicion of Postanesthetic Femoral Paralysis of the Non-Dependent Limb in a Horse

Alessandro Mirra[1], Micaël David Klopfenstein Bregger[2] and Olivier Louis Levionnois[1]*

[1] Division of Anesthesiology and Pain Therapy, Department of Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern, Bern, Switzerland, [2] Swiss Institute for Equine Medicine, Vetsuisse Faculty, University of Bern, Bern, Switzerland

A 15-year-old Selle Francais gelding was presented to the equine referral hospital for treatment of a left guttural pouch mycosis previously diagnosed. After induction, the horse was shortly hoisted by all four feet, moved on a padded surgical table, and positioned in right lateral recumbency. In order to reduce the risk of bleeding during surgical manipulation of the carotid and maxillary arteries, a mean arterial pressure between 60 and 70 mmHg was targeted. After surgery, the horse was moved in a padded recovery box keeping the same lateral recumbency. Four unsuccessful attempts were performed, with the horse always returning to sternal recumbency keeping the left hind limb up. At the fifth attempt, performed 120 min after the end of the general anesthesia, the horse stood up correctly but moderate ataxia and absence of weight bearing on the left hind limb were shown. Both the stifle and the fetlock joint were held in a flexed position and could not be extended properly in order to set the foot on the ground, resulting in a very short step. The horse was calm, not sweating, and willing to move; the muscles of the affected limb were relaxed, and the limb was neither warm nor painful at palpation. Occasionally, the horse flexed the affected hind limb in an exaggerated motion with marked abduction. No additional laboratory analyses were performed. Due to a strong suspicion of neuropathy, a sling support was initiated and a supportive bandage associated with flunixine administration was performed until resolution of the symptoms. The horse fully recovered after 3 days. This case report does not clarify the pathogenesis of the possible postanesthetic neuropathy accounted on the non-dependent limb, highlighting the need for future research in this field. Non-dependent limb neuropathy should be an expected problem even after having ruled out the most commonly known causes predisposing to postanesthetic lameness.

Keywords: femoral paralysis, non-dependent limb, postanesthetic, neuropathy, horse, complication

OPEN ACCESS

Edited by:
Karine Portier, Université de Lyon, France

Reviewed by:
Raphael Labens, School of Animal and Veterinary Sciences, Charles Sturt University, Australia
Miguel Gozalo Marcilla, Faculty of Veterinary Medicine of Botucatu, Brazil

****Correspondence:***
Alessandro Mirra
alessandro.mirra@vetsuisse.unibe.ch

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *21 September 2017*
Accepted: *19 January 2018*
Published: *07 February 2018*

Citation:
Mirra A, Klopfenstein Bregger MD and Levionnois OL (2018) Suspicion of Postanesthetic Femoral Paralysis of the Non-Dependent Limb in a Horse. Front. Vet. Sci. 5:12. doi: 10.3389/fvets.2018.00012

INTRODUCTION

The present case reports the suspicion of postanesthetic femoral paralysis of the non-dependent limb in a horse, an unexpected occurrence, which may induce serious complications.

A 15-year-old Selle Français gelding, with a weight of 570 kg and a body condition score of 4/5 (1) was presented to the equine referral hospital for treatment of a left guttural pouch mycosis. Owner consent for publication of patient's data was obtained. The infection did not affect any arterial

vessel and no bleeding had been reported by the owner or the private veterinarian. Surgery for arterial coil embolization was scheduled (2). Preanesthetic clinical examination revealed a heart rate (HR) of 28 beats/min, a respiratory rate (RR) of 16 breaths/min, a rectal temperature of 37.3°C, and pink mucous membrane with a capillary refill time of 1.5 s. No abnormalities were detected on thorax auscultation and hematology and biochemistry were unremarkable. The horse had been treated for 2 days with local clotrimazol. Therefore, the patient was classified as an American Society of Anesthesiologist 2 category.

General anesthesia-related risks were considered and particular attention was placed on blood pressure management, with an aim to maintain a mean arterial blood pressure (MAP) between 60 and 70 mmHg in order to reduce the risk of bleeding during surgical manipulation of the carotid and maxillary arteries.

As the animal was calm, a 14-G catheter was placed without sedation in the left jugular vein. Acepromazine (Prequillan, Boehringer Ingelheim GmbH, Switzerland) (0.02 mg kg^{-1}) was administered intravenously (IV) 30 min before anesthesia induction. The horse was then moved into a padded induction box where xylazine (Xylasol, Graeub AG, Switzerland) (0.6 mg kg^{-1}) and, immediately after, levomethadone (L-Polamivet, MSD Animal Health GmbH, Switzerland) (0.05 mg kg^{-1}) were administered IV. Marked sedation was achieved within 10 min. Anesthesia was induced in a swing gate with diazepam (Valium, Roche Pharma, Switzerland) (0.05 mg kg^{-1}) IV and ketamine (Ketasol, Graeub AG, Switzerland) (1.5 mg kg^{-1}) IV (mixed in the same syringe), and, after flushing the catheter with saline, thiopental (Thiopental Inresa, Ospedalia AG, Switzerland) (1.5 mg kg^{-1}) IV. The trachea was intubated with a 28 mm internal diameter endotracheal tube. The horse was shortly hoisted by all four feet and positioned in right lateral recumbency onto a padded surgical table. Both hind limbs were positioned parallel to the ground on a specific padded support, with the coxofemoral joint positioned in its spontaneous natural angle. Anesthesia was maintained with isoflurane in oxygen-enriched medical air [fraction of inspired oxygen (FiO_2) = 55%] *via* a circle rebreathing system using an equine anesthetic machine (SurgiVet, Smiths medical, USA). Intravenous fluid therapy consisted of lactated Ringer's solution (5 ml kg^{-1} h^{-1}). A constant rate infusion of lidocaine (lidocaine 2%, Streuli Pharma AG, Switzerland) was administered IV (1.8 mg kg^{-1} h^{-1}). Physiological variables [HR, RR, hemoglobin saturation by pulsoximeter, end-tidal partial pressure of carbon dioxide ($ETCO_2$), and invasive blood pressure] as well as FiO_2 and end-tidal percentage of isoflurane were monitored continuously using a multiparameter monitor (Datex-Ohmeda S/5, Datex-Ohmeda, Finland) and recorded manually every 5 min. A 20G arterial cannula was placed in the lateral metatarsal artery of the non-dependent limb (left). The transducer was zeroed to atmospheric pressure, positioned at the level of the heart, and a fast flush test confirmed normal damping of the system by visual observation.

Initial systolic (SAP), mean, and diastolic (DAP) arterial pressures measured approximately 30 min after anesthesia induction were 115, 74, and 87 mmHg, respectively. Isoflurane concentration was adjusted and a dobutamine IV infusion was prepared to be administered, if necessary. Although the horse maintained adequate $ETCO_2$ in spontaneous ventilation, the breathing pattern was very irregular, and intermittent positive pressure ventilation was initiated 30 min after induction of anesthesia (tidal volume of approximately 6 l, RR of 7 breaths/min, peak inspiratory pressure of 12–15 cmH_2O). At 1 and 2 h after induction of anesthesia, arterial blood was taken for gas analysis, revealing acceptable values (pH 7.36 and 7.33; partial pressure of carbon dioxide 58 and 60 mmHg, partial pressure of oxygen 134 and 130 mmHg; lactate 1.1 and 1.0 mmol l^{-1}). The SAP, MAP, and DAP were maintained during the whole procedure between 82 and 98 mmHg, 62 and 70 mmHg, and 41 and 63 mmHg, respectively, without the assistance of dobutamine. General anesthesia and surgical procedure were uneventful, and lasted 190 and 145 min, respectively. Lidocaine infusion was stopped 30 min before termination of anesthesia.

The horse was again shortly hoisted by all four feet, moved to the padded recovery box, and positioned in right lateral recumbency. Romifidine (Sedivet, Boehringer Ingelheim, Switzerland) (0.02 mg kg^{-1}) was administered in the recovery box through the venous catheter and the horse was left to recover unassisted. The horse swallowed 20 min after end of anesthesia (EA) and the trachea was extubated. Xylazine (0.1 mg kg^{-1}) was administered IV twice at 10 and 15 min after EA because of marked nystagmus. A first unsuccessful attempt to stand was made 40 min after EA, followed by three further unsuccessful attempts. Each attempt was quiet and no injuries were suspected. The horse always returned to sternal recumbency, with the left leg always remaining the non-dependent one. It then stood up correctly on the fifth attempt, 120 min after EA. A recovery score of 2/5 [from 1 (best recovery possible) to 5 (worst recovery possible)] was attributed [following classification from Ref. (3)]. When standing, the horse showed moderate ataxia and absence of weight bearing on the left hind limb. Both the stifle and the fetlock joint were held in a flexed position and could not be extended properly in order to set the foot on the ground, resulting in a very short step. The horse was calm, willing to move, and not sweating; the muscles of the affected limb were relaxed, and the limb was neither warm nor painful on palpation. Occasionally, the horse flexed the affected hind limb in an exaggerated motion with marked abduction. No additional laboratory analyses were performed. As a result of the strong suspicion of neuropathy, a supportive bandage was applied to the left hind limb and the horse was provided sling support. Additionally, flunixine meglumine (Fluniximin, Graeub AG, Switzerland) (1.1 mg kg^{-1}) IV was administered every 12 h, as well as thiamine (1.6 mg kg^{-1}) and pyridoxine (0.7 mg kg^{-1}) IV every 24 h (Corébral, Vetoquinol AG, Switzerland). As the horse was judged able to stand without distress, the sling support was removed on the same evening. Weight bearing progressively improved on the following day without further complication, and complete resolution of lameness was observed the third postoperative day.

BACKGROUND

Mortality associated with equine anesthesia has been reported to occur in 0.8–1.8% of elective surgeries, with values rising to

19.5% in emergency cases despite improvements in anesthetic techniques and physiological monitoring (4). The largest mortality studies conducted to date in horse, the Confidential Enquiry into Perioperative Equine Fatalities 1 and 2 (5), reported that fractures and myopathy were responsible for 32% of postoperative mortality in non-colic surgeries. Myopathy may also occur alongside neuropathy, influencing the outcome and potentially increasing the risk of long bone fractures (4). Despite lack of pathognomonic symptoms, myopathy may be discriminated from neuropathy by presence of muscle stiffness and pain, leading eventually to fasciculation, sweating, and anxiety (6–8). Increased serum muscular enzymes and myoglobin, electromyography, ultrasonography, and nerve/muscular biopsy have been used to distinguish between the two conditions (6, 9–11), although clear differentiation between them can be challenging (8). Postanesthetic myopathy/neuropathy has been mostly reported in the dependent limbs. However, non-dependent forelimb neuropathy (12) and suspicion of bilateral femoral neuropathy have been reported (11). The occurrence of postanesthetic myopathy/neuropathy has been hypothesized to be caused by decreased tissue perfusion and oxygenation (8, 9, 12). The principal causes for their development are arterial hypotension, poor surgical table padding, and inappropriate positioning leading to regional blood flow disturbances, local compression, and mechanical tension on the nerves.

Recommendations have been made to avoid postanesthetic myopathy/neuropathy development (8, 9, 13). The horse must be placed on the operating table in a position that does not put any part of its body under strain; regional venous outflow should be allowed and pressure increase within muscle bellies avoided. Limbs should be allowed to settle naturally and be secured without force. When the horse is lying in lateral recumbency, both non-dependent limbs should be supported parallel to the ground, and the dependent forelimb should be pulled forward to reduce pressure on it from the chest. If access to the medial side of the dependent forelimb is required, the upper forelimb can be flexed. When the horse is lying in dorsal recumbency, care should be taken if leg extension locking the patellae is required and procedures longer than 20 min should be avoided in this position. Padding helps to spread the weight of the horse over a larger area of the body and should be deep enough to prevent the body reaching the table. Finally, a MAP >70 mmHg has been recommended to ensure a good muscular perfusion, decreasing the incidence of postanesthetic myopathy (14). Same recommendations apply to the recovery phase but, for practical reasons, the legs generally lie on the floor without support.

DISCUSSION

Report of neuropathy of the non-dependent hind limb, like in the present case, has not been reported yet to the authors' knowledge.

Differentiation between myopathy and neuropathy can be challenging. They share common causes like arterial hypotension, poor padding of the surgical table, and inappropriate patient positioning, potentially leading to decreased tissue perfusion and oxygenation. Moreover, neuropathy and myopathy may occur in parallel. However, myopathy is generally associated with muscle stiffness, pain at palpation, sweating, and anxiety. In the present case, absence of these clinical signs led us to exclude a component of myopathy. Nerve compression and stretching with consequent nerve ischemia and hypoxia were suspected to be the most probable mechanism behind the observed dysfunction.

As the affected limb was the non-dependent one, factors such as the table padding and horse positioning, which were standard in the present case (8), were unlikely to be the causes of the problem. Hoisting by all four limbs could have potentially induced nerve stretching leading to neuropraxia, although to the author's knowledge, this has never been reported. The coxofemoral joint was positioned in its natural resting position, which should not lead to nerve damage.

Hypotension could have been a predisposing factor for the development of neuropathy. Because the non-dependent limb was elevated over the heart level, a decreased hydrostatic pressure could have led to a reduction of muscle perfusion. However, in the present case, the arterial line was placed in the affected limb, and the MAP was maintained between 62 and 72 mmHg during the whole procedure, the lowest value being recorded during coil embolization. Therefore, intraoperative hypotension was unlikely to be the main cause of the postoperative complication. Since the arterial catheter was placed in the affected limb, good correlation between measured invasive blood pressure values and actual limb blood flow was expected. Dobutamine administration could have helped increasing femoral blood flow and possibly nerves perfusion (15–17). However, in equines, its effect on peripheral perfusion and microcirculation is still not well characterized (17–19).

In the present case, IV lidocaine was administered since the beginning of the surgical procedure. If ischemia was involved in the subsequent nerve dysfunction, its administration may have shortened normalization of the clinical condition; indeed, lidocaine has been shown to reduce reperfusion injury (20, 21).

The risk of developing postanesthetic myopathy/neuropathy increases with anesthesia duration (4). In the present case, the anesthesia lasted 190 min, which could have contributed to the development of neuropathy. The horse required further 120 min to stand up after EA. However, the first attempt was made 40 min after EA, and the underlying femoral paralysis leading to ataxia may have made it difficult for the horse to reach a stable standing position. Development of the neuropathy during recovery seems unlikely since the unsuccessful attempts were all quiet and the horse always returned to sternal recumbency keeping the left hind limb as the non-dependent.

In the present case, the clinical presentation suggested a femoral paralysis, while myopathy was considered rather unlikely because there was lack of pain, sweating, restlessness, muscular stiffness, fasciculation, and anxiety when the horse recovered from anesthesia. However, further analyses could have been helpful in the diagnostic process. Unexpectedly, high plasma creatine kinase values within a few hours after surgery may support a diagnosis of myopathy (8). Nevertheless, the same enzyme may be elevated with other causes of postanesthetic lameness such as peripheral neuropathy, because of secondary muscle damage, or a mixed myopathy–neuropathy (9). Aspartate aminotransferase

and myoglobin can also be elevated in cases of myopathy, with the latter leading to dark red or red/brown urine production (9). Hypoechoic areas within the muscle, when observed by ultrasonography, suggest muscle fiber disruption and acute injury (22) but the prognostic value of such observation is uncertain (6). Finally, muscle and nerve biopsy (11) and electromyography (10, 23) may distinguish between myopathy and neuropathy. However, in absence of local muscular symptoms, identifying a correct location to take the biopsy may be challenging. Moreover, changes associated with denervation are usually detectable by electromyography only 4–5 days after denervation (24, 25). Because of the strong suspicion of neuropathy, the fast improvement of the clinical condition and the low reliability of possible further investigations, no supplementary tests were conducted.

Different treatments have been described for postanesthetic myopathy/neuropathy (6, 8, 9, 11, 12), but no clear guidelines have been established so far. In case of neuropathy symptomatic treatment with nonsteroidal anti-inflammatory agents, corticosteroids and dimethyl sulfoxide have been suggested to reduce neural edema. If the horse is able to stand, a supportive bandage and sling support could be applied. If needed, sedation and/or analgesia must be provided. In case a concomitant myopathy cannot be excluded, further treatment can be used. Dantrolene sodium has been described to relax muscles in cases with severe muscle stiffness. Fluid therapy should be initiated to prevent kidney dysfunction because of myoglobinurea. Acepromazine may also improve lamellar blood flow, and anticoagulants (heparin, aspirin) have been suggested to prevent platelet aggregation and subsequent laminitis syndrome. Additionally, physiotherapy, massage, and ultraviolet light can be considered. In the present case, no signs of discomfort were shown by the animal and intense supportive therapy was not required.

CONCLUDING REMARKS

We report a strong suspicion of postanesthetic femoral paralysis of the non-dependent limb. This case report does not clarify the possible pathogenesis of the suspected nondependent limb postanesthetic neuropathy, highlighting the need for future research in this field. Adequate padding, prudent positioning, and good perfusion pressure must be always considered important factors for avoiding postanesthetic myopathy/neuropathy in horses.

AUTHOR CONTRIBUTIONS

AM, MK, and OL were involved in the care of the patient and were involved in planning this case report. AM was responsible for the conception of this case report and preparation of the first draft. MK and OL provided feedback and were involved in revising the manuscript. All the authors have read and approved the final version of the manuscript.

REFERENCES

1. Carrol CL, Huntington PJ. Body condition scoring and weight estimation of horses. *Equine Vet J* (1988) 20(1):41–5. doi:10.1111/j.2042-3306.1988.tb01451.x
2. Léveillé R, Hardy J, Robertson JT, Willis AM, Beard WL, Weisbrode SE, et al. Transarterial coil embolization of the internal and external carotid and maxillary arteries for prevention of hemorrhage from guttural pouch mycosis in horses. *Vet Surg* (2000) 29(5):389–97. doi:10.1053/jvet.2000.7537
3. Young SS, Taylor PM. Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases. *Equine Vet J* (1993) 25(2):147–51. doi:10.1111/j.2042-3306.1993.tb02926.x
4. Dugdale AH, Taylor PM. Equine anaesthesia-associated mortality: where are we now? *Vet Anaesth Analg* (2016) 43:242–55. doi:10.1111/vaa.12372
5. Johnston GM, Eastment JK, Wood JLN, Taylor PM. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Vet Anaesth Analg* (2002) 29:159–70. doi:10.1046/j.1467-2995.2002.00106.x
6. Webb JK, van Loon JPAM. *The Incidence of Post Anaesthetic Myopathy (PAM) in Horses after General Anaesthesia for MTI in Comparison to the Incidence of PAM in Horses Anaesthetised for Other Reasons*. Utrecht: University of Utrecht, Faculty of Veterinary Medicine (2013).
7. Auer JA, Stick JA. *Equine Surgery, Chapter 21*. 4th ed. Saint Louis: Elsevier Saunders (2012). p. 251–2.
8. Taylor PM, Clarke KW. *Handbook of Equine Anaesthesia. Chapter 7*. Philadelphia: Saunders Elsevier (2007). p. 137–52.
9. Young SS. Post anaesthetic myopathy. *Equine Vet Educ* (2005) 7:60–3. doi:10.1111/j.2042-3292.2005.tb01829.x
10. Wijnberg ID, Back W, De Jong M, Zuidhof MC, Van Den Belt AJM, van der Kolk JH. The role of electromyography in clinical diagnosis of neuromuscular locomotor problems in the horse. *Equine Vet J* (2004) 36:718–22. doi:10.2746/0425164044848019
11. Dyson S, Taylor P, Whitwell K. Femoral nerve paralysis after general anesthesia. *Equine Vet J* (1988) 20:376–80. doi:10.1111/j.2042-3306.1988.tb01550.x
12. Oosterlinck M, Schauvliege S, Martens A, Pille F. Postanesthetic neuropathy/myopathy in the nondependent forelimb in 4 horses. *J Equine Vet Sci* (2013) 33:996–9. doi:10.1016/j.jevs.2013.03.181
13. Duke T, Filzek U, Read MR, Read EK, Ferguson JG. Clinical observations surrounding an increased incidence of postanesthetic myopathy in halothane-anesthetized horses. *Vet Anaesth Analg* (2006) 33:122–7. doi:10.1111/j.1467-2995.2005.00189.x
14. Schauvliege S, Gasthuys F. Drugs for cardiovascular support in anesthetized horses. *Vet Clin North Am Equine Pract* (2013) 29(1):19–49. doi:10.1016/j.cveq.2012.11.011
15. Schier MF, Raisis AL, Secombe CJ, Hosgood G, Musk GC, Lester GD. Effects of dobutamine hydrochloride on cardiovascular function in horses anesthetized with isoflurane with or without acepromazine maleate premedication. *Am J Vet Res* (2016) 77:1318–24. doi:10.2460/ajvr.77.12.1318
16. Wang Y, Tang P, Zhang L, Guo Y, Wan W. Quantitative evaluation of the peripheral nerve blood perfusion with high frequency contrast-enhanced ultrasound. *Acad Radiol* (2010) 17:1492–7. doi:10.1016/j.acra.2010.07.007
17. Raisis AL, Young LE, Blissitt KJ, Walsh K, Meire HB, Taylor PM, et al. Effect of a 30-minute infusion of dobutamine hydrochloride on hind limb blood flow and hemodynamics in halothane-anesthetized horses. *Am J Vet Res* (2000) 61:1282–8. doi:10.2460/ajvr.2000.61.1282
18. Dancker C, Hopster K, Rohn K, Kästner SB. Effects of dobutamine, dopamine, phenylephrine and noradrenaline on systemic haemodynamics and intestinal perfusion in isoflurane anaesthetised horses. *Equine Vet J* (2018) 50:104–10. doi:10.1111/evj.12721
19. Loughran CM, Raisis AL, Hosgood G, Secombe CJ, Lester GD. The effect of dobutamine and bolus crystalloid fluids on the cardiovascular function of isoflurane-anaesthetised horses. *Equine Vet J* (2017) 494:369–74. doi:10.1111/evj.12605
20. Lan W, Harmon D, Wang JH, Ghori K, Shorten G, Redmond P. The effect of lidocaine on in vitro neutrophil and endothelial adhesion molecule expression induced by plasma obtained during tourniquet-induced ischaemia and reperfusion. *Eur J Anaesthesiol* (2004) 21:892–7. doi:10.1017/S0265021504000249

21. Cassutto BH, Gfeller RW. Use of intravenous lidocaine to prevent reperfusion injury and subsequent multiple organ dysfunction syndrome. *J Vet Emerg Crit Care* (2003) 13(3):137–48. doi:10.1046/j.1435-6935.2003.00080.x
22. Valber SJ. Approach the horse with a suspected myopathy. *World Equine Veterinary Association (WEVA), Proceedings of the 11th International Congress*. Guarujá, SP, Brazil (2009).
23. Wijnberg ID, Franssen H. The potential and limitations of quantitative electromyography in equine medicine. *Vet J* (2016) 209:23–31. doi:10.1016/j.tvjl.2015.07.024
24. Cuddon PA. Electrophysiology in neuromuscular disease. *Vet Clin North Am Small Anim Pract* (2002) 32:31–62. doi:10.1016/s0195-5616(03)00079-2
25. van Wessum R, Sloet van Oldruitenborgh-Oosterbaan MM, Clayton HM. Electromyography in the horse in veterinary medicine and in veterinary research—a review. *Vet Q* (1999) 21:3–7. doi:10.1080/01652176.1999.9694983

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

MINI REVIEW
published: 06 March 2018
doi: 10.3389/fvets.2018.00043

Morbidity and Mortality Conferences: A Mini Review and Illustrated Application in Veterinary Medicine

Daniel S. J. Pang, Frédérik Rousseau-Blass and Jessica M. Pang*

Department of Clinical Sciences, Faculty of Veterinary Medicine, Université de Montréal, Saint-Hyacinthe, QC, Canada

This mini review presents current knowledge on the role of morbidity and mortality conferences (M&MCs) as a powerful educational tool and driver to improve patient care. Although M&MCs have existed since the early twentieth century, formal evaluation of their impact on education and patient care is relatively recent. Over time, M&MCs have evolved from single discipline discussions with a tendency to focus on individual errors and assign blame, to multidisciplinary, standardized presentations incorporating error analysis techniques, and educational theory. Current evidence shows that M&MCs can provide a valuable educational experience and have the potential to generate measurable improvements in patient care.

Keywords: morbidity and mortality conference, rounds, meeting, errors, adverse events, complications

OPEN ACCESS

Edited by:
Karine Portier,
Université de Lyon, France

Reviewed by:
Rene Doerfelt,
LMU Munich, Germany
Joost Jan Uilenreef,
Academic Medical Center (AMC),
Netherlands

****Correspondence:***
Daniel S. J. Pang
daniel.pang@umontreal.ca

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *29 November 2017*
Accepted: *21 February 2018*
Published: *06 March 2018*

Citation:
Pang DSJ, Rousseau-Blass F and Pang JM (2018) Morbidity and Mortality Conferences: A Mini Review and Illustrated Application in Veterinary Medicine. Front. Vet. Sci. 5:43. doi: 10.3389/fvets.2018.00043

INTRODUCTION

Adverse events, defined as a complication caused by medical management and resulting in patient harm, are an unfortunately common occurrence in hospitalized human patients (1–5). While estimates vary depending on the outcome(s) used to define adverse events, up to 4% of all hospitalized human patients will experience a serious negative outcome (prolonged hospital stay, disability at discharge, or death) (1, 2). Importantly, half of all adverse events are preventable (1, 2, 4, 5). As a result, there is room for substantial improvement in patient outcomes through better care (2–5).

The potential for adverse events to drive improved patient care and safety, and serve as a valuable educational resource, has long been recognized in human medicine (6–9). Since their inception in the first half of the twentieth century, morbidity and mortality conferences (M&MCs, also known as M&M rounds and reviews) have been the mechanism to achieve these outcomes, and they are implemented in a wide range of medical specialties, most notably surgery and anesthesia (7, 9). Their use is now mandated by the Accreditation Council for Graduate Medical Education in human medicine and is part of the Practice Standards Scheme of the Royal College of Veterinary Surgeons (10, 11).

Fittingly described as familiar yet lacking a clear definition, at a fundamental level M&MCs comprise of caregivers gathering to review adverse events, with the goals of education and improving care (7). In principle, M&MCs should provide an open forum for the collaborative review of adverse events without fear of retribution or blame. The primary goals should be improving patient care and maximizing the educational benefits of a shared experience (6, 12–14). These can be achieved through: presentation and acknowledgment of error(s) [defined as performance that deviates from the ideal; failure to carry out a planned action as intended (error of execution), or the use of an incorrect or inappropriate plan (error of planning)], analysis and discussion of adverse events and contributing factor(s), identification of means for improvement, dissemination of information, and reinforcement of responsibility to provide best practice standard of care (7, 15–17). In practice, however, M&MCs are often poorly defined in terms of format, goals, and outcomes (7, 18, 19). Learning from errors through reflection and discussion is essential to improve practice, though

where this is done ineffectually, or with the emphasis on assigning blame, M&MCs fail to be productive (7, 13, 20).

While there is a large body of literature supporting and advocating the use of M&MCs, their efficacy in terms of measurable outcomes has, until recently, been largely untested. Increasing evidence suggests that a structured, transparent approach to M&MCs results in measurable gains in user satisfaction and participation, education, patient safety, quality of care, and mortality (13, 15, 21–25). This mini review will discuss the demonstrated benefits of M&MCs and available evidence on their optimal format.

BENEFITS

Education

Despite their long history, it has only been relatively recently that prospective trials have been conducted to evaluate the educational contribution of M&MCs (15, 19, 21, 24, 26). These studies have developed and tested structured approaches to M&MCs, encompassing case reporting and selection, analysis of adverse events, presentation, participation, and learning outcomes.

Implementation of a standardized presentation format significantly improved the number of correct responses to multiple choice questions completed at the end of each M&MC and presentation quality (15). The same group had previously developed an M&MC presentation assessment tool using psychometric principles that was feasible (taking <10 min to complete), reliable (high-internal consistency and inter-rater agreement), and valid (construct validity), thus allowing presenters and presentation content to be objectively evaluated (21).

In a large pediatric anesthesia service (approximately 18,000 anesthetics per year), McDonnell et al. sought to improve an overburdened and inefficient M&M system that was associated with a culture of blame and lost educational opportunities (19). M&MCs held following restructuring of the reporting mechanism and focusing case selection on educational potential identified multiple areas for improvement, including situations more commonly associated with adverse events (e.g., fluid management and transfusion, emergent exploratory laparotomies), equipment contributions to error, and wider dissemination of information. These were addressed with targeted educational sessions, equipment changes (e.g., replacement of inaccurate atomizers for local anesthetic delivery with syringes and compatible catheters), and presentation of cases at national meetings and as published case reports, respectively (19).

Similarly, as a result of improved case selection and error analysis, Calder et al. showed that succinct recommendations ("M&M Bottom Lines") could be generated from M&MCs, providing participants with a memorable message that could improve personal practice and be easily disseminated (e.g., "Find one fracture, look for the next one") (24).

Satisfaction and Participation

Mandatory attendance of M&MCs is commonly reported in the literature as a requirement of training (6, 7, 12, 15, 19, 27, 28). In moving to a mandatory M&MC system, McDonnell et al. increased M&MC attendance fivefold (19). Interestingly, this action built the habit of attendance, so that when M&MCs were eventually separated in to their own regular schedule, attendance rates were maintained. Mitchell et al. (15) showed that the adoption of a structured presentation [situation, background, assessment, recommendations (SBAR), presented in detail below] was associated in increased user satisfaction, compared with variable presentation formats decided by individual presenters (17).

Patient Safety

Several studies have reported improvements in patient safety following the presentation of cases at M&MCs and subsequent changes in patient care and management (12, 13, 22, 25, 26, 29, 30). A common theme of these reports is the clear structure to the M&MC process, though the degree and extent of standardization varied. Some studies focused on identifying and enacting mechanisms for improvement coupled with continuous monitoring of progress (12, 13, 20, 25, 29), while others focused on the care pathway (12, 29), standardized presentation, and error analysis (12, 13).

These varied approaches have resulted in a 50% reduction in malpractice claims (20), improved safety culture and quality of care (20, 25, 29, 30), and reductions in mortality of up to 40% (12, 13, 29). Data should be collected prospectively before as well as after implemented changes in management to properly establish the relationship between enacted changes and outcome. Clinical audit, a core element of clinical governance, is an invaluable tool to monitor adherence to changes in practice and related outcomes (31–34). Furthermore, standardization of data collection is a prerequisite for collaborative efforts to assess the impact of proposed changes in care (35).

Within the broader context of patient safety, M&MCs can be viewed as one of a suite of techniques and tools to report, analyze, and prevent errors (36–39). As such, M&MCs should not be applied in isolation but be included in an organizational approach to error management. It is interesting to note that well-managed M&MCs have the potential to encompass several of the key components of improving patient safety: a reporting system, error analysis using a human factors approach, education, and risk reduction. A discussion of error and patient safety is beyond the scope of this Mini Review. Interested readers are referred to reference texts (36, 38, 40, 41).

M&MC FORMAT

Publicly disclosing and discussing an adverse event is a difficult process. All M&MCs comprise components that can be optimized to yield the greatest benefit from such a process. The general structure described in this section follows that of two models whose performance has been evaluated prospectively and shown to be effective: the Ottawa M&M model (OM3) and the SBAR model (15, 21, 24). A fictionalized account of a clinical case is used to illustrate the individual components.

Case Reporting and Selection

Under-reporting of adverse events can stem from lack of awareness of an available reporting system, be it formal or informal, or the inability to submit an anonymous report. Educating new staff members to the existence and use of a reporting system and requiring all submissions be through a single hospital-wide

database improves the capture of adverse events, with an increase in the total number of reports and self-reports (19).

In general, all cases of mortality should be reviewed with an M&MC, though this is not always the case (42). In some centers, deaths resulting from the natural progression of a condition are not reviewed (30). In cases where morbidity has occurred as a result of an adverse event, not all cases may progress to an M&MC or meet the threshold for review at an M&MC (7, 19, 24). In large centers, the number of reported cases can outstrip the time and resources available to hold M&MCs. There are several possibilities for handling these cases:

1. Include such cases in the institutional reporting system, where they can serve to highlight a trend of complications or collected by theme (e.g., drug calculation errors) and presented as a group.
2. Hold a smaller M&MC restricted to the discipline in which the error occurred.
3. Address failures in individual performance with the appropriate supervisor. When an error has occurred as a result of a deviation from a well-established procedure and has not resulted in an adverse event, the case may not meet the criteria for presentation at an M&MC. An example is provided below:

> A dog was given a 10x intravenous overdose of the alpha-adrenergic agonist dexmedetomidine as a result of a drug calculation error by a veterinary student. Standard practice at the clinic was for all student drug calculations (and injectate volumes) to be checked by a veterinary technician before injection. In this case, the error occurred as standard practice was circumvented with the intention to save time. The error was realized within 3 minutes of the injection occurring, the dog was immediately examined, atipamezole was given and the dog was placed under clinical observation for 6 hours. The case was reviewed the same day with the individuals directly involved and the supervising anesthetist.

Such a near-miss incident (no harm resulted as a result of timely intervention or chance) may not proceed to an M&MC but should be recorded in case a pattern of similar events is occurring and to reinforce individual accountability.

Where case selection is necessary, it should be based on the greatest benefit to future patient safety and educational value (19, 24). Cases should be presented and discussed soon after they occur. There is no evidence in support of a specific time frame, but early presentation reinforces the importance of timely acknowledgment of an adverse event (7, 29). In large centers, the establishment of an M&M committee and coordinators facilitates efficient handling of reports and cases are typically presented within 4–8 weeks of reporting (19, 24, 29).

If there is reluctance to participate in, or convene M&MCs, an option to encourage participation is to initially select cases of near-miss incidents. Selecting such a case is still valuable in terms of improving care and providing education by allowing participants to analyze the factors contributing to the event (see root cause analysis, below), make recommendations to avoid similar incidents and learn from the experience.

M&MC Duration and Frequency

The duration of M&MCs is often unreported though is likely to be a function of available time (e.g., over lunch) and the number of cases to be discussed. Reported durations have ranged from 20 min (15 min presentation plus 5 min discussion) to over an hour (6, 15, 21, 28, 30, 42, 43). The OM3 and SBAR models last 1 h and 20 min, respectively.

Similarly, frequency of M&MCs is highly variable, with a monthly interval being a common frequency reported in the literature (3, 7, 12, 18–20, 23–25, 28–30, 42, 43).

Moderator

The moderator should be familiar with the M&MC format, principles of error analysis and have sufficient content expertise to guide the presenter during preparation and the audience in participation and have the authority to establish the desired tone, creating an open, collaborative, and supportive discussion without minimizing or magnifying the error (14, 24, 44).

Presenter

Typically, M&MCs are presented by a clinician directly involved in the case, though whether this is a trainee or senior clinician may vary depending on the complexity of the case and frequency of presentations (18, 24). In programs where presentations are given by trainees, it is important that senior personnel show support in the form of attendance, setting the appropriate tone for discussion, and sharing their experiences (7). Cases may be presented by someone external to the case though those involved with the case should have the option to present (7, 18). If the responsible clinicians are unable to attend, the tone of the M&MC should be the same as though they were present (7).

Attendees/Audience

Audience composition is highly variable, though a multidisciplinary approach is strongly favored, as this enriches the discussion and maximizes dissemination of information (7, 18, 28–30, 42, 44). An inclusive approach has been advocated to include care staff, having the added benefit of fostering an open safety culture (12, 29, 30, 45).

Presentation Format

There are few formats for M&MCs presented in the literature and this has been cited as a limiting factor in maximizing the educational opportunity and unbiased case analysis (7, 15, 18, 21). Consequently, recent work has focused on developing and assessing a standardized M&MC presentation format, the SBAR model (**Table 1**) (21, 25). Communication using SBAR is an example of situational briefing, to efficiently transfer critical information between team members who may occupy different levels in organization hierarchy (46, 47). As described earlier, the SBAR format has educational benefits for attendees and presenters (15, 21).

Root Cause Analysis

The objective of root cause analysis is to identify factors contributing to an adverse event. Several methods have been reported in the M&MC literature, with the common goal of gaining a deeper

TABLE 1 | The situation, background, assessment, recommendations (SBAR) presentation format for morbidity and mortality conferences.

SBAR component	Elements
Situation: brief statement of problem	Diagnosis at admission, statement of procedure, and adverse event
Background: clinical information pertinent to adverse event	History, indication for procedure, diagnostic studies, procedural details, timeline of care, description of adverse event (recognition, management, outcome)
Assessment and analysis: evaluation of adverse event (what and why)	What: sequence of events. Why: root cause analysis[a]
Review of the literature: evidence-based practice	Relevant literature
Recommendations: prevention of recurrence	Identify how event could have been prevented or better managed. Identify learning outcomes and recommendations

Adapted from Mitchell et al. (15, 21).
[a]Numerous methods for root cause analyses exist (see main text).

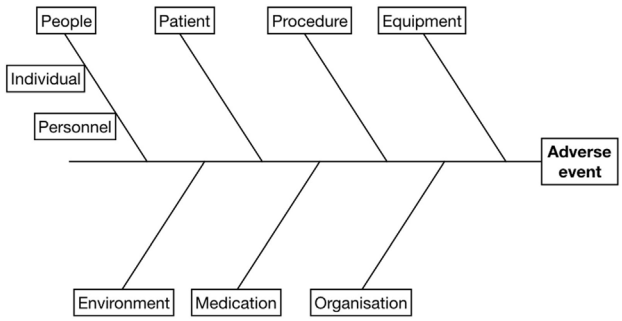

FIGURE 1 | Fishbone diagram used to facilitate root cause analysis. The adverse event is listed at the "head" and potential contributory factors are examined to establish a cause and effect relationship. See Presentations S1 and S2 in Supplementary Material for an example.

understanding of the circumstances surrounding an adverse event (13, 15, 21, 25, 43, 45, 48, 49). The method presented here is the fishbone diagram (also known as, cause and effect, Ishikawa, or Fishikawa diagram). It is recommended for process improvement as it provides a visual framework for analysis and discussion and is one of the seven basic quality control tools (**Figure 1**) (50). The adverse event represents the "head" of the fish and each bone represents a potential contributing factor. The example included in Presentations S1 and S2 in Supplementary Material is based on the work of reason (40, 41) though other, more detailed approaches exist (39). The order and position of individual factors is unrelated to any priority; it may be that a sub-factor is a major contributing factor. A small group discussion may be helpful to determine the role, if any, of each factor, with the group formed by the individual(s) most closely involved with the adverse event and a senior team member with understanding of error analysis. In making these determinations questioning why things occurred, using a "five whys" approach, can be useful (50):

1. Describe the problem.
2. Ask "why" it happened.
3. Continue to ask "why" until the root cause is identified (may take more or less than five "whys").
4. Maintain a focus on the process and not the personalities.

In maintaining a non-punitive environment for M&MCs, it is critical that causes are based on fact (and evidence) rather than opinion. As illustrated with the sample case (below), there are likely to be multiple factors contributing to an adverse event. Identifying these factors facilitates a complete discussion and identifies potential solutions.

Follow-up

Where recommendations have resulted in changes in practice, relevant outcomes should be tracked to ensure that changes are beneficial and do not lead to unexpected negative consequences. Tracking has been successfully employed to identify improvements in mortality rates and patient care (as described earlier) (12, 13, 20, 25, 29, 30). Clinical audit is a suitable method for tracking performance that is easy to institute (51). Where a system or infrastructure deficit has been identified as a major contributing factor to the adverse event, the appropriate member of leadership (e.g., hospital director) should be notified so the deficit(s) can be addressed. A recent survey of surgical residency programs registered with the American College of Veterinary Surgeons suggests that in the majority of cases (26/35 programs, survey response rate 32%), discussions do not translate in to implemented changes in practice or changes are not tracked to assess outcome (42).

CONCLUSION

Current evidence shows that a structured M&MC with a standardized presentation format and root cause analysis, and tracking of outcomes, serves as a valuable educational experience with the greatest potential to improve patient safety and quality of care. The described approaches can easily be adopted and applied in veterinary medicine.

SAMPLE CASE

Case Selection

A 10-year old, warmblood mare experienced pronounced acute hypoxemia during recovery from general anesthesia for bilateral thoracic limb magnetic resonance imaging (MRI). This case was selected for presentation at an M&MC as it contained multiple factors contributing to an adverse event and illustrated an important perturbation of normal physiology during anesthesia. Case selection was made following an initial case review between an anesthesia resident and supervisor.

Presenter and Moderator

The presenter (first year anesthesia resident) was directly involved in the case. The moderator was a senior anesthetist with detailed knowledge of the case.

Audience

The invited audience included equine interns (mandatory participation), residents (mandatory participation), clinicians, and

faculty. All final year veterinary students rotating through the equine hospital and student members of the faculty equine club were also invited. The audience included board-certified internists, theriogenologists, surgeons, and anesthesiologists, and a representative anesthesia technician. Approximately 30 people attended.

Presentation

The SBAR presentation format was used (Presentations S1 and S2 in Supplementary Material). Educational components were provided by presentation and discussion of the adverse event alongside a brief review of relevant respiratory physiology. Duration was set by the context of inclusion in a weekly graduate trainee seminar series and limited to 15 min presentation followed by 10 min discussion. The proportion of time allocated to the discussion was helpful to explore the contributing factors identified and generate recommendations. To set the tone for the presentation and discussion, the opening and closing presentation slides included a statement of the goal of the M&MC (Presentations S1 and S2 in Supplementary Material).

Root Cause Analysis (Contributing Factors Corresponding to the Fishbone Diagram Are Italicized)

Specific problem—horse became hypoxemic during recovery (confirmed with arterial blood gas analysis), which potentially began during transfer from MRI.

1. Why? Body position was changed from left to right lateral for transfer to recovery (*procedure*) and ventilation was inadequate (*procedure* or *equipment*) during transfer.
2. Why? There was confusion and unclear communication between different teams (anesthesia, radiology, animal handlers—*people-personnel*) and the endotracheal tube cuff was prematurely deflated limiting efficacy of positive pressure ventilation (*people-individual*).
3. Why? One anesthetist was managing multiple cases on both sides of the hospital (small and large animal, *organization*) and the anesthetist was not present at the start of transfer (*people-individual & personnel*).
4. Why? A second anesthetist was unavailable that morning (*organization*).
5. Why? This was a planned absence with an email circulated to service chiefs notifying them of short-staffing in anesthesia (*organization*).

Identified contributing factors were added to a fishbone diagram in Presentations S1 and S2 in Supplementary Material.

Follow-up

The equine hospital chief attends all equine M&MCs. Each of the fishbone factors was discussed. The role and responsibilities of different personnel were clarified. Recommendations: (1) A leader is designated to manage transfer. The senior anesthetist is ultimately responsible, but has power to delegate leadership if someone with specific expertise is present, such as senior animal handler. (2) Cases should not be transferred without permission of senior anesthetist. (3) Senior anesthetist has the right to delay or turn away elective cases, and cases may be stopped prematurely in the interests of patient safety. (4) A wider discussion of case transfer, with the potential to introduce a checklist or standard operating protocol, was planned.

AUTHOR CONTRIBUTIONS

DP, FR-B, and JP concept and design, drafting and revising, final approval, and accountability for all aspects of the work.

ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Jean-Pierre Lavoie's championing of M&MCs at the equine hospital of the Centre Hospitalier Universitaire Vétérinaire, Université de Montréal.

FUNDING

DP receives funding from the Natural Sciences and Engineering Research Council of Canada Discovery Grant (424022-2013) and the Fondation J.-Louis Lévesque.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fvets.2018.00043/full#supplementary-material.

PRESENTATION S1 | Example of power point presentation given to accompany sample case (English).

PRESENTATION S2 | Example of power point presentation given to accompany sample case (Francais).

REFERENCES

1. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in Colorado and Utah in 1992. *Surgery* (1999) 126:66–75. doi:10.1067/msy.1999.98664
2. Kohn LT, Corrigan JM, Donaldson MS; Committee on Quality of Health Care in America (Institute of Medicine). *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press (2000).
3. Ksouri H, Balanant PY, Tadié JM, Heraud G, Abboud I, Lerolle N, et al. Impact of morbidity and mortality conferences on analysis of mortality and critical events in intensive care practice. *Am J Crit Care* (2010) 19:135–45. doi:10.4037/ajcc2010590 quiz 146,
4. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* (1991) 324:377–84. doi:10.1056/NEJM199102073240605
5. Vincent C, Moorthy K, Sarker SK, Chang A, Darzi AW. Systems approaches to surgical quality and safety: from concept to measurement. *Ann Surg* (2004) 239:475–82. doi:10.1097/01.sla.0000118753.22830.41
6. Higginson J, Walters R, Fulop N. Mortality and morbidity meetings: an untapped resource for improving the governance of patient safety. *BMJ Qual Saf* (2012) 21:576–85. doi:10.1136/bmjqs-2011-000603
7. Orlander JD, Barber TW, Fincke BG. The morbidity and mortality conference: the delicate nature of learning from error. *Acad Med* (2002) 77:1001–6. doi:10.1097/00001888-200210000-00011
8. Reverby S. Stealing the golden eggs: Ernest Amory Codman and the science and management of medicine. *Bull Hist Med* (1981) 55:156–71.

9. Ruth HS, Haugen FP, Grove DD. Anesthesia Study Commission; findings of 11 years' activity. *J Am Med Assoc* (1947) 135:881–4. doi:10.1001/jama.1947.02890140001001
10. *Accreditation Council for Graduate Medical Education*. (2017). Available from: http://www.acgme.org/What-We-Do/Initiatives/Clinical-Learning-Environment-Review-CLER
11. *Royal College of Veterinary Surgeons Practice Standards Scheme*. (2017). Available from: https://www.rcvs.org.uk/setting-standards/practice-standards-scheme/
12. Kirschenbaum L, Kurtz S, Astiz M. Improved clinical outcomes combining house staff self-assessment with an audit-based quality improvement program. *J Gen Intern Med* (2010) 25:1078–82. doi:10.1007/s11606-010-1427-5
13. Antonacci AC, Lam S, Lavarias V, Homel P, Eavey RA. A report card system using error profile analysis and concurrent morbidity and mortality review: surgical outcome analysis, part II. *J Surg Res* (2009) 153:95–104. doi:10.1016/j.jss.2008.02.051
14. Joseph C, Garrubba M, Melder A, Loh E. Best practice for conducting morbidity and mortality reviews: a literature review. *The Quaterly* (2015).
15. Mitchell EL, Lee DY, Arora S, Kenney-Moore P, Liem TK, Landry GJ, et al. Improving the quality of the surgical morbidity and mortality conference: a prospective intervention study. *Acad Med* (2013) 88:824–30. doi:10.1097/ACM.0b013e31828f87fe
16. Allnut MF. Human factors in accidents. *Br J Anaesth* (1987) 59:856–64. doi:10.1093/bja/59.7.856
17. Leape LL. Reporting of adverse events. *N Engl J Med* (2002) 346:1633–8. doi:10.1056/NEJMNEJMhpr011493
18. Aboumatar HJ, Blackledge CG, Dickson C, Heitmiller E, Freischlag J, Pronovost PJ. A descriptive study of morbidity and mortality conferences and their conformity to medical incident analysis models: results of the morbidity and mortality conference improvement study, phase 1. *Am J Med Qual* (2007) 22:232–8. doi:10.1177/1062860607303292
19. McDonnell C, Laxer RM, Roy WL. Redesigning a morbidity and mortality program in a university-affiliated pediatric anesthesia department. *Jt Comm J Qual Patient Saf* (2010) 36:117–25. doi:10.1016/S1553-7250(10)36020-X
20. Chan LS, Elabiad M, Zheng L, Wagman B, Low G, Chang R, et al. A medical staff peer review system in a public teaching hospital—an internal quality improvement tool. *J Healthc Qual* (2014) 36:37–44. doi:10.1111/j.1945-1474.2012.00208.x
21. Mitchell EL, Lee DY, Arora S, Kwong KL, Liem TK, Landry GL, et al. SBAR M&M: a feasible, reliable, and valid tool to assess the quality of, surgical morbidity and mortality conference presentations. *Am J Surg* (2012) 203:26–31. doi:10.1016/j.amjsurg.2011.07.008
22. Nimptsch U, Mansky T. Quality measurement combined with peer review improved German in-hospital mortality rates for four diseases. *Health Aff (Millwood)* (2013) 32:1616–23. doi:10.1377/hlthaff.2012.0925
23. Szekendi MK, Barnard C, Creamer J, Noskin GA. Using patient safety morbidity and mortality conferences to promote transparency and a culture of safety. *Jt Comm J Qual Patient Saf* (2010) 36:3–9. doi:10.1016/S1553-7250(10)36001-6
24. Calder LA, Kwok ESH, Cwinn AA, Worthington J, Yelle JD, Waggott M, et al. Enhancing the quality of morbidity and mortality rounds: the Ottawa M&M model. *Acad Emerg Med* (2014) 21:314–21. doi:10.1111/acem.12330
25. Deis JN, Smith KM, Warren MD, Throop PG, Hickson GB, Joers BJ, et al. Transforming the morbidity and mortality conference into an instrument for systemwide improvement. In: Henriksen K, Battles JB, Keyes MA, Grady ML, editors. *Advances in Patient Safety: New Directions and Alternative Approaches (Vol. 2: Culture and Redesign)*. Rockville, MD: Agency for Healthcare Research and Quality (2008). 8 p.
26. Smaggus A, Mrkobrada M, Marson A, Appleton A. Effects of efforts to optimize morbidity and mortality rounds to serve contemporary quality improvement and educational goals: a systematic review. *BMJ Qual Saf* (2018) 27:74–84. doi:10.1136/bmjqs-2017-006632
27. Harbison SP, Regehr G. Faculty and resident opinions regarding the role of morbidity and mortality conference. *Am J Surg* (1999) 177:136–9. doi:10.1016/S0002-9610(98)00319-5
28. Xiong X, Johnson T, Jayaraman D, McDonald EG, Martel M, Barkun AN. At the crossroad with morbidity and mortality conferences: lessons learned through a narrative systematic review. *Can J Gastroenterol Hepatol* (2016) 2016:7679196. doi:10.1155/2016/7679196
29. Huddleston JM, Diedrich DA, Kinsey GC, Enzler MJ, Manning DM. Learning from every death. *J Patient Saf* (2014) 10:6–12. doi:10.1097/PTS.0000000000000053
30. Sellier E, David-Tchouda S, Bal G, François P. Morbidity and mortality conferences: their place in quality assessments. *Int J Health Care Qual Assur* (2012) 25:189–96. doi:10.1108/09526861211210411
31. Mair T. Clinical governance, clinical audit, and the potential value of a database of equine colic surgery. *Vet Clin North Am Equine Pract* (2009) 25:193–8. doi:10.1016/j.cveq.2009.04.009
32. Rose N, Toews L, Pang DS. A systematic review of clinical audit in companion animal veterinary medicine. *BMC Vet Res* (2016) 12:40. doi:10.1186/s12917-016-0661-4
33. Mosedale P. Introducing clinical audit to veterinary practice. *In Pract* (1998) 20:40–2. doi:10.1136/inpract.20.1.40
34. Viner BP, Jenner CS. Clinical audit—learning from the medical profession. *Vet Rec* (2005) 157:695–6. doi:10.1136/vr.157.22.695
35. Cummins RO. Moving toward uniform reporting and terminology. *Ann Emerg Med* (1993) 22:33–6. doi:10.1016/S0196-0644(05)80246-X
36. Ludders JW, McMillan M. *Errors in Veterinary Anaesthesia*. Iowa: Wiley Blackwell (2017).
37. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AHS, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* (2009) 360:491–9. doi:10.1056/NEJMsa0810119
38. Reason J. Human error: models and management. *BMJ* (2000) 320:768–70. doi:10.1136/bmj.320.7237.768
39. Wiegmann DA, Shappell SA. *A Human Error Approach to Aviation Accident Analysis*. Hampshire: Ashgate Publishing Limited (2003).
40. Reason J. *The Human Contribution*. Hampshire: Ashgate Publishing Limited (2008).
41. Reason J. Safety in the operating theatre—part 2: human error and organizational failure. *Qual Saf Health Care* (2005) 14:56–61.
42. Kieffer PJ, Mueller POE. A profile of morbidity and mortality rounds within resident training programs of the American College of Veterinary Surgeons. *Vet Surg* (2017). doi:10.1111/vsu.12765
43. Berenholtz SM, Hartsell TL, Pronovost PJ. Learning from defects to enhance morbidity and mortality conferences. *Am J Med Qual* (2009) 24:192–5. doi:10.1177/1062860609332370
44. Prince JM, Vallabhaneni R, Zenati MS, Hughes SJ, Harbrecht BG, Lee KK, et al. Increased interactive format for Morbidity & Mortality conference improves educational value and enhances confidence. *J Surg Educ* (2007) 64:266–72. doi:10.1016/j.jsurg.2007.06.007
45. Schwarz D, Schwarz R, Gauchan B, Andrews J, Sharma R, Karelas G, et al. Implementing a systems-oriented morbidity and mortality conference in remote rural Nepal for quality improvement. *BMJ Qual Saf* (2011) 20:1082–8. doi:10.1136/bmjqs-2011-000273
46. De Meester K, Verspuy M, Monsieurs KG, Van Bogaert P. SBAR improves nurse-physician communication and reduces unexpected death: a pre and post intervention study. *Resuscitation* (2013) 84:1192–6. doi:10.1016/j.resuscitation.2013.03.016
47. Leonard M, Graham S, Bonacum D. The human factor: the critical importance of effective teamwork and communication in providing safe care. *Qual Saf Health Care* (2004) 13(Suppl 1):i85–90. doi:10.1136/qshc.2004.010033
48. Pronovost PJ, Holzmueller CG, Martinez E, Cafeo CL, Hunt D, Dickson C, et al. A practical tool to learn from defects in patient care. *Jt Comm J Qual Patient Saf* (2006) 32:102–8. doi:10.1016/S1553-7250(06)32014-4
49. Mahajan RP. Critical incident reporting and learning. *Br J Anaesth* (2010) 105:69–75. doi:10.1093/bja/aeq133
50. Bauer JE, GL Duffy, Westcott RT, editors. *Improvement Tools*. Milwaukee, WI: ASQ Quality Press (2006).
51. Rose N, Kwong GP, Pang DS. A clinical audit cycle of post-operative hypothermia in dogs. *J Small Anim Pract* (2016) 57:447–52. doi:10.1111/jsap.12547

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

CASE REPORT
published: 13 March 2018
doi: 10.3389/fvets.2018.00042

Use of Nasotracheal Intubation during General Anesthesia in Two Ponies with Tracheal Collapse

Keila K. Ida[1], Aurélie Sauvage[2], Alexandra Gougnard[1], Magda Grauwels[2], Didier Serteyn[1] and Charlotte Sandersen[1]*

[1] *Anesthésiologie et Réanimation Vétérinaires, Département Clinique des Animaux de Compagnie et des Équidés, Faculté de Médecine Vétérinaire, Université de Liège, Liège, Belgium,* [2] *Chirurgie et Clinique Chirurgicale des Petits Animaux, Département Clinique des Animaux de Compagnie et des Équidés, Faculté de Médecine Vétérinaire, Université de Liège, Liège, Belgium*

Ponies with tracheal collapse may have an increased anesthetic risk due to airway obstruction during induction and recovery. To our knowledge, there are no anesthetic descriptions of these patients, despite a reported 5.6% incidence and 77% mortality rate. Two Shetland ponies with tracheal collapse, a 12-year-old male (pony 1) and a 27-year-old female (pony 2), were referred for right eye enucleation due to a perforating corneal ulcer and severe recurrent uveitis, respectively. Pony 1 was stressed, had lung stridor and hyperthermia, and developed inspiratory dyspnea with handling. Radiography confirmed collapse of the entire trachea as well as inflammation of the lower airways. Corticosteroids and bronchodilators were administered by nebulization for 1 week before surgery. Pony 2 had a grade III/VI mitral murmur and a clinical history of esophageal obstructions and tracheal collapse requiring tracheostomy. Both ponies were premedicated with acepromazine and xylazine; anesthesia was induced with midazolam and ketamine. Nasotracheal intubation was performed in left lateral recumbency with extension of the neck and head and was guided by capnography. The nasotracheal tube consisted of two endotracheal tubes attached end-to-end to create a tube of adequate length and diameter. Pony 2 was orotracheally intubated during surgery and later reintubated with a nasotracheal tube. Anesthesia was maintained with isoflurane using volume-controlled ventilation. Analgesia was provided by a retrobulbar blockade with mepivacaine and lidocaine. Cardiovascular support consisted of lactated Ringer's solution and dobutamine. After surgery, the ponies were administered xylazine and supplemented with oxygen through the nasotracheal tube. Recovery was assisted by manual support of the head and tail. Successful extubation was achieved following butorphanol administration after approximately 1 h in standing position. Both ponies were discharged from the clinic a few days after surgery.

Keywords: horses, risk factors, intubation, emergencies, recovery from anesthesia

OPEN ACCESS

Edited by:
Caroline Tessier, INRA UMR703 Ecole Nationale Vétérinaire, Agroalimentaire et de l'alimentation de Nantes-Atlantique, France

Reviewed by:
Yael Shilo-Benjamini, Koret School of Veterinary Medicine, Israel
Joao Henrique Neves Soares, Virginia Tech, United States

****Correspondence:***
Keila K. Ida
keila.ida@ulg.ac.be

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *17 September 2017*
Accepted: *20 February 2018*
Published: *13 March 2018*

Citation:
Ida KK, Sauvage A, Gougnard A, Grauwels M, Serteyn D and Sandersen C (2018) Use of Nasotracheal Intubation during General Anesthesia in Two Ponies with Tracheal Collapse. Front. Vet. Sci. 5:42. doi: 10.3389/fvets.2018.00042

INTRODUCTION

Case Presentations

Pony 1 was a 12-year-old male Shetland pony weighing 84 kg with a perforating corneal ulcer of the right eye that was referred for enucleation. The clinical history included tracheal collapse, inflammation of the lower respiratory airways, and laminitis. On physical examination, the pony was stressed, dyspneic, and hyperthermic, and had nasal discharge and crackles on lung auscultation. Radiographic

examination confirmed collapse of the entire trachea and showed a bronchoalveolar pattern in the lungs. Surgery for eye removal was scheduled after 1 week of nebulization with corticosteroids and bronchodilators, and treatment with oral suxibuzone. At the time of surgery, the pony was no longer hyperthermic, and had a hematocrit of 44% and a total plasma protein concentration of 53 g/l.

Pony 2 was a 27-year-old female Shetland pony weighing 136 kg with severe recurrent uveitis in the right eye that was referred for enucleation. The left eye had been enucleated 4 months prior in our institution. At that time, severe tracheal collapse requiring tracheostomy occurred 6 h after recovery from anesthesia. The animal had a grade III/VI mitral valve murmur and was blind in the right eye. At presentation, the pony was calm, vital parameters were within normal limits, and no clinical signs of tracheal collapse were observed. The pony had a hematocrit of 32% and a total plasma protein concentration of 67 g/l.

Anesthesia and Airway Management

Three endotracheal tubes were prepared on the day before surgery, each consisting of a pair of endotracheal tubes connected end-to-end. Two pairs of endotracheal tubes [5.0-mm internal diameter (ID) and 6.0-ID; and 7.5-ID and 9.0-ID] were attached to each other with the largest tube positioned distally. One pair of endotracheal tubes (8.0-ID and 10-ID) was attached with the smallest tube positioned distally. The proximal connector of the more distal tube of each pair was removed and attached with adhesive tape to the distal extremity of the more proximal tube. The balloon cuff of the more proximal tube was removed, while the balloon cuff of the more distal tube was connected to a tubing extension and a three-way stopcock (**Figure 1**).

Similar anesthetic protocol and airway management were used for both ponies on different days. Materials for a tracheostomy were prepared in case of emergency. Food was withdrawn for 12 h with free access to water prior to anesthesia. On the day of surgery (and for 5 days following surgery), the animals were administered gentamicin (6.6 mg/kg IV, SID), sodium penicillin (22,000 mg/kg IM, SID), and flunixin meglumine (1.1 mg/kg IV; SID). Acepromazine (0.1 mg/kg) was administered intramuscularly and, after 1 h, xylazine (0.6 mg/kg) was administered through a 14-G catheter fixed in the right jugular vein. In pony 2, butorphanol (0.02 mg/kg IV) was administered with acepromazine and xylazine as premedication. Anesthesia was induced with midazolam (0.06 mg/kg IV) and ketamine (2.2 mg/kg IV).

Once in left lateral recumbency, the ponies were moved to the surgical theater on a surgical table. Lidocaine (10%) was sprayed into the right nostril and the head was positioned in full extension to create an angle of 180° between the neck and the mandible. In pony 1, the 6.0-5.0-ID pair of endotracheal tubes with silicone spray applied externally was introduced into the right nostril and forwarded to the trachea, guided by capnography. Inflation of the cuff indicated that the endotracheal tubes were too small. Intubation with an 11-ID endotracheal tube was not successful and it was replaced by the 8.0-10-ID pair of endotracheal tubes. Nasotracheal intubation was accomplished 11 min after induction of anesthesia, during which time the pony was breathing spontaneously, with oxygen supplementation through the left nostril. In pony 2, nasotracheal intubation was performed similarly and was accomplished within 2 min after induction of anesthesia, using the 7.5-9.0-ID pair of endotracheal tubes. The tubes were attached to the nostrils with adhesive tape. The balloon cuff was kept inside the mouth of the animal, the tubing extension was kept partially within the mouth, and the remaining tubing extension and three-way stopcock were maintained outside the mouth. None of the three pieces was in contact with the tracheal wall.

The animals were mechanically ventilated (Tafonius, Vetronics, Devon, UK) using volume-controlled ventilation with a respiratory rate (RR) of 14–16 bpm, tidal volumes (V_T) of 8–13 and 8–11 ml/kg for ponies 1 and 2, respectively, and peak inspiratory pressure of 20–25 cmH_2O, which allowed for an end-tidal

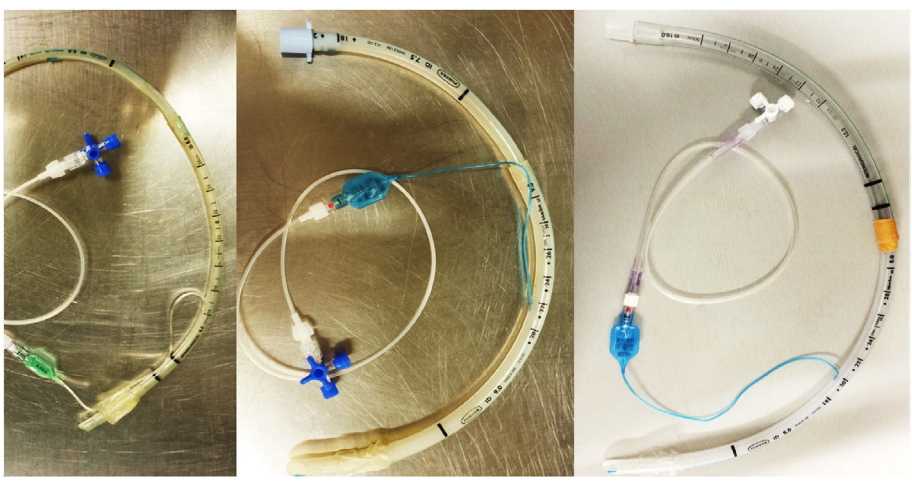

FIGURE 1 | Three pairs of endotracheal tubes connected end to end were prepared on the day before surgery: tubes of 5.0-mm internal diameter (ID) with 6.0-mm ID, 7.5-mm ID with 9.0-mm ID, and 8.0-mm ID with 10-mm ID. The proximal connector of the more distal tube of each pair was removed and attached with adhesive tape to the distal extremity of the more proximal tube. The balloon cuff of the more proximal tube was removed, while the balloon cuff of the more distal tube was connected to a tubing extension and a three-way stopcock that was maintained outside the animal's mouth. It could have been used to pull out the distal tube in case of detachment.

carbon dioxide concentration ($ETCO_2$) of 35–50 mmHg. After a few minutes of mechanical ventilation of pony 2, the absence of capnography curves while breathing movements were present indicated accidental extubation. The endotracheal tube was removed and replaced by a 16-ID tube introduced orotracheally; this tube was left in place throughout the surgery.

During anesthesia, the expired fraction of isoflurane was maintained at 0.8–1.3%. Heart rate and rhythm were monitored using an electrocardiogram (Tafonius). A 20-G catheter was inserted into the right metatarsal artery for monitoring invasive arterial pressure and for acquiring samples for blood gas analysis (**Tables 1** and **2**). Lactated Ringer's solution (10 ml/kg/h) and dobutamine (0.5–1.0 μg/kg/min) were administered for maintaining the mean arterial pressure at 70–85 mmHg. Results of blood gas analysis (Cobas b 123, Roche, Brussels, Belgium) were within reference values for the species (**Tables 1** and **2**).

The partial pressure of alveolar oxygen (PAO_2) was calculated according to a standard formula: $PAO_2 = [FIO_2 \times (Patm - P H_2O)] - (PaCO_2/0.8)$, where FIO_2 is the fraction of inspired oxygen; Patm is the atmospheric pressure at the time of anesthesia (770 mmHg in Liège, Belgium per http://www.worldweatheronline.com); PH_2O is the partial pressure of water vapor (defined as 47 mmHg, at a rectal temperature of 37°C); $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood; and 0.8 is the respiratory quotient; The alveolar dead space-to-tidal volume ratio (Vd/V_T) was calculated as: $Vd/V_T = [(PaCO_2 - ETCO_2)/PaCO_2] \times 100$.

Surgery was started following a retrobulbar blockade with 2.5 ml lidocaine (2%) and 2.5 ml mepivacaine (1%) and using a 20G × 70 mm needle that was inserted caudal to the orbital rim through the periorbital fascia. The procedure lasted 125 and 45 min in ponies 1 and 2, respectively. At the end of surgery, isoflurane was interrupted and RR was decreased to 1 bpm for recovering spontaneous breathing. In pony 2, the orotracheal tube was removed and replaced by a nasotracheal tube (7.5–9.0 ID) that was introduced with capnography guidance and attached to the nostrils with adhesive tape.

The animals were moved to the recovery room where they were maintained in left recumbency and supplemented with oxygen (6 l/min) through the nasotracheal tube. Xylazine (0.2 mg/kg IV) was administered, and the animal was allowed to recover with manual support of the tail and head by two veterinarians. Sternal recumbency and a standing position were accomplished in the first attempt at 20 and 24 min after disconnection from the ventilator in pony 1, and at 25 and 35 min in pony 2. Both ponies were mildly ataxic but recovery was overall calm. They were walked to their boxes and monitored until full recovery.

After an hour in standing position, the first attempt to extubate pony 1 was unsuccessful due to severe tachypnea and cough; therefore, the tube was not removed. Successful extubation without tachypnea and cough was achieved 5 min following administration of butorphanol (0.02 mg/kg IV) at 1h15 and 1h35 after achieving a standing position in ponies 1 and 2, respectively. No episode of respiratory distress was observed for 5 and 7 days, respectively, and the ponies were discharged from the clinic.

BACKGROUND

In ponies, non-congenital tracheal collapse occurs as a progressive degeneration of the hyaline cartilage rings and weakening of the dorsal trachealis muscle. It is a relatively common disease associated with a poor prognosis in this breed (1). In an American university teaching hospital, tracheal collapse was observed in 13 of 231 (5.6%) American Miniature Horses examined in a 22-year

TABLE 1 | Oxygenation, arterial blood gas parameters, and plasma electrolyte concentrations of a 12-year-old male pony under isoflurane anesthesia with volume-controlled ventilation through a nasotracheal tube.

Analyte (unit)	Minutes after induction of anesthesia	
	90	120
FIO_2	0.82	0.85
pH	7.386	7.363
$PaCO_2$ (mmHg)	47.4	51.7
PaO_2 (mmHg)	422.0	442.3
SaO_2 (%)	98.4	99.1
$ETCO_2$ (mmHg)	42	42
Vd/V_T (%)	11.4	18.8
PAO_2 (mmHg)	534	550
$P(A\text{-}a)O_2$ (mmHg)	112	108
HCO_3^- (mmol/l)	27.8	28.7
BE (mmol/l)	2.46	2.68
Hematocrit (%)	35.8	36.3
Na^+ (mmol/l)	120.7	123.8
K^+ (mmol/l)	2.89	2.84
Cl^- (mmol/l)	94.1	93.7
Ca^{2+} (mmol/l)	1.164	1.242

FIO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SaO_2, oxygen saturation; $ETCO_2$, end-tidal carbon dioxide concentration; Vd/V_T, alveolar dead space-to-tidal volume ratio; PAO_2, partial pressure of alveolar oxygen; $P(A\text{-}a)O_2$, alveolar-arterial oxygen pressure gradient; HCO_3^-, bicarbonate concentration; BE, base excess.

TABLE 2 | Oxygenation, arterial blood gas parameters, and plasma electrolyte concentrations of a 27-year-old female pony under isoflurane anesthesia with volume-controlled ventilation through an orotracheal tube.

Analyte (unit)	40 min after induction of anesthesia
FIO_2	0.96
pH	7.411
$PaCO_2$ (mmHg)	39.9
PaO_2 (mmHg)	527.9
SaO_2 (%)	98.8
$ETCO_2$ (mmHg)	30
Vd/V_T (%)	24.8
PAO_2 (mmHg)	644
$P(A\text{-}a)O_2$ (mmHg)	116
HCO_3^- (mmol/l)	24.8
BE (mmol/l)	0.16
Hematocrit (%)	26.3
Na^+ (mmol/l)	134.2
K^+ (mmol/l)	3.47
Cl^- (mmol/l)	105.8
Ca^{2+} (mmol/l)	1.343

FIO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; SaO_2, oxygen saturation; $ETCO_2$, end-tidal carbon dioxide concentration; Vd/V_T, alveolar dead space-to-tidal volume ratio; PAO_2, partial pressure of alveolar oxygen; $P(A\text{-}a)O_2$, alveolar-arterial oxygen pressure gradient; HCO_3^-, bicarbonate concentration; BE, base excess.

period; mortality rate was 77% (1). In our institution, during a 4-year period, tracheal collapse was observed in 10 of 473 ponies (2.1%) and mortality rate was 40%.

Clinical signs of tracheal collapse include inspiratory stridor, cough, and dyspnea, which can lead to airway obstruction, cyanosis, and death (2). Medical treatment consists of anti-inflammatory drugs to treat concurrent respiratory tract disease and, in mild cases, keeping the animal calm to avoid respiratory distress (3). Surgical treatment may be indicated in severe cases, but the procedure is rare, with only four ponies described in the literature (2–4).

Although tracheal collapse is a life-threatening disease, the owners often are not aware of its presence, since respiratory distress may occur only during stressful conditions such as anxiety, pain, hypothermia, and hyperthermia (3). These conditions can be observed during recovery from anesthesia and, therefore, ponies with tracheal collapse may have increased anesthetic risk, especially if the diagnosis is not known at the time of the procedure. The exact risk is unknown since in previous reports the tracheal collapse had been surgically corrected and therefore, was not an issue during recovery from anesthesia (2–4). Reports describing anesthesia or airway management of ponies with tracheal collapse undergoing surgical procedures other than insertion of tracheal stents were not found. In our institution, 5 of 10 ponies with tracheal collapse required general anesthesia for colic surgery or enucleation, including the 2 described here. Two other ponies were euthanized during surgery; however, 1 pony, together with pony 2 during its first enucleation surgery, had undiagnosed tracheal collapse and developed respiratory complications at recovery. These data suggest that ponies with tracheal collapse are at a higher anesthetic risk for respiratory complications and that this risk can be decreased by carefully planning anesthetic and airway management prior to surgery. Therefore, the goal of this case report was to describe the anesthesia and airway management of two ponies with tracheal collapse, providing guidelines that can be used in similar cases to decrease anesthetic risk.

DISCUSSION

The anesthetic protocol described here was aimed at preventing any stressful condition, such as anxiety, pain, dysphoria, cough, and hypothermia that could trigger tachypnea and tracheal collapse. Airway management focused on providing adequate oxygenation and ventilation during surgery, as well as oxygen supplementation during recovery from anesthesia.

Pain, anxiety, and dysphoria were prevented by using systemic analgesics, a non-steroidal anti-inflammatory drug (NSAID), sedatives, and retrobulbar blockade (regional anesthesia). Stressful conditions were also prevented during recovery from anesthesia, to avoid tachypnea and tracheal collapse. Analgesia was achieved as part of a multimodal approach using drugs with different mechanisms of action for pain relief. Xylazine produces analgesia through central alpha-2 receptors, providing the sedative and myorelaxant effects required at premedication and recovery from anesthesia. Cardiorespiratory depression, a potential dose-dependent side effect, was minimized by using a low dose of xylazine that could be antagonized if necessary (5), especially in cases of cardiac impairment, such as in pony 2. Ketamine is as a non-competitive antagonist of *N*-methyl-D-aspartate receptors, which are associated with the inhibition of nociceptive central hypersensitization and in the decrease of the incidence of opioid tolerance, which is achieved with subanesthetic doses (6). Flunixine meglumine, a NSAID, is the most frequently used analgesic in horses. Its mechanism of action is based on inhibition of cyclooxygenase and, thus, prostaglandin synthesis, which is associated with inflammatory pain (7). Regional anesthesia through retrobulbar blockade with lidocaine also plays an important role in decreasing afferent nociceptive transmission. Additional analgesics, such as opioids, can be used when clinically indicated. In horses, opioids (mainly butorphanol) are effective antitussives and analgesics that enhance sedation caused by other sedatives, such as alpha-2 agonists (7, 8). The use of opioids in ponies with tracheal collapse would have the advantage of increasing sedation while reducing the dose of the alpha-2-agonist required. This multimodal analgesia is also an important means to prevent coughing during intubation. We would like to clarify that the decision not to use opioids in pony 1 prior to surgery was not an oversight, but rather was based on our constant monitoring for any sign of pain and stress. However, neither pony had clinical signs of pain or sympathetic stimulation, even though isoflurane was maintained at a low concentration (23–53% lower than the minimum alveolar concentration for horses). There were no differences or alterations in the cardiovascular and respiratory response to surgery or in the isoflurane requirements between ponies 1 and 2, even though the latter was administered butorphanol prior to surgery. Both animals were calm during recovery from anesthesia and did not show signs of pain, such as tachycardia or reaction to palpation of the surgical wound, suggesting the multimodal analgesia was effective. As mentioned before, we were prepared to administer additional opioids if the ponies had signs of pain and stress. In fact, during the first extubation attempt, pony 1 started to cough, probably as a reflex due to stimulation caused by removal of the endotracheal tube. This stimulus caused stress to the animal, which triggered respiratory distress and did not allow for extubation without tracheal collapse. At this point, butorphanol was administered, which played an important role in facilitating removal of the tube. The butorphanol was effective in controlling the stress and cough reflex due to its sedative and antitussive effects, and also could have provided analgesia in the event that pain was contributing to the stress (8).

Total intravenous anesthesia has been described previously for surgical treatment of tracheal collapse in a pony (3). We could have used this type of anesthesia in pony 2, since surgery lasted less than 1 h, but because we could not predict the length of surgery in pony 1 (it lasted more than 2 h), isoflurane anesthesia was chosen. Isoflurane also has less of a cumulative effect that could have impaired the quality of recovery from anesthesia (9–11). Alternatively, surgery could have been performed in a standing sedated animal, since transpalpebral enucleation in standing healthy horses has been documented (12, 13). However, standing sedation would not have addressed the anesthetic risk appropriately, particularly considering that pony 1 was in poor physical condition and had pulmonary disease, and pony 2 had

mitral insufficiency and was geriatric. Sedation does not allow for ventilatory support through intubation and positive pressure ventilation, nor does it allow for more complete monitoring, such as with direct arterial pressure and capnography, to immediately detect potential complications. Spontaneous ventilation increases the risk of tracheal collapse due to the high negative inspiratory pressure (3). High doses of detomidine may be required during standing enucleation to ensure absence of response to surgical stimulation (13), and may induce dyspnea. In addition, deep sedation with alpha-2 agonists is known to be associated with severe cardiorespiratory depression (5), which would not have been tolerated by the ponies of this report due to their compromised clinical status. Therefore, the use of a balanced protocol with general anesthesia was chosen to minimize stress and episodes of dyspnea, to maintain ventilatory patency, and to minimize cardiovascular depression.

The choice of anesthetic drugs should be based on the clinical assessment of each patient; doses should be titrated to effect. Even though pony 2 had a heart murmur, no cardiovascular complications occurred despite using a similar anesthetic management as that used during prior enucleation of the other eye. In addition, the occurrence of any cardiovascular depression or adverse effect (which was not observed) could be immediately detected and promptly treated since the animal was monitored closely using electrocardiography, invasive blood pressure monitoring, capnography, and arterial blood gas analysis.

The drugs and doses used in the two ponies were appropriate for avoiding apnea after induction of anesthesia, allowing time for intubation and for checking $ETCO_2$ values for correct placement of the endotracheal tube. If apnea occurs, the tube can be inserted orotracheally to allow ventilation. In addition, endotracheal intubation to the level of the mid-trachea does not prevent potential tracheal collapse and obstruction distally. We were prepared for an emergency tracheostomy if needed, but neither pony required such intervention. Blood gases were not analyzed during recovery to document adequate management of oxygenation, which was a limitation. The ponies recovered quickly from anesthesia and an arterial blood sample was not collected to avoid additional stimulation or stress. Both ponies were administered supplemental oxygen through the endotracheal tube during the surgical procedure and recovery from anesthesia; no clinical signs of hypoxemia (e.g., cyanosis, tachycardia, and tachypnea) were observed.

Nasotracheal intubation is performed blindly in horses and requires small size endotracheal tubes, which may be misplaced into the esophagus. Accurate placement of the tube within the trachea could be confirmed by capnographic monitoring or intubation could be guided by endoscopy, which adds time to the intubation process compared with orotracheal intubation. Furthermore, a nasotracheal tube is usually narrow to be able to fit through the nares, which increases airway resistance during ventilation and may result in nasal hemorrhage. The choice of nasotracheal (vs. orotracheal) intubation allows the tube to be kept in place after full recovery from anesthesia, until the pony is sufficiently calm to be extubated. Alternatively, orotracheal intubation for surgery could be replaced by nasotracheal intubation for the recovery from anesthesia as was done in pony 2. In this case, orotracheal intubation was preferred because it is faster and the animal was in apnea. Because our attempt to insert an 11-ID endotracheal tube was unsuccessful in pony 1, we determined that the size of the tube in place was adequate for the patient and thus did not require changing for recovery. A nasotracheal tube, but not an orotracheal tube, is well tolerated by a conscious horse. The option of leaving the orotracheal tube in place during recovery (14), can be considered if nasotracheal intubation is not successful.

A commercial silicone 7-14-ID endotracheal tube specific for foals may have been safer than connecting two endotracheal tubes, but was not available in our clinic. The need to connect two endotracheal tubes was due to the fact that tubes with a diameter narrow enough to pass through the nasal cavities were too short to reach the trachea. Our solution was to connect the extremities of two tubes, the smaller nested into the larger one, to create a tube with an adequate length and diameter. The connection was accomplished using adhesive tape, which was a limitation. The major concern was that the tubes might detach from one another, leading to entrapment of the distal tube in the trachea. In that case, the distal tube could have been removed by pulling out the balloon tubing connected to the three-way stopcock that was maintained outside the animal's mouth. However, despite these concerns, detachment did not occur and the connected tubes worked well. A glue could be added to decrease the risk of detachment of the distal tube. However, we chose not to do so to avoid further decrease of safety by adding another material that could detach in small pieces (difficult to remove) from the tube once wet. The cyanoacrylate glue warms up the material that can be slightly melted, which would also further impair safety.

CONCLUDING REMARKS

The anesthetist should anticipate additional stress and possible respiratory distress during induction and recovery in ponies affected by tracheal collapse and therefore provide preventive measures such as the ones described in this case report. In summary, anesthetic management of these cases should focus on the following: (1) preventing stress by providing good sedation in the induction phase; (2) orotracheal or nasotracheal intubation for surgery; and (3) in the recovery phase, adequate sedation and analgesia and nasotracheal intubation for prolonged extubation.

ETHICS STATEMENT

Owner consent was obtained for including the animals in this case report.

AUTHOR CONTRIBUTIONS

KI contributed to the data acquisition, analysis, and interpretation, drafted and revised the work, and approved the final version to be published. AS, AG, and CS contributed to the data acquisition, analysis, and interpretation, revised the work and approved the final version to be published. MG and DS contributed to the data analysis and interpretation, and revised and approved the final version to be published.

REFERENCES

1. Aleman M, Nieto JE, Benak J, Johnson LR. Tracheal collapse in American Miniature Horses: 13 cases (1985–2007). *J Am Vet Med Assoc* (2008) 233:1302–6. doi:10.2460/javma.233.8.1302
2. Busschers E, Epstein KL, Holt DE, Parente EJ. Extraluminal, C shaped polyethylene prostheses in two ponies with tracheal collapse. *Vet Surg* (2010) 39:776–83. doi:10.1111/j.1532-950X.2010.00715.x
3. Couëtil LL, Gallatin LL, Blevins W, Khadra I. Treatment of tracheal collapse with an intraluminal stent in a miniature horse. *J Am Vet Med Assoc* (2004) 225:1727–32, 1701–2. doi:10.2460/javma.2004.225.1727
4. Simmons T, Petersen M, Parker J, Dietze A, Rebhun W. Tracheal collapse due to chondrodysplasia in a miniature horse foal. *Equine Pract* (1988) 10:39–40.
5. England GC, Clarke KW. Alpha 2 adrenoceptor agonists in the horse-a review. *Br Vet J* (1996) 152:641–57. doi:10.1016/S0007-1935(96)80118-7
6. Muir WW. NMDA receptor antagonists and pain: ketamine. *Vet Clin North Am Equine Pract* (2010) 26:565–78. doi:10.1016/j.cveq.2010.07.009
7. Sanchez LC, Robertson SA. Pain control in horses: what do we really know? *Equine Vet J* (2014) 46:517–23. doi:10.1111/evj.12265
8. Westermann CM, Laan TT, van Nieuwstadt RA, Bull S, Fink-Gremmels J. Effects of antitussive agents administered before bronchoalveolar lavage in horses. *Am J Vet Res* (2005) 66:1420–4. doi:10.2460/ajvr.2005.66.1420
9. Lerche P. Total intravenous anesthesia in horses. *Vet Clin North Am Equine Pract* (2013) 29:123–9. doi:10.1016/j.cveq.2012.11.008
10. Menzies MP, Ringer SK, Conrot A, Theurillat R, Kluge K, Kutter AP, et al. Cardiopulmonary effects and anaesthesia recovery quality in horses anaesthetized with isoflurane and low-dose S-ketamine or medetomidine infusions. *Vet Anaesth Analg* (2016) 43:623–34. doi:10.1111/vaa.12359
11. Larenza MP, Ringer SK, Kutter AP, Conrot A, Theurillat R, Kummer M, et al. Evaluation of anesthesia recovery quality after low-dose racemic or S-ketamine infusions during anesthesia with isoflurane in horses. *Am J Vet Res* (2009) 70:710–8. doi:10.2460/ajvr.70.6.710
12. Hewes CA, Keoughan GC, Gutierrez-Nibeyro S. Standing enucleation in the horse: a report of 5 cases. *Can Vet J* (2007) 48:512–4.
13. Pollock PJ, Russell T, Hughes TK, Archer MR, Perkins JD. Transpalpebral eye enucleation in 40 standing horses. *Vet Surg* (2008) 37:306–9. doi:10.1111/j.1532-950X.2008.00382.x
14. Kerr CL, McDonell WN. Oxygen supplementation and ventilatory support. In: Muir WW, Hubbell JAE, editors. *Equine Anesthesia*. Saint Louis: W.B. Saunders (2009). p. 332–52.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors and the institution did not receive any payment or services from a third party for any aspect of the submitted work.

frontiers in Veterinary Science

PERSPECTIVE
published: 16 March 2018
doi: 10.3389/fvets.2018.00053

Anesthesia-Associated Relative Hypovolemia: Mechanisms, Monitoring, and Treatment Considerations

Jessica Noel-Morgan[1] and William W. Muir[2,3]*

[1] Center for Cardiovascular & Pulmonary Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States, [2] QTest Labs, Columbus, OH, United States, [3] College of Veterinary Medicine, Lincoln Memorial University, Harrogate, TN, United States

Although the utility and benefits of anesthesia and analgesia are irrefutable, their practice is not void of risks. Almost all drugs that produce anesthesia endanger cardiovascular stability by producing dose-dependent impairment of cardiac function, vascular reactivity, and compensatory autoregulatory responses. Whereas anesthesia-related depression of cardiac performance and arterial vasodilation are well recognized adverse effects contributing to anesthetic risk, far less emphasis has been placed on effects impacting venous physiology and venous return. The venous circulation, containing about 65–70% of the total blood volume, is a pivotal contributor to stroke volume and cardiac output. Vasodilation, particularly venodilation, is the primary cause of relative hypovolemia produced by anesthetic drugs and is often associated with increased venous compliance, decreased venous return, and reduced response to vasoactive substances. Depending on factors such as patient status and monitoring, a state of relative hypovolemia may remain clinically undetected, with impending consequences owing to impaired oxygen delivery and tissue perfusion. Concurrent processes related to comorbidities, hypothermia, inflammation, trauma, sepsis, or other causes of hemodynamic or metabolic compromise, may further exacerbate the condition. Despite scientific and technological advances, clinical monitoring and treatment of relative hypovolemia still pose relevant challenges to the anesthesiologist. This short perspective seeks to define relative hypovolemia, describe the venous system's role in supporting normal cardiovascular function, characterize effects of anesthetic drugs on venous physiology, and address current considerations and challenges for monitoring and treatment of relative hypovolemia, with focus on insights for future therapies.

Keywords: relative hypovolemia, distributive shock, mean circulatory filling pressure, anesthesia, fluid therapy, functional hemodynamics, dynamic index, preload responsiveness

OPEN ACCESS

Edited by:
Keila Ida,
University of Liège, Belgium

Reviewed by:
Olivier Levionnois,
University of Bern, Switzerland
Rene Doerfelt,
LMU Munich, Germany

****Correspondence:***
Jessica Noel-Morgan
morgan.net@icloud.com

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *15 December 2017*
Accepted: *02 March 2018*
Published: *16 March 2018*

Citation:
Noel-Morgan J and Muir WW (2018) Anesthesia-Associated Relative Hypovolemia: Mechanisms, Monitoring, and Treatment Considerations. Front. Vet. Sci. 5:53. doi: 10.3389/fvets.2018.00053

Abbreviations: CO, cardiac output; CVCDI, caudal vena cava distensibility index; CVP, central venous pressure; ΔVpeak, aortic flow peak velocity variation; DO2, oxygen delivery; HR, heart rate; iNOS, inducible nitric oxide; K_{ATP} channels, ATP-sensitive potassium channels; LiDCO, lithium dilution cardiac output; MCFP, mean circulatory filling pressure; MSP, mean systemic pressure; MV, mechanical ventilation; PAC, pulmonary artery catheter; PPV, pulse pressure variation; Pv-aCO2, venoarterial difference in PCO2; RV, right ventricle; SPV, systolic pressure variation; SV, stroke volume; ScvO2, central venous oxygen saturation; SvO2, mixed venous oxygen saturation; SVV, stroke volume variation; Vs, stressed circulating blood volume; Vt, tidal volume; Vus, unstressed intravascular volume; VVC, venous vascular capacitance.

INTRODUCTION

To survive anesthesia is to survive a potentially life-threatening event. What other form of medical practice is designed to intentionally depress or inhibit a spectrum of neurophysiologic processes so as to be able to painlessly inflict varying degrees of medical or surgical psychological or physical trauma. Although the potential benefits and utility of anesthesia and analgesia are obvious, the practice of anesthesia is not without risk, particularly in animals. Indeed, the adverse events associated with anesthetizing animals, although similar to those reported in humans, are far more common than reported for humans (1–4). A recent study investigating adverse events associated with anesthesia in dogs and cats suggested that approximately 40% of animals had at least one adverse event and as many as 1% had up to six adverse events (5). Anesthetic death is reported to occur in approximately 0.5, 1.0, and 10 in every 1,000 anesthetic episodes in otherwise healthy dogs, cats, and horses, respectively (6–10). These rates are two to three orders of magnitude greater than those reported for healthy humans (approximately 0.001 per 1,000) (1). Among the many potential explanations for this discrepancy, human error, inadequate training, lack of experience or familiarity with the drugs and equipment used to produce anesthesia, insufficient monitoring, and haste or distraction, have been identified as specific causes for adverse outcomes in human medicine (3). Species differences aside, the incidence of adverse events, including intraoperative cardiac arrest, is considerably greater in animals than in humans (2, 8, 9, 11). Reemergence from anesthesia, breakthrough pain, hypoventilation, respiratory arrest, airway complications, and hypotension are comparatively common adverse events reported in dogs, cats, and horses (5, 8, 10, 11). Anesthesia-associated hypotension is frequently attributed to a decrease in ventricular contractile performance, arterial vasodilation, or both (5, 10–14). Far less emphasis has been placed upon alterations in venous physiology or the effects of anesthetic drugs on the venous system's contribution to cardiac output (CO). Increasing evidence, however, suggests that anesthetic drugs produce significant and clinically relevant effects on venous function that result in increases in venous capacitance and compliance, and a reduced response to vasoactive substances (15–17). Anesthetic drug impairment of venous function is an insidious and relatively unappreciated cause of relative hypovolemia that reduces CO, predisposes to hypotension, and can lead to vasodilatory shock especially in sick (e.g., septic), depressed, or debilitated animals (17–19). The focus of this short perspective is to define relative hypovolemia, describe the function of the venous system and its role in maintaining normal cardiovascular function, emphasize the effects of anesthetic drugs on venous physiology, and outline considerations for monitoring and treating relative hypovolemia.

VENOUS PHYSIOLOGY AND CO

Maintenance of adequate CO and arterial blood pressure are dependent upon a normal blood volume, vascular tone (arterial and venous), venous return (more appropriately "venous excess"), heart rate (HR), ventricular function, and multiple autoregulatory (compensatory) mechanisms, and are vital for preserving tissue perfusion and oxygen delivery (DO2) (15, 16, 20, 21). Venous return is CO during steady state conditions and is modulated by central venous pressure (CVP): the heart cannot pump what it does not receive. The venous system contains 65–70% of the total blood volume and small veins and venules in the abdomen, spleen, liver, and venous plexus of the skin are more than 30× more compliant than arteries (**Figure 1**) (15, 22–25). Splanchnic and cutaneous veins contain a large population of both alpha-1 and 2 adrenergic receptors that are highly sensitive to central nervous system sympathetic output, adjustments in baroreceptor reflex activity in response to changes in arterial blood pressure, and endogenous or exogenously administered vasoactive substances (26–29). Splanchnic venous capacitance vessels in particular are much more sensitive to a decrease in carotid sinus pressure or an increase in sympathetic nerve activity than arteries, allowing healthy non-anesthetized animals to lose up to 15–20% of their total blood volume without initiating a significant compensatory hemodynamic response, primarily owing to the reservoir response of the splanchnic veins (26). Alpha-1 adrenergic effects mediated by baroreceptor reflex adjustments contribute significantly to alterations in splanchnic venous capacity (15, 23, 27, 29). Adjustments in venous capacitance aid in maintaining an effective or "stressed" circulating blood volume [the blood volume required to produce measurable increase in transmural pressure: stressed circulating blood volume (Vs)], and are a primary determinant of venous return and therefore CO (15, 16, 21, 24, 30, 31). The unstressed intravascular volume (Vus) is the blood volume required to fill the circulatory system to capacity without increasing cardiovascular transmural pressure (**Figure 2**) (15, 23). The Vus is composed of a recruitable volume and a residual volume that is functionally analogous to the expiratory reserve and residual volumes that compose the functional residual capacity in the lung. The Vs comprises approximately

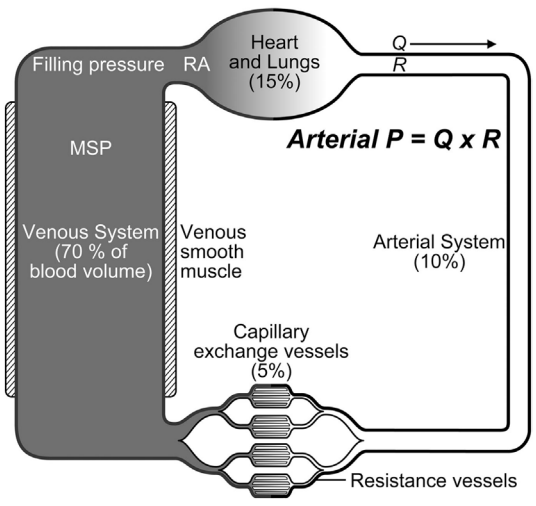

FIGURE 1 | Blood is unevenly distributed throughout the systemic circulation. The large and small veins contain approximately 70% of the blood volume. Arterial pressure (P) is determined by blood flow (Q) and systemic vascular resistance (R); MSP, mean systemic pressure; RA, right atrium.

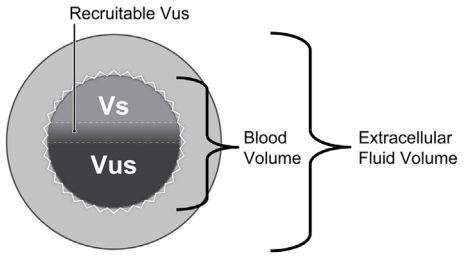

FIGURE 2 | The total blood volume within the vasculature can be divided into two components: stressed circulating blood volume (Vs: approximately 30% of the blood volume) and unstressed intravascular volume (Vus: approximately 70% of the blood volume). The Vs is hemodynamically active (i.e., effective circulating blood volume) and is the principal determinant of the mean systemic pressure, a primary determinant of venous return. The Vus is the volume of blood required to fill the vascular space without increasing blood pressure. A portion of the Vus (up to 15–20 mL/kg; shaded area between the dashed horizontal lines) serves as a blood reservoir and can be recruited to augment the Vs during times of stress or replenish the Vs during hypovolemia. The wavy white line surrounding the inner circle (i.e., volume) suggests that the volume contained therein can become smaller or larger depending upon changes in vasomotor tone.

30% of the predicted total blood volume (20–25 mL/kg) in most animals, while the Vus can provide a portion of its volume (recruitable reserve volume; approx. 15–20 mL/kg) when maximally activated (24, 28, 31). This volume of blood is equivalent to the administration of 45–60 mL/kg of IV crystalloid, if it is assumed that only one-third of a crystalloid fluid bolus remains in the vascular compartment (32). Only Vs, the "effective" circulating volume, is hemodynamically active, and only a portion of Vus is available to provide a rapidly recruitable reserve volume that can be mobilized during times of need (e.g., exercise, trauma, hemorrhage).

The driving pressure for blood flow returning to the heart from peripheral veins is theorized to be determined by the pressure gradient between a proposed "pivoting pressure," termed the mean circulatory filling pressure (MCFP), and the right atrium (CVP) (15, 21, 23, 33–35). The MCFP is the equilibration pressure measured at all points in the circulation when the heart is stopped. This pressure is assumed to be located in the venous capacitance vessels, particularly the splanchnic vasculature, and is modified by the effects of both arterial baroreceptor and chemoreceptor reflex mechanisms on venous vascular compliance, and capacitance (36–38). Some consider it to be a flawed and untenable physiologic concept, although many hold the opinion that it does provide a conceptual framework for explaining how changes in venous reservoir compliance and capacitance are associated with alterations in CO when ventricular function is normal or minimally impaired (16, 19–21, 34, 35, 39). Notably, both absolute and relative hypovolemia (decrease in Vs) trigger central and peripheral sympathetically mediated compensatory mechanisms (19, 38). Subsequent activation of alpha-1 receptors in the venous vasculature decreases venous capacitance, aiding in the maintenance of MCFP, venous return and CO by shifting blood from Vus to Vs (24, 27, 40, 41). A compensatory decrease in splanchnic blood volume, for example, has been shown to increase Vs by as much as 10–15 mL/kg in hemorrhaged dogs (25, 28, 31). Importantly, the recruitment (redistribution) of blood from splanchnic and other blood reservoirs (e.g., spleen, lung) may be impaired in animals that are septic, acidotic, hypothermic, aged, or are intolerant of recommended amounts of anesthetic drugs (17, 18).

HYPOVOLEMIA

Hypovolemia is categorized as either absolute or relative. Absolute hypovolemia (i.e., reduction in total circulating blood volume) is either controlled (hemorrhage that has been stopped) or uncontrolled (hemorrhage that has not stopped) and implies the loss of blood, plasma or water from the vascular compartment. Absolute hypovolemia can be conceptualized as a decrease in blood volume relative to a normally sized vascular compartment (**Figure 3**). Alternatively, relative hypovolemia implies a normal, or possibly increased, blood volume that is not adequate to fill the vascular compartment because the volume (capacity) of the vascular compartment has increased. Hypovolemia from any cause can reduce venous return, CO and arterial blood pressure, regardless of whether or not compensatory mechanisms are inadequate or impaired, thereby limiting tissue perfusion and DO2 to tissues (15, 16). Severe hypovolemia leads to the development of oxygen debt and is directly correlated with lactic acidemia and mortality (42, 43). Vasodilation, predominantly venodilation, is an important cause of relative hypovolemia produced by anesthetic drugs and can be exacerbated in sick, septic, hypothermic, or aged animals. Relative hypovolemia frequently contributes to low CO and hypotension during anesthesia and is a more frequent, insidious, and occult mechanism responsible for cardiovascular collapse and death than decreases in HR and cardiac function typically emphasized as the primary reasons for anesthesia-related adverse events (10–14, 17).

CAUSES OF RELATIVE HYPOVOLEMIA

The principal cause for relative hypovolemia is vasodilation, especially venodilation. Vasodilation during anesthesia is a natural consequence of (1) drug toxicity (e.g., sensitivity to anesthetic drugs or anesthetic overdose), (2) impairment or loss of compensatory mechanisms, (3) coexisting or induced metabolic ($pH < 7.15$) or respiratory ($PaCO2 > 80$ mm Hg) acidosis; or concurrent, (4) traumatic or surgically induced inflammation, (5) sepsis, (6) cardiogenic shock, and (7) hypothermia. Multiple cellular mechanisms have been implicated in the development of vasodilation and vasodilatory shock that include: a decrease in L-type calcium channel ion transport or myofilament sensitivity to calcium, activation of vascular smooth muscle ATP-sensitive potassium channels (K_{ATP} channels), excess production of the inducible form of nitric oxide (iNOS; e.g., sepsis), and deficiency of the hormone vasopressin (**Table 1**) (18, 44, 45). Tissue ischemia and/or hypoxia increase intracellular hydrogen ion concentration and decrease cellular ATP production activating K_{ATP} channels resulting in smooth muscle hyperpolarization and vasodilation. Sepsis increases the synthesis of nitric oxide due to the increased expression of iNOS synthase and cGMP generation, resulting in

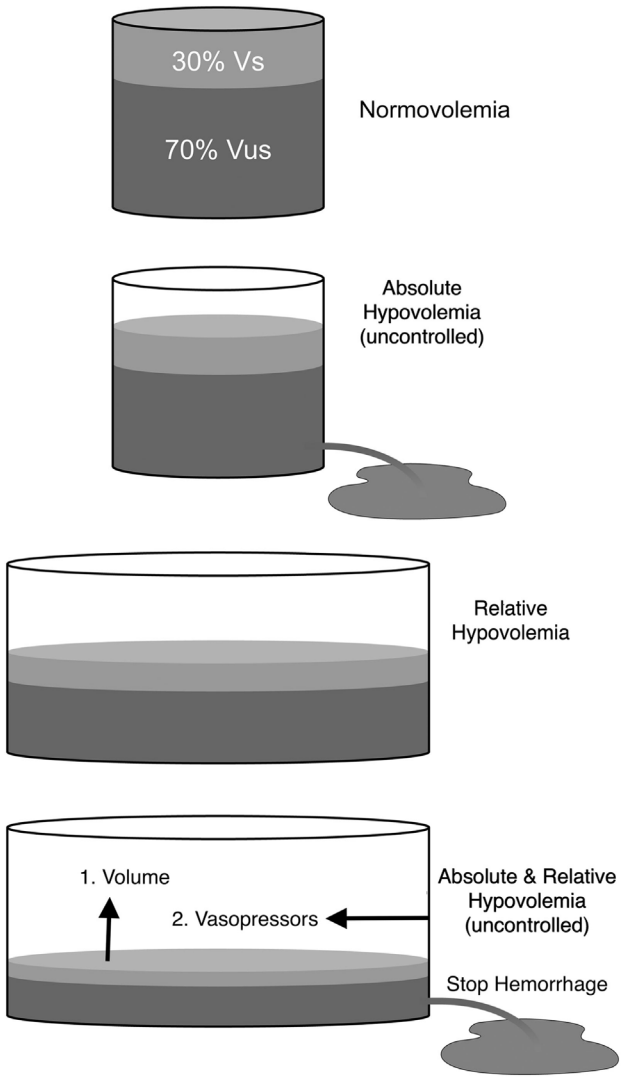

FIGURE 3 | Schematic representation of total blood volume within the vasculature. Normovolemia: blood volume and vascular capacity are normal. Absolute hypovolemia: blood volume is decreased relative to normal vascular capacity (e.g., hemorrhage). Absolute hypovolemia is either uncontrolled (volume loss continues) or controlled (volume loss has been stopped). Relative hypovolemia: blood volume is normal, increased or decreased, but vascular capacity is increased (e.g., anesthetic overdose; sepsis). Absolute hypovolemia is treated with fluids (e.g., crystalloids; blood). Relative hypovolemia is treated primarily with fluids and vasopressors. Vs, stressed circulating blood volume; Vus, unstressed intravascular volume.

vasorelaxation and resistance to vasoactive drugs (e.g., dopamine, norepinephrine, vasopressin). The combined effects of ischemia-induced acidosis and production of vasodilatory prostaglandins (e.g., PGI2, PGE1, synthetic prostacyclin), activation of K_{ATP} channels, and the production of iNOS in animals that are septic or have chronic heart failure, in conjunction with the confounding effects of acidosis and hypothermia, create an ideal environment for vasodilatation, relative hypovolemia and vascular hyporesponsiveness or refractoriness to fluid administration and the administration vasoactive compounds (46–48).

TABLE 1 | General and cellular mechanisms responsible for anesthesia-associated relative hypovolemia.

Decreased central sympathetic output
Decreased cardiovascular reflex responses
Decreased baroreceptor reflex activity
Decreased VSM contractile response or sensitivity to:
Neurohumoral and adrenoceptor agonists (e.g., norepinephrine)
Depressed mechanisms regulating VSM cytosolic Ca^{2+}
Reduced VSM intracellular Ca^{2+} concentration
Reduced VSM L-type calcium channel ion transport
Reduced VSM myofilament sensitivity to calcium
Activation of K^+ATP channels

VSM, vascular smooth muscle; ATP, adenosine triphosphate.

ANESTHETIC MECHANISMS RESPONSIBLE FOR RELATIVE HYPOVOLEMIA

Almost all drugs that produce anesthesia endanger cardiovascular stability by producing dose-dependent impairment of cardiac function, vascular reactivity and compensatory autoregulatory responses (**Table 2**) (17). Most produce some impairment of ventricular function, vascular tone and inhibit central or peripheral sympathetic ganglionic transmission of barostatic control when administered at clinically relevant doses (49–52). All but one (i.e., ketamine) are known to modify multiple vasoregulatory mechanisms, leading to a differential reduction in vascular contractile responses, redistribution of blood flow, and increases in vascular capacitance primarily by inhibition of sympathetic nervous system activity and depression of adrenergic neurotransmission and baroreceptor reflex sensitivity (49–54). Venodilation is an important component of the vascular vasodilatory effects of both injectable (e.g., propofol) and inhalant (e.g., isoflurane) general anesthetics (**Table 2**) (47–53, 55). Importantly, most hypnotic (GABA-A agonist) intravenous anesthetics generally exert important vascular actions following bolus IV injections, while volatile anesthetics produce vasodilatory effects at clinically relevant concentrations (44). Therapeutic concentrations of both propofol and isoflurane, for example, have been shown to decrease Vs by increasing venous capacitance, while producing minimal changes in either CO or systemic vascular resistance (50, 53, 56, 57). The maintenance of normal or near-normal CO when either drug is administered has been explained by a decrease in the resistance to venous return and slightly improved stroke volume (SV) due to a decrease in afterload (58). In contrast to propofol and isoflurane, both ketamine and etomidate have been shown to produce minimal effects on venous vascular capacitance in normovolemic humans (59, 60). Ketamine decreased venous capacitance in hypovolemic dogs suggesting that it should be considered the drug of choice for induction to anesthesia and as partial intravenous anesthesia in high risk subjects (60). Summarizing, vascular capacitance modulates CO during hemorrhage and acute volume loading (39). Anesthetic drug-induced increases in venous compliance or capacitance predispose to relative hypovolemia and effectively reduce Vs, CO, and DO2 to tissues, potentially leading to the development of oxygen debt. The combination of relative and absolute

TABLE 2 | Pharmacologic effects of clinically relevant doses of commonly administered anesthetic drugs.[a]

Drug	HR	Arterial blood pressure	CO	Cardiac contractile force	MSP or MCFP	Vasomotor tone	Baroreceptor reflex activity	Sympathetic nerve activity	Splanchnic venous capacitance	Venous return
Inhalant anesthetic	↑↓±	↓↓	↓↓	↓	↓↓	↓↓	↓↓	↓↓	↑↑	↓↓
Injectable hypnotic										
Propofol	±↓	↓↓	↓	↓	↓	↓	↓	↓	↑↑	↓↓
Etomidate	±	↓	↓	↓	±↓	±↓	±↓	±↓	↑	±↓
Barbiturate	±↑	±	↓	↓	±↓	↓	↓	↓	↑	↓
Neurosteriod	±↓	↓	↓	±↓	±↓	±↓	↓	↓	↑	↓
Chloralose	↓	±	±	±	±	±	±	±	±	±
Disociative										
Ketamine	↑	↑	↑±	↑±	--	--	--	--↑	--	--
Tiletamine	↑	↑	↑±	↑±	--	--	--	--↑	--	--
Opioid										
Morphine	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Hydromorphone	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Fentanyl	↓	--↓	--↓	--↓	--	--	--↓	--↓	--	--↓
Alpha-2 agonist	↓↓	↑→↓	↓↓	--↓	↑→↓	↑→↓	--↓	--	↓→↑	↑→↓
Benzodiazepine										
Diazepam Midazolam	--	--	--↓	--	--↓	--↓	--	--↓	--↓	--↓
Phenothiazine										
Acepromazine	±↓	↓	--↓	--↓	↓	↓	↓	↓	↑	↓
Local anesthetics										
Lidocaine	±↑	↓	--↓	--↓	↓	↓	--	↓	↑	↓
Bupivacaine	±↑	↓	--↓	--↓	↓	↓	--	↓	↑	↓

[a]*Clinically relevant dosages are generally equal to or less than those recommended by the manufacturer. Idealized effects expected from normal, healthy humans and animals; ↑, increase; ↓, decrease; ±, increase or decrease; --, little or no change; ↑→↓, increase followed by decrease; ↓→↑, decrease followed by increase. Data compiled from unpublished data (Muir WW, Del Rio CL, Ueyama Y. The effects of anesthetic drugs on mean circulatory filling pressure in isoflurane anesthetized dogs. (2015). Unpublished manuscript.) and (35, 39, 49, 51–53, 57, 61–78).*

HR, heart rate; CO, cardiac output.

hypovolemia during anesthesia and surgery in physiologically compromised animals is particularly troublesome, since some animals may rapidly develop irreversible and refractory shock after the loss of relatively small amounts of blood (5–10 mL/kg) (**Figure 2**).

CONSIDERATIONS ON MONITORING AND TREATMENT OF RELATIVE HYPOVOLEMIA

Identifying and treating relative hypovolemia and tissue hypoperfusion may pose a challenge to the anesthesiologist. During anesthesia, maintenance or prompt reestablishment of appropriate DO2 to all tissues is a main concern (17). Effective circulatory volume, cardiac filling, global, regional and microcirculatory flow, and adequate perfusion pressure are all important elements to consider (79, 80).

Presently, perioperative monitoring is largely based on macrocirculatory variables, which may fail to detect relative hypovolemia (81–85). Indeed, despite the recognition of their importance, bedside determination of absolute volemia, monitoring of venous hemodynamics or of microhemodynamics remain cumbersome at best (15). Sophisticated methods for assessment of systemic vascular compliance and Vs have been proposed, but such techniques are yet to be fully validated, particularly in patients with severely compromised vascular tone or receiving vasoactive drugs (86). Therefore, dynamic assessment of a combination of variables along the hemodynamic circuit is helpful for deciphering ongoing processes.

Selection of monitoring procedures depends on a number of factors involving available technology and resources, the anesthesiologist's familiarity with each technique, patient status, and the surgical or medical procedure being performed. In this regard, continuous clinical reassessment of patient status and anesthetic depth remain important tools that should be applied to all (87). Adding to this, standard hemodynamic and global perfusion monitoring of HR and rhythm, arterial pressures, pulse oximetry, expired gases including end-tidal carbon dioxide and inhalant anesthetic concentrations, arterial blood gases, and lactate, offer a wealth of information, particularly when monitored and interpreted collectively and trended over time (82, 87–90). Of note, ongoing perfusion and oxygenation deficits may occur even when blood pressure is considered normal, and urinary output has been shown to bear limited relation with blood volume, effective blood flow, or renal function during anesthesia (91–93).

Conceptually, CVP is an easily obtainable surrogate to right atrial pressure, capable of providing insights into the interaction between venous return and cardiac function (94). As a single numerical value, it provides limited information, but when

appropriately used and interpreted, within the clinical and interventional context, in combination with static and *dynamic* variables (and especially CO or SV, if available), it may add valuable information about a patient's condition, particularly when values are outside the normal range, or when extreme, unpredicted, or seemingly paradoxical changes occur, related or not with therapeutic interventions (15, 21, 87, 94–96). An excessively high CVP, for instance, may be indicative of right heart failure, increased pulmonary vascular resistance, or volume overload (87). Still, it has been argued in humans that, while a normal CVP is close to zero and the pressure gradient produced by a normal MCFP 8–10 mmHg promotes venous return, any sufficient increase in CVP and/or fall in MCFP may reduce venous return and SV (96). Indeed, elevated CVP has been associated with impairment of microcirculatory flow and acute kidney injury in critical patients (90, 96, 97). Although not a perfect surrogate for mixed venous oxygen saturation, central venous access offers the possibility of central venous oxygen saturation (ScvO2) attainment, in addition to the determination of venoarterial difference in PCO2 (Pv-aCO2). Combined with plasma lactate levels, ScvO2 and Pv-aCO2 offer important information regarding the patient's status, enabling inferences regarding CO and the presence of dysoxia, sepsis and/or anemia (87, 98).

Measurement of SV and CO is uncommon in veterinary medicine, and is typically reserved for high-risk or critical patients, particularly those refractory to initial therapy (82, 87). Recent reviews have emphasized the limited research validating each method in the veterinary clinical setting, in addition to possible logistic and cost-related considerations (99–101). While several studies have investigated the use of indicator dilution (e.g., using pulmonary artery catheter thermodilution or lithium dilution CO), and echocardiography-based methods for determining CO in different species, these technologies remain impractical in clinical practice (102–110). Of note, echocardiography/Doppler-derived measurements are less invasive, offer unique information on cardiac structure and function, and may offer good estimation of hemodynamic data, but are largely operator-dependent, requiring specialized training and costly equipment (82, 99, 111, 112).

With the aim of sustaining effective circulatory volume, microcirculatory flow and perfusion, the anesthesiologist must assess the appropriateness of fluid administration for each individual patient (summarized by the mnemonic CIT TAIT: context, indication, targets, timing, amount, infusion strategy, and type of fluid) (113), followed by possible use, timing and choice of alternate or ancillary therapy based on vasoactive (pressors, dilators) and/or inotropic support (80, 83, 87, 92, 93, 96, 113–120).

In the context of decreased effective circulating blood volume related to anesthesia and surgical trauma, fluids are generally proposed as a first line therapy, aiming to increase plasma volume, MCFP and the pressure gradient for venous return (83). However, not all patients respond to fluid administration with an increase SV and/or CO (i.e., fluid or preload responsiveness) (121). Beyond fluid dynamics, anesthetic agents and depth, mechanical ventilation (MV), blood flow distribution, endothelial function, integrity of the glycocalyx, and right and left ventricular status all play critical roles in this response (17, 83, 113, 121–124). The question of how to optimize preload, afterload, and contractility remains haunted by the recognition that: both insufficient and excess fluids may result in perfusion deficits and perioperative morbidity; premature or incorrect employment of pressors may also promote further microcirculatory compromise by hindering adequate flow and DO2; and inotropes should be judiciously employed, with guidelines recommending their use only when monitored cardiac function is accompanied by low CO and signs of hypoperfusion despite preload optimization (80, 82, 83, 85, 92, 93, 96, 125, 126).

Newer evidence and monitoring options for fluid resuscitation suggest that formulas for replacement and maintenance should be reexamined (127). Among many proposed strategies (e.g., "liberal," "restrictive," "zero-balance," "dynamic fluid balance," and "goal-directed" therapies), a universal algorithm accounting for all possible patient-case combinations remains unrealistic. Current recommendations propose a preplanned approach, tailored to each patient, that employs fluids only on clear indication (83, 92, 93, 113, 125, 127–131). To this end, functional hemodynamics, using *dynamic* indices such as systolic pressure variation (SPV), pulse pressure variation (PPV), stroke volume variation (SVV), plethysmographic variability index, aortic flow peak velocity variation (ΔVpeak), and caudal vena cava distensibility index (CVCDI), have demonstrated promise in predicting preload responsiveness and help guide fluid therapy (82, 83, 92, 121, 132–137).

Comprehensive studies, meta-analyses, and reviews are available that elaborate on use of *dynamic* indices to guide fluid therapy (121, 137–139). Among important highlights, full awareness of all mechanisms and limitations pertaining to each is essential. For instance, many of these methods require MV within very specific settings, and without breathing efforts or arrhythmias during the measurement period (140, 141). Patient cardiovascular and pulmonary status, and particularities of surgical interventions, are also important factors that impact cardiopulmonary interactions and related pressure gradients (121, 132–134, 136, 137, 141–145). Spontaneous breathing, right ventricular (RV) failure, and increased RV afterload have been associated with false-positive results for PPV and SVV (i.e., elevated values not related to preload responsiveness) (95, 146–150). False-negative results have been observed with insufficient tidal volumes (Vt), decreased lung compliance, and increased vascular compliance (95, 141, 144, 151–153). Other conditions possibly altering cutoff values or compromising their effectiveness are elevated positive end-expiratory pressure, increased Vt, changes in vascular tone, increased abdominal pressure, and changes in chest wall compliance (**Table 3**) (111, 118, 140, 142, 154–159). It is important to note that clinical use of these indices must be investigated in detail, in each species, before translation into clinical practice is feasible. For example, does the dogs' greater chest wall compliance relative to lung compliance impact predictive and cutoff values for each *dynamic* index (160–162). Lower HR and respiratory rates in horses may also pose limitations (140). Among veterinary-pertinent studies (105, 118, 122, 160–173), a recent investigation with hypotensive dogs found PPV ≥ 15% had 50% sensitivity and 96% specificity in predicting preload responsiveness, further estimating PPV ≥ 19.5 for 100% sensitivity (76% specificity) (171). Another investigation

TABLE 3 | Factors potentially interfering with PPV and SVV.[a]

Spontaneous breathing
Cardiac arrhythmias
Tidal volume (Vt, insufficient, excessive)
Elevated positive end-expiratory pressure
Inspiratory to expiratory ratio
Heart rate to respiratory rate ratio
Lung compliance
Chest wall compliance (including open chest)
Increased right ventricular afterload
Increased intraabdominal pressure
Right and/or left ventricular failure
Increased vascular compliance
Changes in vascular tone

[a]*Refer text for details.*
PPV, pulse pressure variation; SVV, stroke volume variation.

with healthy dogs disclosed cutoff values for ΔVPeak ≥ 9.4% (89% sensitivity, 100% specificity), SPV ≥ 6.7% (78% sensitivity, 93% specificity), and CVCDI ≥ 24% (78% sensitivity, 73% specificity), as being predictive of preload responsiveness (172). These promising results warrant further investigations under different clinical and operative scenarios. A concept to be kept in mind, however, is that, even when potentially preload-responsive, the assessment of whether fluids are actually needed, tolerated, or the best management for the condition requires comprehensive clinical judgment, considering the patient's pathophysiological status (81, 82, 85, 113, 174, 175). *Dynamic* indices may, nevertheless, offer an additional piece of information to help optimize fluid therapy and further aid decisions targeting use and timing of ancillary or alternate therapeutic interventions (176).

Species-specific clinical trials investigating the efficacy and safety of IV fluid resuscitation are woefully underrepresented in the veterinary literature (83, 87, 124, 174, 177, 178). Those that do exist are frequently poorly designed, uncontrolled, and underpowered (117). Even fewer studies have focused on the volume kinetics of IV fluids for the treatment of relative hypovolemia associated with injectable or inhalant anesthetic protocols. One study in isoflurane (3%) anesthetized dogs demonstrated that 80 mL/kg of a balanced electrolyte solution (Plasmalyte-A) produced no effect on arterial blood pressure, SV or CO until the inhalant anesthetic concentration was reduced to 1.6% (122) suggesting that IV fluid therapy may be useless as a treatment for anesthetic-associated relative hypovolemia. Another investigation in hypotensive isoflurane anesthetized dogs concluded that arterial blood pressure measurements were a poor predictor of the hemodynamic response to fluid administration (179). Current suggested guidelines for dogs, cats, and horses have, for the most part, been adopted from experimental studies in rodents, dogs, and pigs, volume kinetic studies conducted in sheep and humans, and clinical trials or meta-analyses completed in humans (180–200). These experimental and clinical studies suggest that fluid choice, optimal fluid volumes (mL/kg), and the rate of fluid administration (mL/kg/min or h) are context-sensitive (i.e., physical condition, age, surgical procedure, anesthetic choice, etc.) and highly likely to be species-dependent, highlighting the importance of personalizing fluid resuscitation protocols. Taken together these studies suggest that: (1) goal-directed fluid therapy is superior to "rules of thumb" (e.g., 3 mL crystalloid/1 mL blood loss) or standardized formulas (3–10 mL/kg/h); (2) a balanced crystalloid solution (201), is the best first choice fluid unless laboratory data suggest otherwise; (3) monitoring techniques should include at least one validated *dynamic* index [e.g., PPV (165, 170, 171, 173)]; (4) an IV fluid bolus should not exceed 20–30 mL/kg (199); and (5) maximal rates of fluid administration should range from 0.02 (maintenance) to 1.0 mL/kg/min (resuscitation) during anesthesia (200).

Fluid therapy for the treatment of anesthetic-associated relative hypovolemia and hypotension remains largely ineffective and predisposes to fluid overload (87, 202, 203). Not unintentionally, CIT TAIT implies an option to "sit tight" and withhold fluids temporarily or longer (113). In this regard, aside from replenishing Vus reserves, fluid administration should aim to restore Vs and target specified hemodynamic improvement, further considering long term (e.g., impact on organ function, ICU days, survival) measurable outcomes (174, 178, 204). The most appropriate sequence of events to be considered for treating anesthetic-associated hypotension or signs of low blood flow (e.g., prolonged capillary refill time, weak peripheral pulses, increased PPV) during anesthesia should be to: (1) adjust [e.g., stop; reduce, refine, replace: (3R's of anesthesia)] the anesthetic protocol, (2) administer a balanced crystalloid based upon clinical signs and monitoring data, and (3) administer a vasoactive (e.g., norepinephrine, vasopressin) drug for vasodilation or inotropic (e.g., dobutamine) drug for poor cardiac performance (205). All three events may be required simultaneously, especially in high-risk subjects that have already lost blood (>15–20 mL/kg) or are septic (**Figure 3**). Notably, the volatile anesthetics sevoflurane and isoflurane have been shown to preserve the endothelial glycocalyx against injury in ketamine anesthetized rats (206–209), whereas propofol increases glycocalyx shedding and vascular permeability (210) and excessive fluid administration triggers atrial natriuretic peptide release increasing vascular membrane permeability and interstitial fluid accumulation (202). Dexmedetomidine has been demonstrated to produce protective effects against ischemia–reperfusion injury in heart, kidney, and brain in rodent animal models (211). These beneficial drug-related actions combined with each drug's known effects on MCFP (**Table 2**) suggest that balanced anesthesia with isoflurane, ketamine, and dexmedetomidine may help to limit the development of anesthetic-associated endothelial glycocalyx injury and relative hypovolemia.

CONCLUSION

In summary, anesthesia-induced relative hypovolemia remains an underappreciated and often occult cause of poor tissue perfusion. The venous side of the circulation contains the majority of the blood volume and is a pivotal contributor to SV and CO. Vasodilation, particularly venodilation, is a primary cause of relative hypovolemia induced by anesthetic drugs. As with any hypovolemic state, relative hypovolemia may reduce venous return, CO, tissue oxygen delivery, and eventually arterial blood pressure, when compensatory mechanisms are inadequate or impaired. Tissue oxygen debt can lead to significant morbidity and mortality. Conventional, clinical monitoring, and diagnosis

of relative hypovolemia during anesthesia relies on subjective clinical and objective macrohemodynamic measurements (e.g., CVP; arterial blood pressure), and global perfusion assessments (e.g., capillary refill time and color, blood gases, lactate). Beyond correction of anesthetic plane, drug choice, and ventilation, therapeutic intervention typically consists of fluid administration, vasoactive and/or inotropic agents, seeking to optimize preload, afterload and cardiac function, with the ultimate goal of maintaining or restoring the effective circulatory volume (Vs), and microcirculatory flow. While many current fluid therapy strategies and fluid monitoring techniques remain under active research and debate, intravenous fluid therapy remains a first line therapy. Intravenous fluid therapy should be personalized and tailored to each patient's requirements based upon a clear indication, consideration of potential benefits vs. harms, and objective measures for determining its effects. Variability in current practices related to crystalloid or colloid "fluid bolus," "fluid challenge," or assessment of "preload responsiveness" including methods for the assessment of "hemodynamic improvement," in addition to longer term outcomes, preclude comparisons for substantive conclusions (121, 178, 204, 212–216). Recent studies have focused on data for objective characterization of some of these terms, but no consensus has been established (137, 204, 213, 217–219). Continued research is required, specifically focused on veterinary patients (i.e., for each species and in diverse clinical situations) before they can be effectively translated into clinical practice.

AUTHOR CONTRIBUTIONS

WM originated the concept for the article. JN-M and WM contributed to drafting and reviewing the manuscript.

REFERENCES

1. Li G, Warner M, Lang BH, Huang L, Sun LS. Epidemiology of anesthesia-related mortality in the United States, 1999–2005. *Anesthesiology* (2009) 110(4):759–65. doi:10.1097/ALN.0b013e31819b5bdc
2. Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow. *Best Pract Res Clin Anaesthesiol* (2011) 25(2):123–32. doi:10.1016/j.bpa.2011.02.008
3. Cooper JB, Newbower RS, Long CD, McPeek B. Preventable anesthesia mishaps: a study of human factors. 1978. *Qual Saf Health Care* (2002) 11(3):277–82. doi:10.1136/qhc.11.3.277
4. Steadman J, Catalani B, Sharp CR, Cooper L. Life-threatening perioperative anesthetic complications: major issues surrounding perioperative morbidity and mortality. *Trauma Surg Acute Care Open* (2017) 2:1–7. doi:10.1136/tsaco-2017-000113
5. McMillan M, Darcy H. Adverse event surveillance in small animal anaesthesia: an intervention-based, voluntary reporting audit. *Vet Anaesth Analg* (2016) 43(2):128–35. doi:10.1111/vaa.12309
6. Brodbelt DC, Blissitt KJ, Hammond RA, Neath PJ, Young LE, Pfeiffer DU, et al. The risk of death: the confidential enquiry into perioperative small animal fatalities. *Vet Anaesth Analg* (2008) 35(5):365–73. doi:10.1111/j.1467-2995.2008.00397.x
7. Bille C, Auvigne V, Libermann S, Bomassi E, Durieux P, Rattez E. Risk of anaesthetic mortality in dogs and cats: an observational cohort study of 3546 cases. *Vet Anaesth Analg* (2012) 39(1):59–68. doi:10.1111/j.1467-2995.2011.00686.x
8. Matthews NS, Mohn TJ, Yang M, Spofford N, Marsh A, Faunt K, et al. Factors associated with anesthetic-related death in dogs and cats in primary care veterinary hospitals. *J Am Vet Med Assoc* (2017) 250(6):655–65. doi:10.2460/javma.250.6.655
9. Johnston GM, Eastment JK, Wood J, Taylor PM. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Vet Anaesth Analg* (2002) 29(4):159–70. doi:10.1046/j.1467-2995.2002.00106.x
10. Wagner AE. Complications in equine anesthesia. *Vet Clin North Am Equine Pract* (2008) 24(3):735–52, x. doi:10.1016/j.cveq.2008.10.002
11. Dugdale AH, Taylor PM. Equine anaesthesia-associated mortality: where are we now? *Vet Anaesth Analg* (2016) 43(3):242–55. doi:10.1111/vaa.12372
12. Mazaferro E, Wagner AE. Hypotension during anesthesia in dogs and cats: recognition, causes, and treatment. *Compend Contin Educ Pract Vet North Am Edn* (2001) 23(8):728–34.
13. Young SS, Taylor PM. Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases. *Equine Vet J* (1993) 25(2):147–51. doi:10.1111/j.2042-3306.1993.tb02926.x
14. Espinosa P, Le Jeune SS, Cenani A, Kass PH, Brosnan RJ. Investigation of perioperative and anesthetic variables affecting short-term survival of horses with small intestinal strangulating lesions. *Vet Surg* (2017) 46(3):345–53. doi:10.1111/vsu.12618
15. Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* (2008) 108(4):735–48. doi:10.1097/ALN.0b013e3181672607
16. Reddi BA, Carpenter RH. Venous excess: a new approach to cardiovascular control and its teaching. *J Appl Physiol (1985)* (2005) 98(1):356–64. doi:10.1152/japplphysiol.00535.2004
17. Wolff CB, Green DW. Clarification of the circulatory patho-physiology of anaesthesia – implications for high-risk surgical patients. *Int J Surg* (2014) 12(12):1348–56. doi:10.1016/j.ijsu.2014.10.034
18. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* (2001) 345(8):588–95. doi:10.1056/NEJMra002709
19. Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock-part I: physiology. *Crit Care Med* (2013) 41(1):255–62. doi:10.1097/CCM.0b013e3182772ab6
20. Brengelmann GL. Letter to the editor: why persist in the fallacy that mean systemic pressure drives venous return? *Am J Physiol Heart Circ Physiol* (2016) 311(5):H1333–5. doi:10.1152/ajpheart.00536.2016
21. Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care* (2016) 20:271. doi:10.1186/s13054-016-1438-7
22. Folkow B, Mellander S. Veins and venous tone. *Am Heart J* (1964) 68:397–408. doi:10.1016/0002-8703(64)90308-4
23. Shen T, Baker K. Venous return and clinical hemodynamics: how the body works during acute hemorrhage. *Adv Physiol Educ* (2015) 39(4):267–71. doi:10.1152/advan.00050.2015
24. Greenway CV, Seaman KL, Innes IR. Norepinephrine on venous compliance and unstressed volume in cat liver. *Am J Physiol* (1985) 248(4 Pt 2):H468–76.
25. Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res* (1973) 33(1):22–33. doi:10.1161/01.RES.33.1.22
26. Hainsworth R, Karim F. Responses of abdominal vascular capacitance in the anaesthetized dog to changes in carotid sinus pressure. *J Physiol* (1976) 262(3):659–77. doi:10.1113/jphysiol.1976.sp011614
27. Shigemi K, Brunner MJ, Shoukas AA. Alpha- and beta-adrenergic mechanisms in the control of vascular capacitance by the carotid sinus baroreflex system. *Am J Physiol* (1994) 267(1 Pt 2):H201–10.
28. Rothe CF. Reflex control of veins and vascular capacitance. *Physiol Rev* (1983) 63(4):1281–342. doi:10.1152/physrev.1983.63.4.1281
29. Ruffolo RR Jr. Distribution and function of peripheral alpha-adrenoceptors in the cardiovascular system. *Pharmacol Biochem Behav* (1985) 22(5):827–33. doi:10.1016/0091-3057(85)90535-0
30. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* (1955) 35(1):123–9. doi:10.1152/physrev.1955.35.1.123
31. Hainsworth R. Vascular capacitance: its control and importance. *Rev Physiol Biochem Pharmacol* (1986) 105:101–73. doi:10.1007/BFb0034498
32. Jacob M, Chappell D, Hofmann-Kiefer K, Helfen T, Schuelke A, Jacob B, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care* (2012) 16(3):R86. doi:10.1186/cc11344

33. Henderson WR, Griesdale DE, Walley KR, Sheel AW. Clinical review: Guyton – the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Crit Care* (2010) 14(6):243. doi:10.1186/cc9247
34. Guyton AC, Lindsey AW, Kaufmann BN. Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol* (1955) 180(3):463–8.
35. Maas JJ. Mean systemic filling pressure: its measurement and meaning. *Neth J Crit Care* (2015) 19(1):6–11.
36. Heymans C. Reflexogenic areas of the cardiovascular system. *Perspect Biol Med* (1960) 3:409–17. doi:10.1353/pbm.1960.0038
37. Kahler RL, Goldblatt A, Braunwald E. The effects of acute hypoxia on the systemic venous and arterial systems and on myocardial contractile force. *J Clin Invest* (1962) 41:1553–63. doi:10.1172/JCI104612
38. Smith EE, Crowell JW. Influence of hypoxia on mean circulatory pressure and cardiac output. *Am J Physiol* (1967) 212(5):1067–9.
39. Scott-Douglas NW, Robinson VJ, Smiseth OA, Wright CI, Manyari DE, Smith ER, et al. Effects of acute volume loading and hemorrhage on intestinal vascular capacitance: a mechanism whereby capacitance modulates cardiac output. *Can J Cardiol* (2002) 18(5):515–22.
40. Schiller AM, Howard JT, Convertino VA. The physiology of blood loss and shock: new insights from a human laboratory model of hemorrhage. *Exp Biol Med (Maywood)* (2017) 242(8):874–83. doi:10.1177/1535370217694099
41. Ryan KL, Rickards CA, Hinojosa-Laborde C, Cooke WH, Convertino VA. Sympathetic responses to central hypovolemia: new insights from microneurographic recordings. *Front Physiol* (2012) 3:110. doi:10.3389/fphys.2012.00110
42. Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. *Chest* (1992) 102(1):208–15. doi:10.1378/chest.102.1.208
43. Rixen D, Siegel JH. Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. *Crit Care* (2005) 9(5):441–53. doi:10.1186/cc3526
44. Scroggin RD Jr, Quandt J. The use of vasopressin for treating vasodilatory shock and cardiopulmonary arrest. *J Vet Emerg Crit Care (San Antonio)* (2009) 19(2):145–57. doi:10.1111/j.1476-4431.2008.00352.x
45. Jacob M, Chappell D, Becker BF. Regulation of blood flow and volume exchange across the microcirculation. *Crit Care* (2016) 20(1):319. doi:10.1186/s13054-016-1485-0
46. Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. *Am J Physiol* (1988) 254(1 Pt 2): H20–7.
47. Boerma EC, Ince C. The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. *Intensive Care Med* (2010) 36(12):2004–18. doi:10.1007/s00134-010-1970-x
48. Ginimuge PR, Jyothi SD. Methylene blue: revisited. *J Anaesthesiol Clin Pharmacol* (2010) 26(4):517–20.
49. Akata T. General anesthetics and vascular smooth muscle: direct actions of general anesthetics on cellular mechanisms regulating vascular tone. *Anesthesiology* (2007) 106(2):365–91. doi:10.1097/00000542-200702000-00026
50. Stadnicka A, Stekiel TA, Bosnjak ZJ, Kampine JP. Inhibition by enflurane of baroreflex mediated mesenteric venoconstriction in the rabbit ileum. *Anesthesiology* (1993) 78(5):928–36. doi:10.1097/00000542-199305000-00018
51. Stekiel TA, Stekiel WJ, Tominaga M, Stadnicka A, Bosnjak ZJ, Kampine JP. Isoflurane-mediated inhibition of the constriction of mesenteric capacitance veins and related circulatory responses to acute graded hypoxic hypoxia. *Anesth Analg* (1995) 80(5):994–1001. doi:10.1097/00000539-199505000-00025
52. Yamazaki M, Stekiel TA, Bosnjak ZJ, Kampine JP, Stekiel WJ. Effects of volatile anesthetic agents on in situ vascular smooth muscle transmembrane potential in resistance- and capacitance-regulating blood vessels. *Anesthesiology* (1998) 88(4):1085–95. doi:10.1097/00000542-199804000-00030
53. Hoka S, Yamaura K, Takenaka T, Takahashi S. Propofol-induced increase in vascular capacitance is due to inhibition of sympathetic vasoconstrictive activity. *Anesthesiology* (1998) 89(6):1495–500. doi:10.1097/00000542-199812000-00028
54. Sellgren J, Biber B, Henriksson BA, Martner J, Ponten J. The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. *Acta Anaesthesiol Scand* (1992) 36(8):784–90. doi:10.1111/j.1399-6576.1992.tb03565.x
55. Green DW. Cardiac output decrease and propofol: what is the mechanism? *Br J Anaesth* (2015) 114(1):163–4. doi:10.1093/bja/aeu424
56. Ebert TJ, Muzi M. Propofol and autonomic reflex function in humans. *Anesth Analg* (1994) 78(2):369–75. doi:10.1213/00000539-199402000-00029
57. Goodchild CS, Serrao JM. Cardiovascular effects of propofol in the anaesthetized dog. *Br J Anaesth* (1989) 63(1):87–92. doi:10.1093/bja/63.1.87
58. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *Br J Anaesth* (2016) 116(6):784–9. doi:10.1093/bja/aew126
59. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology* (1992) 76(5):725–33. doi:10.1097/00000542-199205000-00010
60. Sohn JT, Lee SJ, Hwang KI, Kim SH, Lee HK, Chung YK. Ketamine sodium thiopental venous capacitance in dog. *Korean J Anesthesiol* (1998) 34:896–903. doi:10.4097/kjae.1998.34.5.896
61. Tyberg JV. How changes in venous capacitance modulate cardiac output. *Pflugers Arch* (2002) 445(1):10–7. doi:10.1007/s00424-002-0922-x
62. Hirakawa S, Ito H, Kondo Y, Watanabe I, Hiei K, Banno S, et al. The mean circulatory pressure, reproducibility of its measurements and the effect of phenylephrine with a note on the effect of pentobarbital. *Jpn Circ J* (1975) 39(4):403–9. doi:10.1253/jcj.39.403
63. Stekiel TA, Ozono K, McCallum JB, Bosnjak ZJ, Stekiel WJ, Kampine JP. The inhibitory action of halothane on reflex constriction in mesenteric capacitance veins. *Anesthesiology* (1990) 73(6):1169–78. doi:10.1097/00000542-199012000-00015
64. Arimura H, Hoka S, Bosnjak ZJ, Kampine JP. Alteration of vascular capacitance and blood flow distribution during halothane anesthesia. *J Anesth* (1994) 8(4):467–71. doi:10.1007/BF02514628
65. Hoka S, Takeshita A, Yamamoto K, Ito N, Yoshitake J. The effects of ketamine on venous capacitance in rats. *Anesthesiology* (1985) 62(2):145–8. doi:10.1097/00000542-198502000-00009
66. Lehot JJ, Bastien O, Pelissier FT, Villard J, Estanove S. [Vascular effects of ketamine during anesthesia with diazepam and fentanyl]. *Ann Fr Anesth Reanim* (1992) 11(1):8–11. doi:10.1016/S0750-7658(05)80313-2
67. Cohen RA, Coffman JD. Effect of morphine on limb capacitance and resistance vessels. *Clin Sci (Lond)* (1981) 60(1):5–9. doi:10.1042/cs0600005
68. Hsu HO, Hickey RF, Forbes AR. Morphine decreases peripheral vascular resistance and increases capacitance in man. *Anesthesiology* (1979) 50(2):98–102. doi:10.1097/00000542-197902000-00005
69. Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. *J Clin Invest* (1974) 54(6):1247–58. doi:10.1172/JCI107869
70. Freye E. The effect of fentanyl on the resistance and capacitance vessels of the dog's hindlimb. *Arzneimittelforschung* (1977) 27(5):1037–9.
71. Henney RP, Vasko JS, Brawley RK, Oldham HN, Morrow AG. The effects of morphine on the resistance and capacitance vessels of the peripheral circulation. *Am Heart J* (1966) 72(2):242–50. doi:10.1016/0002-8703(66)90448-0
72. Stick JA, Chou CC, Derksen FJ, Arden WA. Effects of xylazine on equine intestinal vascular resistance, motility, compliance, and oxygen consumption. *Am J Vet Res* (1987) 48(2):198–203.
73. Hogan QH, Stadnicka A, Bosnjak ZJ, Kampine JP. Effects of lidocaine and bupivacaine on isolated rabbit mesenteric capacitance veins. *Reg Anesth Pain Med* (1998) 23(4):409–17. doi:10.1097/00115550-199823040-00017
74. Ogilvie RI, Zborowska-Sluis D. Effects of nitroglycerin and nitroprusside on vascular capacitance of anesthetized ganglion-blocked dogs. *J Cardiovasc Pharmacol* (1991) 18(4):574–80. doi:10.1097/00005344-199110000-00014
75. Baraka A, Haroun S, Baroody M, Nawfal M, Sibai A. Action of adrenergic agonists on resistance v capacitance vessels during cardiopulmonary bypass. *J Cardiothorac Anesth* (1989) 3(2):193–5. doi:10.1016/S0888-6296(89)92738-5
76. Butterworth JF, Piccione W Jr, Berrizbeitia LD, Dance G, Shemin RJ, Cohn LH. Augmentation of venous return by adrenergic agonists during spinal anesthesia. *Anesth Analg* (1986) 65(6):612–6. doi:10.1213/00000539-198606000-00009
77. Arimura H, Bosnjak ZJ, Hoka S, Kampine JP. Catecholamine-induced changes in vascular capacitance and sympathetic nerve activity in dogs. *Can J Physiol Pharmacol* (1992) 70(7):1021–31. doi:10.1139/y92-141

78. Thiele RH, Nemergut EC, Lynch C III. The physiologic implications of isolated alpha(1) adrenergic stimulation. *Anesth Analg* (2011) 113(2):284–96. doi:10.1213/ANE.0b013e3182124c0e
79. Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. *Shock* (2010) 33(2):113–22. doi:10.1097/SHK.0b013e3181b8569d
80. Chawla LS, Ince C, Chappell D, Gan TJ, Kellum JA, Mythen M, et al. Vascular content, tone, integrity, and haemodynamics for guiding fluid therapy: a conceptual approach. *Br J Anaesth* (2014) 113(5):748–55. doi:10.1093/bja/aeu298
81. Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, et al. Clinical review: update on hemodynamic monitoring – a consensus of 16. *Crit Care* (2011) 15(4):229. doi:10.1186/cc10291
82. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* (2014) 40(12):1795–815. doi:10.1007/s00134-014-3525-z
83. Navarro LH, Bloomstone JA, Auler JO Jr, Cannesson M, Rocca GD, Gan TJ, et al. Perioperative fluid therapy: a statement from the International Fluid Optimization Group. *Perioper Med (Lond)* (2015) 4:3. doi:10.1186/s13741-015-0014-z
84. Bundgaard-Nielsen M, Jorgensen CC, Secher NH, Kehlet H. Functional intravascular volume deficit in patients before surgery. *Acta Anaesthesiol Scand* (2010) 54(4):464–9. doi:10.1111/j.1399-6576.2009.02175.x
85. Tatara T. Context-sensitive fluid therapy in critical illness. *J Intensive Care* (2016) 4:20. doi:10.1186/s40560-016-0150-7
86. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesth Analg* (2012) 115(4):880–7. doi:10.1213/ANE.0b013e31825fb01d
87. Pachtinger GE, Drobatz K. Assessment and treatment of hypovolemic states. *Vet Clin North Am Small Anim Pract* (2008) 38(3):629–43, xii. doi:10.1016/j.cvsm.2008.01.009
88. Stevenson CK, Kidney BA, Duke T, Snead EC, Mainar-Jaime RC, Jackson ML. Serial blood lactate concentrations in systemically ill dogs. *Vet Clin Pathol* (2007) 36(3):234–9. doi:10.1111/j.1939-165X.2007.tb00217.x
89. Nel M, Lobetti RG, Keller N, Thompson PN. Prognostic value of blood lactate, blood glucose, and hematocrit in canine babesiosis. *J Vet Intern Med* (2004) 18(4):471–6. doi:10.1111/j.1939-1676.2004.tb02569.x
90. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* (2017) 43(3):304–77. doi:10.1007/s00134-017-4683-6
91. Alpert RA, Roizen MF, Hamilton WK, Stoney RJ, Ehrenfeld WK, Poler SM, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery* (1984) 95(6):707–11.
92. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. *J Intensive Care* (2016) 4:27. doi:10.1186/s40560-016-0154-3
93. Yeager MP, Spence BC. Perioperative fluid management: current consensus and controversies. *Semin Dial* (2006) 19(6):472–9. doi:10.1111/j.1525-139X.2006.00209.x
94. Magder S. Right atrial pressure in the critically Ill: how to measure, what is the value, what are the limitations? *Chest* (2017) 151(4):908–16. doi:10.1016/j.chest.2016.10.026
95. Noel-Morgan J, Otsuki DA, Auler JO Jr, Fukushima JT, Fantoni DT. Pulse pressure variation is comparable with central venous pressure to guide fluid resuscitation in experimental hemorrhagic shock with endotoxemia. *Shock* (2013) 40(4):303–11. doi:10.1097/SHK.0b013e3182a0ca00
96. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. *Ann Intensive Care* (2014) 4:21. doi:10.1186/s13613-014-0021-0
97. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* (2001) 345(19):1368–77. doi:10.1056/NEJMoa010307
98. De Backer D. Detailing the cardiovascular profile in shock patients. *Crit Care* (2017) 21(Suppl 3):311. doi:10.1186/s13054-017-1908-6
99. Corley KT, Donaldson LL, Durando MM, Birks EK. Cardiac output technologies with special reference to the horse. *J Vet Intern Med* (2003) 17(3):262–72. doi:10.1111/j.1939-1676.2003.tb02447.x
100. Shih A. Cardiac output monitoring in horses. *Vet Clin North Am Equine Pract* (2013) 29(1):155–67. doi:10.1016/j.cveq.2012.11.002
101. Marshall K, Thomovsky E, Johnson P, Brooks A. A review of available techniques for cardiac output monitoring. *Top Companion Anim Med* (2016) 31(3):100–8. doi:10.1053/j.tcam.2016.08.006
102. Mason DJ, O'Grady M, Woods JP, McDonell W. Assessment of lithium dilution cardiac output as a technique for measurement of cardiac output in dogs. *Am J Vet Res* (2001) 62(8):1255–61. doi:10.2460/ajvr.2001.62.1255
103. Mason DJ, O'Grady M, Woods JP, McDonell W. Comparison of a central and a peripheral (cephalic vein) injection site for the measurement of cardiac output using the lithium-dilution cardiac output technique in anesthetized dogs. *Can J Vet Res* (2002) 66(3):207–10.
104. LeBlanc NL, Scollan KF, Stieger-Vanegas SM. Cardiac output measured by use of electrocardiogram-gated 64-slice multidector computed tomography, echocardiography, and thermodilution in healthy dogs. *Am J Vet Res* (2017) 78(7):818–27. doi:10.2460/ajvr.78.7.818
105. Sasaki K, Mutoh T, Mutoh T, Kawashima R, Tsubone H. Electrical velocimetry for noninvasive cardiac output and stroke volume variation measurements in dogs undergoing cardiovascular surgery. *Vet Anaesth Analg* (2017) 44(1):7–16. doi:10.1111/vaa.12380
106. Beaulieu KE, Kerr CL, McDonell WN. Evaluation of a lithium dilution cardiac output technique as a method for measurement of cardiac output in anesthetized cats. *Am J Vet Res* (2005) 66(9):1639–45. doi:10.2460/ajvr.2005.66.1639
107. Beaulieu KE, Kerr CL, McDonell WN. Evaluation of transpulmonary thermodilution as a method to measure cardiac output in anesthetized cats. *Can J Vet Res* (2009) 73(1):1–6.
108. Shih AC, Queiroz P, Vigani A, Da Cunha A, Pariaut R, Ricco C, et al. Comparison of cardiac output determined by an ultrasound velocity dilution cardiac output method and by the lithium dilution cardiac output method in juvenile horses with experimentally induced hypovolemia. *Am J Vet Res* (2014) 75(6):565–71. doi:10.2460/ajvr.75.6.565
109. Linton RA, Young LE, Marlin DJ, Blissitt KJ, Brearley JC, Jonas MM, et al. Cardiac output measured by lithium dilution, thermodilution, and transesophageal Doppler echocardiography in anesthetized horses. *Am J Vet Res* (2000) 61(7):731–7. doi:10.2460/ajvr.2000.61.731
110. Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. *Crit Care* (2006) 10(Suppl 3):S8. doi:10.1186/cc4355
111. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F. Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care Med* (2002) 166(10):1310–9. doi:10.1164/rccm.200202-146CC
112. Levitov A, Frankel HL, Blaivas M, Kirkpatrick AW, Su E, Evans D, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically Ill patients-part II: cardiac ultrasonography. *Crit Care Med* (2016) 44(6):1206–27. doi:10.1097/CCM.0000000000001847
113. van Haren F. Personalised fluid resuscitation in the ICU: still a fluid concept? *Crit Care* (2017) 21(Suppl 3):313. doi:10.1186/s13054-017-1909-5
114. Butler AL. Goal-directed therapy in small animal critical illness. *Vet Clin North Am Small Anim Pract* (2011) 41(4):817–38, vii. doi:10.1016/j.cvsm.2011.05.002
115. Boag AK, Hughes D. Assessment and treatment of perfusion abnormalities in the emergency patient. *Vet Clin North Am Small Anim Pract* (2005) 35(2):319–42. doi:10.1016/j.cvsm.2004.10.010
116. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* (2016) 315(8):801–10. doi:10.1001/jama.2016.0287
117. Muir WW, Ueyama Y, Noel-Morgan J, Kilborne A, Page J. A systematic review of the quality of IV fluid therapy in veterinary medicine. *Front Vet Sci* (2017) 4:127. doi:10.3389/fvets.2017.00127
118. Nouira S, Elatrous S, Dimassi S, Besbes L, Boukef R, Mohamed B, et al. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* (2005) 33(10):2339–43. doi:10.1097/01.CCM.0000182801.48137.13
119. Chen HC, Sinclair MD, Dyson DH. Use of ephedrine and dopamine in dogs for the management of hypotension in routine clinical cases under isoflurane anesthesia. *Vet Anaesth Analg* (2007) 34(5):301–11. doi:10.1111/j.1467-2995.2006.00327.x

120. Lonjaret L, Lairez O, Minville V, Geeraerts T. Optimal perioperative management of arterial blood pressure. *Integr Blood Press Control* (2014) 7:49–59. doi:10.2147/IBPC.S45292
121. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* (2002) 121(6):2000–8. doi:10.1378/chest.121.6.2000
122. Valverde A, Gianotti G, Rioja-Garcia E, Hathway A. Effects of high-volume, rapid-fluid therapy on cardiovascular function and hematological values during isoflurane-induced hypotension in healthy dogs. *Can J Vet Res* (2012) 76(2):99–108.
123. Myatra SN, Monnet X, Teboul JL. Use of 'tidal volume challenge' to improve the reliability of pulse pressure variation. *Crit Care* (2017) 21(1):60. doi:10.1186/s13054-017-1637-x
124. Michard F. Volume management using dynamic parameters: the good, the bad, and the ugly. *Chest* (2005) 128(4):1902–3. doi:10.1378/chest.128.4.1902
125. Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs. 'restrictive' perioperative fluid therapy – a critical assessment of the evidence. *Acta Anaesthesiol Scand* (2009) 53(7):843–51. doi:10.1111/j.1399-6576.2009.02029.x
126. Herget-Rosenthal S, Saner F, Chawla LS. Approach to hemodynamic shock and vasopressors. *Clin J Am Soc Nephrol* (2008) 3(2):546–53. doi:10.2215/CJN.01820407
127. Holte K, Foss NB, Andersen J, Valentiner L, Lund C, Bie P, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth* (2007) 99(4):500–8. doi:10.1093/bja/aem211
128. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* (2003) 238(5):641–8. doi:10.1097/01.sla.0000094387.50865.23
129. MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* (2006) 93(12):1469–74. doi:10.1002/bjs.5593
130. Rivers EP. Fluid-management strategies in acute lung injury – liberal, conservative, or both? *N Engl J Med* (2006) 354(24):2598–600. doi:10.1056/NEJMe068105
131. Cuthbertson BH. Goldilocks, elephants, and surgical fluids. *Br J Anaesth* (2013) 110(1):144–5. doi:10.1093/bja/aes449
132. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* (2001) 119(3):867–73. doi:10.1378/chest.119.3.867
133. Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Crit Care* (2007) 11(5):R100. doi:10.1186/cc6117
134. Auler JO Jr, Galas F, Hajjar L, Santos L, Carvalho T, Michard F. Online monitoring of pulse pressure variation to guide fluid therapy after cardiac surgery. *Anesth Analg* (2008) 106(4):1201–6. doi:10.1213/01.ane.0000287664.03547.c6
135. Cannesson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth* (2008) 101(2):200–6. doi:10.1093/bja/aen133
136. Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg* (2013) 117(6):1380–92. doi:10.1213/ANE.0b013e3182a9557e
137. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care* (2016) 6(1):111. doi:10.1186/s13613-016-0216-7
138. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* (2009) 37(9):2642–7. doi:10.1097/CCM.0b013e3181a590da
139. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care* (2014) 18(6):650. doi:10.1186/s13054-014-0650-6
140. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* (2009) 110(5):1092–7. doi:10.1097/ALN.0b013e31819db2a1
141. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* (2005) 31(4):517–23. doi:10.1007/s00134-005-2586-4
142. Reuter DA, Goepfert MS, Goresch T, Schmoeckel M, Kilger E, Goetz AE. Assessing fluid responsiveness during open chest conditions. *Br J Anaesth* (2005) 94(3):318–23. doi:10.1093/bja/aei043
143. Monge Garcia MI, Gil Cano A, Gracia Romero M. Dynamic arterial elastance to predict arterial pressure response to volume loading in preload-dependent patients. *Crit Care* (2011) 15(1):R15. doi:10.1186/cc9420
144. Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. *Crit Care Med* (2017) 45(3):415–21. doi:10.1097/CCM.0000000000002183
145. Pinsky MR. Defining the boundaries of preload responsiveness at the bedside. *Pediatr Crit Care Med* (2015) 16(1):82–3. doi:10.1097/PCC.0000000000000291
146. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* (2000) 162(1):134–8. doi:10.1164/ajrccm.162.1.9903035
147. Vieillard-Baron A, Chergui K, Augarde R, Prin S, Page B, Beauchet A, et al. Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. *Am J Respir Crit Care Med* (2003) 168(6):671–6. doi:10.1164/rccm.200301-135OC
148. Vieillard-Baron A, Chergui K, Rabiller A, Peyrouset O, Page B, Beauchet A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med* (2004) 30(9):1734–9. doi:10.1007/s00134-004-2361-y
149. Mahjoub Y, Pila C, Friggeri A, Zogheib E, Lobjoie E, Tinturier F, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* (2009) 37(9):2570–5. doi:10.1097/CCM.0b013e3181a380a3
150. Wyler von Ballmoos M, Takala J, Roeck M, Porta F, Tueller D, Ganter CC, et al. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care* (2010) 14(3):R111. doi:10.1186/cc9060
151. Lakhal K, Ehrmann S, Benzekri-Lefevre D, Runge I, Legras A, Dequin PF, et al. Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care* (2011) 15(2):R85. doi:10.1186/cc10083
152. Lefrant JY, De Backer D. Can we use pulse pressure variations to predict fluid responsiveness in patients with ARDS? *Intensive Care Med* (2009) 35(6):966–8. doi:10.1007/s00134-009-1479-3
153. Pereira de Souza Neto E, Grousson S, Duflo F, Ducreux C, Joly H, Convert J, et al. Predicting fluid responsiveness in mechanically ventilated children under general anaesthesia using dynamic parameters and transthoracic echocardiography. *Br J Anaesth* (2011) 106(6):856–64. doi:10.1093/bja/aer090
154. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR, Lecarpentier Y, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* (1999) 159(3):935–9. doi:10.1164/ajrccm.159.3.9805077
155. Renner J, Gruenewald M, Quaden R, Hanss R, Meybohm P, Steinfath M, et al. Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model. *Crit Care Med* (2009) 37(2):650–8. doi:10.1097/CCM.0b013e3181959864
156. de Waal EE, Rex S, Kruitwagen CL, Kalkman CJ, Buhre WF. Dynamic preload indicators fail to predict fluid responsiveness in open-chest conditions. *Crit Care Med* (2009) 37(2):510–5. doi:10.1097/CCM.0b013e3181958bf7
157. Jacques D, Bendjelid K, Duperret S, Colling J, Piriou V, Viale JP. Pulse pressure variation and stroke volume variation during increased intra-abdominal pressure: an experimental study. *Crit Care* (2011) 15(1):R33. doi:10.1186/cc9980
158. Mallat J, Lemyze M, Thevenin D. Ability of respiratory pulse pressure variation to predict fluid responsiveness in ARDS: still an unanswered question? *Crit Care* (2011) 15(3):432; author reply 432. doi:10.1186/cc10222

159. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. *Anesthesiology* (2011) 115(2):231–41. doi:10.1097/ALN.0b013e318225b80a
160. Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* (1987) 67(4):498–502. doi:10.1097/00000542-198710000-00009
161. Szold A, Pizov R, Segal E, Perel A. The effect of tidal volume and intravascular volume state on systolic pressure variation in ventilated dogs. *Intensive Care Med* (1989) 15(6):368–71. doi:10.1007/BF00261495
162. Klein AV, Teixeira-Neto FJ, Garofalo NA, Lagos-Carvajal AP, Diniz MS, Becerra-Velasquez DR. Changes in pulse pressure variation and plethysmographic variability index caused by hypotension-inducing hemorrhage followed by volume replacement in isoflurane-anesthetized dogs. *Am J Vet Res* (2016) 77(3):280–7. doi:10.2460/ajvr.77.3.280
163. Berkenstadt H, Friedman Z, Preisman S, Keidan I, Livingstone D, Perel A. Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth* (2005) 94(6):721–6. doi:10.1093/bja/aei116
164. Kim HK, Pinsky MR. Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med* (2008) 36(10):2858–62. doi:10.1097/CCM.0b013e3181865aea
165. Fielding CL, Stolba DN. Pulse pressure variation and systolic pressure variation in horses undergoing general anesthesia. *J Vet Emerg Crit Care (San Antonio)* (2012) 22(3):372–5. doi:10.1111/j.1476-4431.2012.00746.x
166. Rabozzi R, Franci P. Use of systolic pressure variation to predict the cardiovascular response to mini-fluid challenge in anaesthetised dogs. *Vet J* (2014) 202(2):367–71. doi:10.1016/j.tvjl.2014.08.022
167. Diniz MS, Teixeira-Neto FJ, Candido TD, Zanuzzo FS, Teixeira LR, Klein AV, et al. Effects of dexmedetomidine on pulse pressure variation changes induced by hemorrhage followed by volume replacement in isoflurane-anesthetized dogs. *J Vet Emerg Crit Care (San Antonio)* (2014) 24(6):681–92. doi:10.1111/vec.12246
168. Kawazoe Y, Nakashima T, Iseri T, Yonetani C, Ueda K, Fujimoto Y, et al. The impact of inspiratory pressure on stroke volume variation and the evaluation of indexing stroke volume variation to inspiratory pressure under various preload conditions in experimental animals. *J Anesth* (2015) 29(4):515–21. doi:10.1007/s00540-015-1995-y
169. Sasaki K, Mutoh T, Mutoh T, Taki Y, Kawashima R. Noninvasive stroke volume variation using electrical velocimetry for predicting fluid responsiveness in dogs undergoing cardiac surgery. *Vet Anaesth Analg* (2017) 44(4):719–26. doi:10.1016/j.vaa.2016.11.001
170. Endo Y, Tamura J, Ishizuka T, Itami T, Hanazono K, Miyoshi K, et al. Stroke volume variation (SVV) and pulse pressure variation (PPV) as indicators of fluid responsiveness in sevoflurane anesthetized mechanically ventilated euvolemic dogs. *J Vet Med Sci* (2017) 79(8):1437–45. doi:10.1292/jvms.16-0287
171. Fantoni DT, Ida KK, Gimenes AM, Mantovani MM, Castro JR, Patricio GCF, et al. Pulse pressure variation as a guide for volume expansion in dogs undergoing orthopedic surgery. *Vet Anaesth Analg* (2017) 44(4):710–8. doi:10.1016/j.vaa.2016.11.011
172. Bucci M, Rabozzi R, Guglielmini C, Franci P. Respiratory variation in aortic blood peak velocity and caudal vena cava diameter can predict fluid responsiveness in anaesthetised and mechanically ventilated dogs. *Vet J* (2017) 227:30–5. doi:10.1016/j.tvjl.2017.08.004
173. Drozdzynska MJ, Chang YM, Stanzani G, Pelligand L. Evaluation of the dynamic predictors of fluid responsiveness in dogs receiving goal-directed fluid therapy. *Vet Anaesth Analg* (2018) 45(1):22–30. doi:10.1016/j.vaa.2017.06.001
174. Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care* (2010) 16(4):289–96. doi:10.1097/MCC.0b013e32833b6bab
175. Magder S. Further cautions for the use of ventilatory-induced changes in arterial pressures to predict volume responsiveness. *Crit Care* (2010) 14(5):197. doi:10.1186/cc9223
176. Michard F, Richards G, Biais M, Lopes M, Auler JO. Using pulse pressure variation or stroke volume variation to diagnose right ventricular failure? *Crit Care* (2010) 14(6):451; author reply 451. doi:10.1186/cc9303
177. Davis H, Jensen T, Johnson A, Knowles P, Meyer R, Rucinsky R, et al. 2013 AAHA/AAFP fluid therapy guidelines for dogs and cats. *J Am Anim Hosp Assoc* (2013) 49(3):149–59. doi:10.5326/JAAHA-MS-5868
178. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. *Crit Care* (2014) 18(6):696. doi:10.1186/s13054-014-0696-5
179. Muir WW, Ueyama Y, Pedraza-Toscano A, Vargas-Pinto P, Delrio CL, George RS, et al. Arterial blood pressure as a predictor of the response to fluid administration in euvolemic nonhypotensive or hypotensive isoflurane-anesthetized dogs. *J Am Vet Med Assoc* (2014) 245(9):1021–7. doi:10.2460/javma.245.9.1021
180. Byers CG. Fluid therapy: options and rational selection. *Vet Clin North Am Small Anim Pract* (2017) 47(2):359–71. doi:10.1016/j.cvsm.2016.09.007
181. Naumann DN, Beaven A, Dretzke J, Hutchings S, Midwinter MJ. Searching for the optimal fluid to restore microcirculatory flow dynamics after haemorrhagic shock: a systematic review of preclinical studies. *Shock* (2016) 46(6):609–22. doi:10.1097/SHK.0000000000000687
182. Boller E, Boller M. Assessment of fluid balance and the approach to fluid therapy in the perioperative patient. *Vet Clin North Am Small Anim Pract* (2015) 45(5):895–915. doi:10.1016/j.cvsm.2015.04.011
183. Mapstone J, Roberts I, Evans P. Fluid resuscitation strategies: a systematic review of animal trials. *J Trauma* (2003) 55(3):571–89. doi:10.1097/01.TA.0000062968.69867.6F
184. Kramer GC. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. *J Trauma* (2003) 54(5 Suppl):S89–99. doi:10.1097/01.TA.0000065609.82142.F1
185. Hahn RG. The transfusion trigger in major surgery. *Acta Anaesthesiol Scand* (2018) 62(2):270. doi:10.1111/aas.13042
186. Hahn RG. Adverse effects of crystalloid and colloid fluids. *Anaesthesiol Intensive Ther* (2017) 49(4):303–8. doi:10.5603/AIT.a2017.0045
187. Hahn RG. Changing practices of fluid therapy. *Acta Anaesthesiol Scand* (2017) 61(6):576–9. doi:10.1111/aas.12892
188. Hahn RG. Arterial pressure and the rate of elimination of crystalloid fluid. *Anesth Analg* (2017) 124(6):1824–33. doi:10.1213/ANE.0000000000002075
189. Li Y, Xiaozhu Z, Guomei R, Qiannan D, Hahn RG. Effects of vasoactive drugs on crystalloid fluid kinetics in septic sheep. *PLoS One* (2017) 12(2):e0172361. doi:10.1371/journal.pone.0172361
190. Hahn RG, Lyons G. The half-life of infusion fluids: an educational review. *Eur J Anaesthesiol* (2016) 33(7):475–82. doi:10.1097/EJA.0000000000000436
191. Ho L, Lau L, Churilov L, Riedel B, McNicol L, Hahn RG, et al. Comparative evaluation of crystalloid resuscitation rate in a human model of compensated haemorrhagic shock. *Shock* (2016) 46(2):149–57. doi:10.1097/SHK.0000000000000610
192. Hahn RG, Drobin D, Zdolsek J. Distribution of crystalloid fluid changes with the rate of infusion: a population-based study. *Acta Anaesthesiol Scand* (2016) 60(5):569–78. doi:10.1111/aas.12686
193. Hahn RG. Must hypervolaemia be avoided? A critique of the evidence. *Anaesthesiol Intensive Ther* (2015) 47(5):449–56. doi:10.5603/AIT.a2015.0062
194. Hahn RG. Why crystalloids will do the job in the operating room. *Anaesthesiol Intensive Ther* (2014) 46(5):342–9. doi:10.5603/AIT.2014.0058
195. Hahn RG. Haemodilution made difficult. *Br J Anaesth* (2013) 111(4):679–80. doi:10.1093/bja/aet321
196. Hahn RG. Fluid therapy in uncontrolled hemorrhage – what experimental models have taught us. *Acta Anaesthesiol Scand* (2013) 57(1):16–28. doi:10.1111/j.1399-6576.2012.02763.x
197. Hahn RG, Lindahl CC, Drobin D. Volume kinetics of acetated Ringer's solution during experimental spinal anaesthesia. *Acta Anaesthesiol Scand* (2011) 55(8):987–94. doi:10.1111/j.1399-6576.2011.02493.x
198. Hahn RG. Volume kinetics for infusion fluids. *Anesthesiology* (2010) 113(2):470–81. doi:10.1097/ALN.0b013e3181dcd88f
199. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med* (2014) 161(5):347–55. doi:10.7326/M14-0178
200. Tatara T, Tsunetoh T, Tashiro C. Crystalloid infusion rate during fluid resuscitation from acute haemorrhage. *Br J Anaesth* (2007) 99(2):212–7. doi:10.1093/bja/aem165
201. Muir W. Effect of intravenously administered crystalloid solutions on acid-base balance in domestic animals. *J Vet Intern Med* (2017) 31(5):1371–81. doi:10.1111/jvim.14803
202. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol* (2016) 17(1):109. doi:10.1186/s12882-016-0323-6

203. Benes J, Kirov M, Kuzkov V, Lainscak M, Molnar Z, Voga G, et al. Fluid therapy: double-edged sword during critical care? *Biomed Res Int* (2015) 2015:729075. doi:10.1155/2015/729075
204. Toscani L, Aya HD, Antonakaki D, Bastoni D, Watson X, Arulkumaran N, et al. What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis. *Crit Care* (2017) 21(1):207. doi:10.1186/s13054-017-1796-9
205. Zhang Z, Chen K. Vasoactive agents for the treatment of sepsis. *Ann Transl Med* (2016) 4(17):333. doi:10.21037/atm.2016.08.58
206. Chen C, Chappell D, Annecke T, Conzen P, Jacob M, Welsch U, et al. Sevoflurane mitigates shedding of hyaluronan from the coronary endothelium, also during ischemia/reperfusion: an ex vivo animal study. *Hypoxia (Auckl)* (2016) 4:81–90. doi:10.2147/HP.S98660
207. Li J, Yuan T, Zhao X, Lv GY, Liu HQ. Protective effects of sevoflurane in hepatic ischemia-reperfusion injury. *Int J Immunopathol Pharmacol* (2016) 29(2):300–7. doi:10.1177/0394632016638346
208. Annecke T, Chappell D, Chen C, Jacob M, Welsch U, Sommerhoff CP, et al. Sevoflurane preserves the endothelial glycocalyx against ischaemia-reperfusion injury. *Br J Anaesth* (2010) 104(4):414–21. doi:10.1093/bja/aeq019
209. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. *Anaesthesia* (2014) 69(7):777–84. doi:10.1111/anae.12661
210. Lin MC, Lin CF, Li CF, Sun DP, Wang LY, Hsing CH. Anesthetic propofol overdose causes vascular hyperpermeability by reducing endothelial glycocalyx and ATP production. *Int J Mol Sci* (2015) 16(6):12092–107. doi:10.3390/ijms160612092
211. Engelhard K, Werner C, Eberspacher E, Bachl M, Blobner M, Hildt E, et al. The effect of the alpha 2-agonist dexmedetomidine and the N-methyl-D-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats. *Anesth Analg* (2003) 96(2):524–31. doi:10.1097/00000539-200302000-00041
212. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med* (2015) 41(9):1529–37. doi:10.1007/s00134-015-3850-x
213. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. *Crit Care Med* (2017) 45(2):e161–8. doi:10.1097/CCM.0000000000002067
214. Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology* (2011) 115(3):541–7. doi:10.1097/ALN.0b013e318229a500
215. Marik PE. Fluid therapy in 2015 and beyond: the mini-fluid challenge and mini-fluid bolus approach. *Br J Anaesth* (2015) 115(3):347–9. doi:10.1093/bja/aev169
216. Biais M, de Courson H, Lanchon R, Pereira B, Bardonneau G, Griton M, et al. Mini-fluid challenge of 100 ml of crystalloid predicts fluid responsiveness in the operating room. *Anesthesiology* (2017) 127(3):450–6. doi:10.1097/ALN.0000000000001753
217. Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. *Crit Care Med* (2016) 44(5):880–91. doi:10.1097/CCM.0000000000001517
218. Aldrich J. Shock fluids and fluid challenge. In: Silverstein D, Hopper K, editors. *Small Animal Critical Care Medicine*. St. Louis, USA: Saunders Elsevier (2009).
219. Magder S. Central venous pressure: a useful but not so simple measurement. *Crit Care Med* (2006) 34(8):2224–7. doi:10.1097/01.CCM.0000227646.98423.98

Conflict of Interest Statement: The authors declare that the manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 03 April 2018
doi: 10.3389/fvets.2018.00060

Development and Implementation of a Perianesthetic Safety Checklist in a Veterinary University Small Animal Teaching Hospital

*Gwennaëlle Menoud, Shannon Axiak Flammer, Claudia Spadavecchia and Mathieu Raillard**

Section of Anesthesiology and Pain Therapy, Department of Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern, Bern, Switzerland

Introduction: The use of a surgical safety checklist is recommended by the World Health Organization and is associated with advantages: improved communication and reduced complications and mortality. Adapting checklists to the environment in which they are used improves their efficiency, but their implementation can be challenging. The aim of this study was to develop and implement a perianesthetic safety checklist for a small animal hospital.

Materials and methods: A panel of eight anesthesia diplomates and seven residents and doctoral students were gathered. The Delphi method was used to generate a checklist. The checklist was presented individually to each user by the primary investigator and introduced into the clinical routine over a 5-week period. An interdisciplinary meeting was then held, and the checklist was modified further. Six months after introduction, the use of the checklist was directly observed during 69 anesthetic cases and a survey was sent to the users. A second implementation was organized after formally presenting the checklist to the staff, designating the anesthesia clinical lead as the person responsible for printing and controlling use of the checklist. A second evaluation was performed 3 months later (64 anesthetic cases).

Results: Using the Delphi process led to the creation of a checklist consisting of three parts: "sign in" (before induction of anesthesia), "time out" (before the beginning of the procedure), "sign out" (at the end of the procedure). At the first assessment, the checklist was printed and used in 32% of cases and not printed in 41% of cases. Response rate of the survey was fair (19/32 surveys): 14/19 users thought the checklist contributed to improving communication; 15/19 reported improved safety and better management of the animals; 9/19 users avoided mistakes (77% would have omitted the administration of antimicrobial prophylaxis); 10/19 thought it was time consuming. At the second assessment, the checklist was used in 45% of cases (printed but not used in 55%). The use of the sign-out section of the checklist was significantly improved.

Conclusion and clinical relevance: This study illustrates an innovative use of the Delphi method to create a safety checklist. Challenges associated with implementation are reported.

Keywords: veterinary, anesthesia, checklist, Delphi method, implementation, perioperative, safety

OPEN ACCESS

Edited by:
Karine Portier,
Université de Lyon, France

Reviewed by:
Keila Ida,
University of Liège, Belgium
Céline Pouzot-Nevoret,
VetAgro Sup, France
Bruna Santangelo,
VetAgro Sup, France

***Correspondence:**
Mathieu Raillard
mathieu_raillard@yahoo.it

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *11 December 2017*
Accepted: *12 March 2018*
Published: *03 April 2018*

Citation:
Menoud G, Axiak Flammer S, Spadavecchia C and Raillard M (2018) Development and Implementation of a Perianesthetic Safety Checklist in a Veterinary University Small Animal Teaching Hospital. Front. Vet. Sci. 5:60. doi: 10.3389/fvets.2018.00060

INTRODUCTION

Safety checklists are designed to help prevent human errors in complex and high intensity working environments (1). The use of perioperative checklists was shown to reduce mortality and complication rates (2), improve communication and perception of safety in human hospital anesthesia teams (3), and reduce the incidence and severity of complications in veterinary settings (4).

Although a valid anesthesia checklist has been made available by the Association of Veterinary Anaesthetists (AVA),[1] no checklist is universal because critical steps might differ from one institution to another. The AVA checklist does not address the specific safety issues of a large referral practice and therefore, the checklist should be adapted (5, 6).

The Delphi method was first developed by Dalkey and Helmer to obtain a reliable opinion consensus on specific topics (7) by gathering a group of experts to answer questions in three or more rounds. The method was designed to provide consensus in situations where there is conflicting scientific evidence or disagreements (8). Initially, the organizing team collects key questions on the topic of interest and selects suitable experts. In the first round, the experts are invited to express their opinion or to answer specific questions. These opinions or answers are grouped under a limited number of statements. In the second round, each expert ranks the statements in order of importance. Rankings are then summarized. In the third round, after considering the group's response, the experts re-rank each statement and can change their initial ranking. The re-rankings are summarized, and the degree of consensus is assessed. If the degree of consensus is acceptable, the process ceases, if not, the third round is repeated until consensus is achieved. The Delphi method has been used by Tscholl et al. to generate a perianesthetic checklist in a human hospital (3). Applying the Delphi method to develop a perianesthetic checklist for a veterinary teaching hospital might represent an efficient way to obtain an accurate and robust instrument within a short time frame.

Once developed for a specific environment, a safety checklist has to be integrated into the daily clinical routine. This challenging step needs to be planned carefully, as it demands time and commitment from the entire team (5, 6).

The aims of the present study were: (i) to develop a veterinary perianesthetic safety checklist using the Delphi method; (ii) to plan and subsequently evaluate the implementation of this instrument in the clinical routine of a small animal teaching hospital.

MATERIALS AND METHODS

All veterinary anesthesiologists of the Vetsuisse Faculty (University of Bern and Zurich) were invited *via* email to participate in a specialist meeting. The meeting was scheduled for the day that allowed the highest number of participants. The veterinary perianesthetic safety checklist was designed using the World Health Organization (WHO) surgical safety checklist (9) as a model. Three main sections were envisaged: "sign in" (before induction of anesthesia), "time out" (before the beginning of the procedure), and "sign out" (at the end of the procedure). The goal of the meeting was for the experts to agree on a limited number of items to include in each section of the checklist using the Delphi method. The checklist agreed upon at the completion of the third round, was proposed for clinical use in the small animal teaching hospital of the University of Bern.

This first version of the checklist was introduced over a 5-week period and the main investigator (GM) was available to assist users individually. At the end of this period, an evaluation form was distributed to all checklist users (anesthesia clinicians, residents, technicians) and an interdisciplinary meeting was held that included the checklist users and the surgery team. Based on the feedback, a final version of the checklist was created. It was made available in the anesthesia induction area and users were informed orally about the availability of the new checklist. The checklist remained with the animal, kept by the anesthetist together with the anesthesia record throughout the procedure.

Six months later, a 17 question online survey[2] (Data Sheet S1 in Supplementary Material) was sent per email to the anesthetists and the surgeons of the small animal hospital on clinics or having recently used the checklist (32 persons including veterinarians and technicians). It was created using an adaptation of the Safety Attitude Questionnaire (SAQ), an instrument developed to measure perceptions and attitudes in safety-related domains in health care (10), to assess the opinion of the checklist users.

Additionally, during a 3-week period, the main investigator (Gwennaëlle Menoud) observed the use of the checklist in clinical cases using a standard evaluation form (Data Sheet S2 in Supplementary Material). The observation started with the first surgical case of the day and continued according to the daily schedule in order to follow the highest possible number of cases; therefore, case selection was random. The main investigator verified the use of the checklist and noted when items on the checklist were discussed, but not recorded. In addition, she recorded the identity of the checklist user and surgical team, any reluctance to discuss the checklist, and the duration of the "time-out."

Based on the results of the online survey and direct observations, a second implementation phase was deemed necessary. It was decided that the lead anesthesia clinician (one person per day) would be responsible for printing the checklist and ensuring that all staff members would use it. All lead anesthesia clinicians were informed *via* email and during the monthly team meeting. Furthermore, the entire staff of the small animal teaching hospital (clinicians, residents, interns, students, technicians) were invited to a formal oral presentation illustrating the background, usefulness, and correct use of the checklist (including demonstration videos). The pitfalls and causes of failed implementation were discussed to raise user awareness. Three months later, a second evaluation was conducted over 3 weeks, by the main investigator, using the same methodology as previously described. **Figure 1** illustrates the time line of development and implementation of this safety checklist.

[1] https://ava.eu.com/wp-content/uploads/2015/11/AVA-Anaesthetic-Safety-Checklist-FINAL-UK-WEB-copy-2.pdf (Accessed: March 22, 2018).

[2] https://www.google.com/forms (Accessed: March 22, 2018).

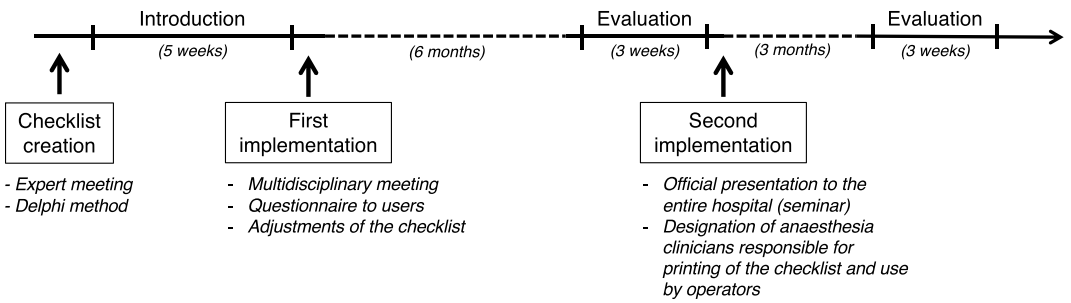

FIGURE 1 | Time line of development, implementation, and evaluation of a perianesthetic safety checklist in the Small Animal Teaching hospital of the University of Bern. The checklist was created in an expert meeting using the Delphi method. The checklist was introduced in the clinics over a 5-week period. After introduction, a survey among the users was made and a multidisciplinary meeting was held, allowing the checklist to be adjusted to practice. Six months later, an evaluation of the use of the checklist was performed over a 3-week period. The tool was implemented a second time following oral introduction of the tool to the team and the designation of a responsible person. A second evaluation was performed 3 months later.

Descriptive statistics were used to summarize the data and a Chi-square test was used to compare checklist use before and after the second implementation phase. SigmaPlot for Windows version 10.0 (Systat Software Inc., San Jose, CA, USA) was used for the analysis and statistical significance was set at $p < 0.05$.

RESULTS

The first expert meeting took place on 22/01/2016 at the University of Bern. A panel of eight diplomates of the European or American College of Veterinary Anesthesia and Analgesia (ECVAA/ACVAA) and seven residents and doctoral students from the veterinary anesthesia sections of the Universities of Bern and Zurich (Switzerland) were gathered.

A first version of the perianesthetic safety checklist was successfully generated using the Delphi method. The two items retained in the "sign in" part of the checklist were: (i) the verification of the animal's identity and (ii) the responsible veterinarian. The panel agreed that it was the responsible veterinarian's responsibility to (i) remain available throughout the procedure and (ii) ensure that the owner gave informed consent for general anesthesia before the procedure so these items did not need to be checked. Four points were highlighted by the Delphi method as equally important in the "time out" section: (i) the introduction of all persons present in the operating room, (ii) the confirmation of the animal's identity, (iii) a clear discussion between the anesthetists and surgeons regarding possible complications; and (iv) the verification of administration of appropriate antimicrobial prophylaxis. In the "sign out" section, two items were retained: (i) the postoperative plan and (ii) the recovery organization. The palpation and emptying of the urinary bladder was considered an important complementary item and was, therefore, included in the checklist, because it was often forgotten and important for the animal's comfort. Following the Delphi, it appeared that the most salient safety issues in our hospital were associated with the suboptimal communication between anesthesia and surgery teams at key time points. This is why, from this step on, the surgery team was present for every decision.

Following the 5-week introduction phase, evaluations were collected. A multidisciplinary meeting including eight surgeons and nine anesthetists, who had used the checklist, contributed to its further adjustment. Elements added to the "time out" section were (i) the display of preoperative radiographs, (ii) the administration of eyedrops, and (iii) the number of swabs available. In the "sign out" section, the swab count was added. The final version of the perianesthetic safety checklist is presented in **Figure 2**.

The response rate to the online survey regarding the final checklist version was fair (19/32 respondents). On a scale from 1 (yes) to 5 (no), 14/19 users thought the checklist contributed to improved communication between surgeons and anesthetists (nine gave a score of 1, five a score of 2); 14/19 reported improved safety and management of the animals (seven respondents scored 1 and seven scored 2); nine users avoided mistakes because of the checklist (all would have omitted the administration of antimicrobial prophylaxis); and 10/19 respondents thought it was time consuming (six respondents scored 1 and four scored 2). Eight users answered the optional section question "Is the checklist used? If not, why?" (possibility to add multiple comments in the option "other"). Three users reported to have no time; one user reported that the checklist was not useful; and one user was unaware of its existence. Two users complained about the unavailability of printed checklists. One user did not use it for short and simple cases. Two users reported they forgot about it in emergency situations.

During the first 3-week evaluation period, direct observations were carried out on 69 anesthetic cases (37/69 were cases undergoing surgery). There were a total of 211 small animals that underwent general anesthesia during that period. The checklist was used in 22/69 (32%) cases, not printed in 28/69 (41%) cases, and printed but not used in 19/69 (27%) cases. The "sign in," "time out," and "sign out" sections were filled out in 14/69 (20%), 32/69 (46%), and 10/69 (14%) cases, respectively. Of the 32 cases in which the "time out" was discussed, 14/32 (44%) were discussed but not written down on the form, whereas 18/32 (56%) were both discussed and recorded. Information exchange during the "time out" was minimal (less than five items discussed) in 2/32 (6%) cases, moderate (between 5 and 8 items discussed) in 17/32

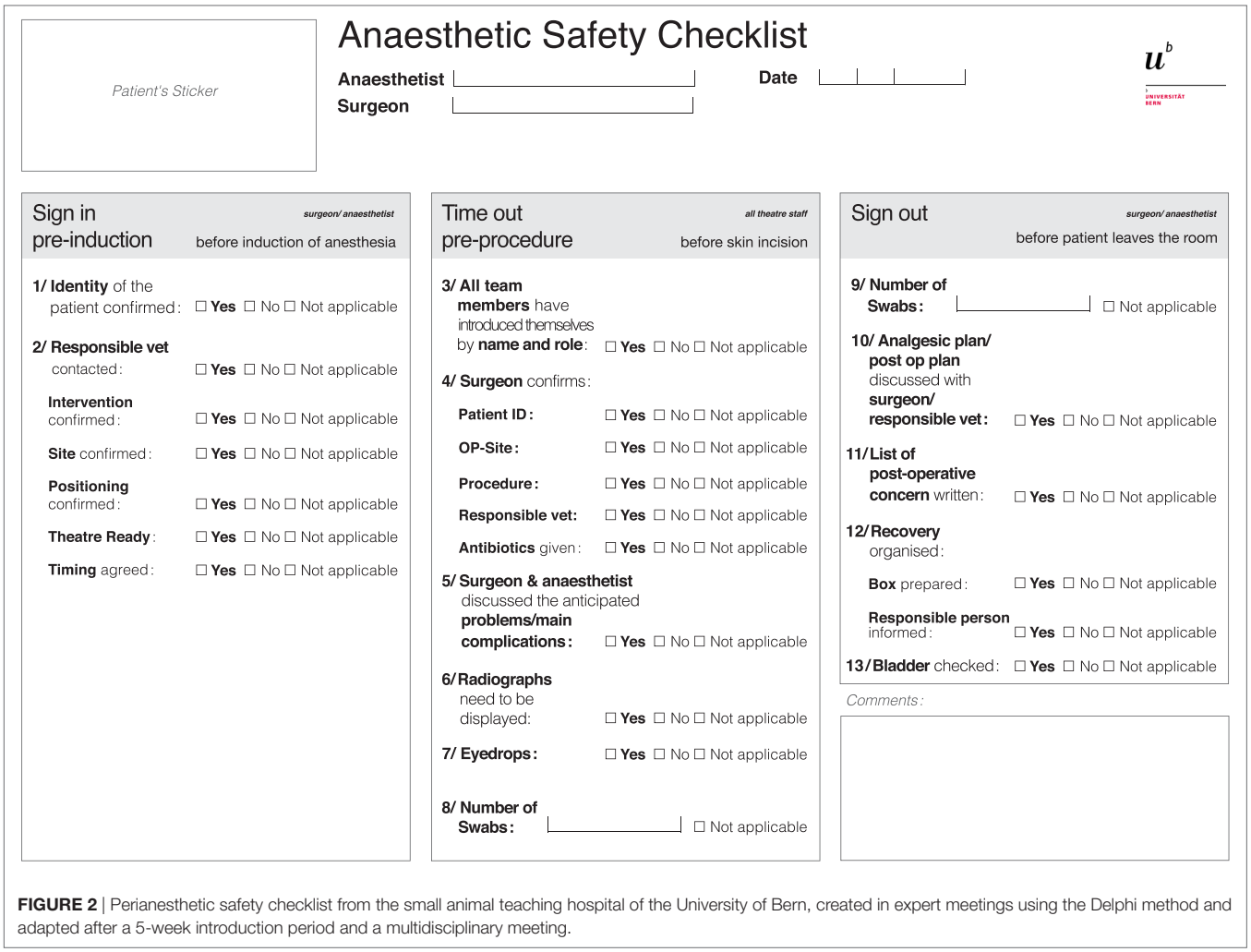

FIGURE 2 | Perianesthetic safety checklist from the small animal teaching hospital of the University of Bern, created in expert meetings using the Delphi method and adapted after a 5-week introduction period and a multidisciplinary meeting.

(53%) cases and satisfactory (>8 items discussed) in 13/32 (41%) cases. The average duration of the "time out" was 25 s.

During direct observation of the second implementation, 64 anesthetic cases were assessed (30/64 were followed by surgery). There were a total of 195 small animals that underwent general anesthesia during that period. The checklist was printed in all cases and used in 29/64 (45%) cases. Overall, the "sign in," the "time out," and the "sign out" were discussed in 17/64 (27%), 29/64 (45%), and 16/64 (25%) cases, respectively. When anesthesia was followed by surgery, the "sign in," "time out," and "sign out" were filled out in 17/30 (57%), 29/30 (97%), and 16/30 (53%), respectively. Of the 29 cases in which the "time out" was discussed, 1/29 (3%) was discussed but not written on the form, whereas 28/29 (97%) were also written down. Information exchange during the "time out" was minimal in 2/30 (7%) cases, moderate in 3/30 (10%) cases, and satisfactory in 25/30 (83%) cases. The average duration of the "time out" was 16 s.

The checklist was printed more after the second implementation ($p = 0.001$). There was no difference in its overall use after the second implementation ($p = 0.158$), but the "time out" was recorded more ($p = 0.001$). The use of the "sign out" section improved after the second implementation ($p = 0.047$).

DISCUSSION

The Delphi method allowed efficient selection of the items to include in the first version of the perianesthetic safety checklist. Indeed, only minor adjustments were necessary to finalize the checklist, once clinical experience had been gathered. Conversely, the introduction of the checklist into the clinical routine was difficult despite the planned implementation. Multiple interventions were required to optimize it. Communication did improve and this was verified by the observation that the "time out" was performed in almost all cases after the second implementation; information exchange was also efficient (more items discussed in a shorter time). Furthermore, based on user feedback, it is likely that the checklist contributed to more regular administration of antimicrobial prophylaxis but the general impact on perioperative safety could not be evaluated.

Checklists should be adapted to the setting in which they are used in Ref. (1, 11). We developed our checklist on the model of the WHO surgical safety checklist, which has proven its efficacy in increasing safety in human care (2), and kept its general tripartite structure. The Delphi method has already been proposed as a suitable method in development of a

perianesthetic safety checklist in a human hospital (3), but a multidisciplinary meeting was necessary to adapt it further to our setting. The final version of the checklist is short, straightforward, and comprehensive. These properties are supposed to facilitate integration into the hospital's routine (12) and reflect steps identified as critical to perianesthetic safety in the clinical routine.

The first implementation of the checklist was not successful in terms of compliance. Several reasons were identified: (i) the lack of a responsible person for the checklist; (ii) the frequent lack of printed copies of the checklist; and (iii) the use of the checklist for all anesthesia cases despite a design best suited for surgical procedures. These reasons probably contributed to the fact that users did not feel involved. A first important change, at the second implementation, consisted of designating responsible people for the printing and the distribution of the checklist. Defining rules and responsibilities were found to be essential in this context (13). Conley et al. mention that it is important to explain to the team members the aim and the use of the checklist before they start using it (13). If an implementation is imposed without introduction, it can be interpreted as constraint and restriction on the freedom of practice (14). If users are not aware of the checklist's benefits and appropriate way of use, they might be uninterested or frustrated (13). In fact, half of the first survey respondents complained that the checklist was time consuming, when in fact time lost during the "time out" discussion was reasonable (25 s). It is likely that the initial introduction of the tool to the entire staff was not efficient enough to be taken seriously in our hospital. Our intention was to correct this with a formal oral presentation to the entire staff. In a normal working day in our small animal hospital, "on" staff includes approximately 20 veterinarians, 25 technicians, and 5–15 final year students (the entire staff being double this); all were invited to the presentation.

Different strategies have been proposed to improve staff member compliance including improved visibility of the checklist such as hanging posters in the operating rooms (14) or adding pink "time out" flyers to the sterile packs (14). Other advertising methods could also be considered such as announcements in the hospital newsletter and website, emails, or the display of the checklist as a screen saver. To date, we have not yet decided our next measures.

The timely administration of prophylactic antibiotics was shown to increase with the use of a safety checklist in some studies (15). The results of our survey show that many respondents had remembered to administer the antimicrobials thanks to the checklist. This could be considered an improvement in safety.

This study had several limitations. First, we had no quantification of the complication rates prior to the checklist introduction, which precludes conclusions on its real benefit in terms of safety. Second, it is possible that the users of the checklist recognized the primary investigator and that her presence influenced the use of the checklist during the periods of clinical evaluation. Third, in many instances, some items of the checklist were actually controlled but not recorded on the document meaning that some data could not be evaluated.

CONCLUSION

The Delphi method can be used to generate a veterinary perianesthetic safety checklist. Responsible persons and clear communication of aim and expectations of the checklist are important when introducing a checklist in the clinical routine. Habits of a university veterinary teaching hospital can be changed, but implementation of a perianesthetic checklist can be a challenging process.

AUTHOR CONTRIBUTIONS

GM: data collection, analysis, interpretation, and redaction of the paper. SF and CS: study design, data analysis and interpretation, and redaction of the paper. MR: study design, data collection, analysis, interpretation, redaction of the paper.

ACKNOWLEDGMENTS

The authors thank the veterinary anesthesia section of the Vetsuisse Faculty, University of Zürich and the small animal surgery team of the Vetsuisse Faculty, University of Bern for their contribution to the design and implementation of the checklist.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fvets.2018.00060/full#supplementary-material.

DATA SHEET S1 | Individual evaluation of the checklist by the user (anesthetist and surgeon).

DATA SHEET S2 | Evaluation form used to evaluate the three parts of the anesthesia procedure.

REFERENCES

1. Borchard A, Schwappach DLB, Barbir A, Bezzola P. A systematic review of the effectiveness, compliance, and critical factors for implementation of safety checklists in surgery. *Ann Surgery* (2012) 256:925–33. doi:10.1097/SLA.0b013e3182682f27
2. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AHS, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* (2009) 360(5):491–9. doi:10.1056/NEJMsa0810119
3. Tscholl DW, Weiss M, Kolbe M, Staender S, Seifert B, Landert D, et al. An anesthesia preinduction checklist to improve information exchange, knowledge of critical information, perception of safety, and possibly perception of teamwork in anesthesia teams. *Anesth Analg* (2015) 121:948–56. doi:10.1213/ANE.0000000000000671
4. Bergström A, Dimopoulou M, Eldh M. Reduction of surgical complications in dogs and cats by the use of a surgical safety checklist. *Vet Surg* (2016) 45:571–6. doi:10.1111/vsu.12482
5. Leape LL. The checklist conundrum. *N Engl J Med* (2014) 370:1063–4. doi:10.1056/NEJMe1315851
6. McMillan M. Checklists in veterinary anaesthesia: why bother? *Vet Rec* (2014) 175:556–9. doi:10.1136/vr.g7515
7. Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. *Manage Sci* (1963) 9:458–67. doi:10.1287/mnsc.9.3.458

8. Jones J, Hunter D. Qualitative research: consensus methods for medical and health services research. *BMJ* (1995) 311:376–80. doi:10.1136/bmj.311.7001.376
9. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AHS, Dellinger EP, et al. Changes in safety attitude and relationship to decreased postoperative morbidity and mortality following implementation of a checklist-based surgical safety intervention. *BMJ Qual Saf* (2011) 20:102–7. doi:10.1136/bmjqs.2009.040022
10. Sexton JB, Helmreich RL, Neilands TB, Rowan K, Vella K, Boyden J, et al. The safety attitudes questionnaire: psychometric properties, benchmarking data, and emerging research. *BMC Health Serv Res* (2006) 6:44. doi:10.1186/1472-6963-6-44
11. de Vries EN, Hollmann MW, Smorenburg SM, Gouma DJ, Boermeester MA. Development and validation of the SURgical PAtient Safety System (SURPASS) checklist. *Qual Saf Health Care* (2009) 18:121–6. doi:10.1136/qshc.2008.027524
12. Blanco M, Clarke JR, Martindell D. Wrong site surgery near misses and actual occurrences. *AORN J* (2009) 90:215–22. doi:10.1016/j.aorn.2009.07.010
13. Conley DM, Singer SJ, Edmondson L, Berry WR, Gawande AA. Effective surgical safety checklist implementation. *J Am Coll Surg* (2011) 212:873–9. doi:10.1016/j.jamcollsurg.2011.01.052
14. Norton EK, Rangel SJ. Implementing a pediatric surgical safety checklist in the OR and beyond. *AORN J* (2010) 92:61–71. doi:10.1016/j.aorn.2009.11.069
15. Weiser TG, Haynes AB, Dziekan G, Berry WR, Lipsitz SR, Gawande AA, et al. Effect of a 19-item surgical safety checklist during urgent operations in a global patient population. *Ann Surg* (2010) 251:976–80. doi:10.1097/SLA.0b013e3181d970e3

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor and reviewer KI declared their involvement as co-editors in the Research Topic and confirmed the absence of any other collaboration.

frontiers in Veterinary Science

PERSPECTIVE
published: 08 June 2018
doi: 10.3389/fvets.2018.00096

Advanced Atrio-Ventricular Blocks in a Foal Undergoing Surgical Bladder Repair: First Step to Cardiac Arrest?

Vincent Marolf [1]¶, Alessandro Mirra [1], Nathalie Fouché [2] and Cristobal Navas de Solis [2]¶*

[1] Department of Clinical Veterinary Science, Division of Anaesthesiology and Pain Treatment, Vetsuisse Faculty, University of Bern, Bern, Switzerland, [2] Swiss Institute of Equine Medicine (ISME), Vetsuisse-Faculty, University of Bern and Agroscope, Bern, Switzerland

OPEN ACCESS

Edited by:
Karine Portier,
VetAgro Sup, France

Reviewed by:
Agnes E. M. Benamou-Smith,
VetAgro Sup, France
Tristan Merlin,
VetAgro Sup, France
Regula Bettschart,
Universität Zürich, Switzerland

***Correspondence:**
Vincent Marolf
vincent.marolf@uliege.be

¶ Present Address:
Vincent Marolf
Centre Vétérinaire Médi-Vet SA, Lausanne, Switzerland
Cristobal Navas de Solis
Texas Veterinary Medical Center, Texas A&M University, TX, College Station, United States

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: 13 December 2017
Accepted: 20 April 2018
Published: 08 June 2018

Citation:
Marolf V, Mirra A, Fouché N and Navas de Solis C (2018) Advanced Atrio-Ventricular Blocks in a Foal Undergoing Surgical Bladder Repair: First Step to Cardiac Arrest? Front. Vet. Sci. 5:96. doi: 10.3389/fvets.2018.00096

A 3-day-old Swiss Warmblood colt was diagnosed with uroabdomen after urinary bladder rupture. The foal had classical electrolyte abnormalities (hyponatremia, hypochloremia and hyperkalemia) on presentation. The foal was supported prior to surgery with intravenous fluids and the electrolyte abnormalities were treated with physiologic saline, glucose and insulin. Urine could not be drained from the abdomen prior to surgery because the omentum was continuously occluding the drainage cannula and due to progressive abdominal distension, it was decided to pursue surgery without further correction of electrolyte abnormalities. After induction of anaesthesia, signs of hypoxemia were present. Controlled mandatory ventilation using a pressure-controlled ventilation mode with positive end-expiratory pressure was initiated. Urine was drained from the abdomen by free flow. Atrio-ventricular (AV) blocks unresponsive to intravenous antimuscarinic drugs developed. After low dose of epinephrine and cardiac massage, sinus rhythm was restored. Surgery was completed successfully and the foal recovered from anaesthesia. The postoperative period was uneventful and the foal was discharged from the hospital three days later. Based on a clinical case, the purpose of the manuscript is to provide the clinician with potential causes, prevention and treatment of this already known but rarely observed dysrhythmia which could lead to fatal consequences. Definitions of cardiac arrest and asystole are reappraised. We discuss the fact that advanced AV-blocks should be treated as a cardiovascular emergency with advanced life support. The early recognition of advanced AV blocks is the first step to reduce perioperative mortality and morbidity of foal suffering from uroabdomen.

Keywords: uroperitoneum, bradycardia, atropine, arrhythmia, hypotension

DESCRIPTION

A 3-day-old 60 kg Swiss Warmblood colt was presented to the university veterinary hospital approximately two hours after the onset of clinical symptoms observed by the owner in the morning. The foal was recumbent, tachycardic (160 beats/minute), tachypneic (60 breaths/minute), with abdominal distention, pale-pink mucous membranes and a capillary refill time of 2.5 s. Uroperitoneum due to a ruptured bladder was diagnosed with abdominal ultrasonography and peritoneal fluid aspirate analysis (yellow, cloudy aspirate; creatinine 1evel: 1,264 μmol/l). Surgical bladder repair after medical stabilization was planned. Complete blood count analyzed at initial presentation revealed leukocytosis with left shift, lymphopenia and monocytosis. Complete serum biochemistry revealed hyponatremia, hyperkalemia, hypochloremia,

normocalcemia, (Na+: 107 mmol/l, K+: 4.9 mmol/l; Cl- 71 mmol/l, Ca2+: 3.24 mmol/l), hyperglycemia (11.71 mmol/l), azotemia (BUN: 10.01 mmol/l, creatinine: 327 µmol/l) and increased activities of liver enzymes. Packed cell volume and total solids were measured at 46% and 71.2 g/l; respectively. Fluid therapy with 3 litres of 0.9% NaCl given as bolus followed by 5% glucose solution in saline solution at 5 ml/kg/hr and an intramuscular injection of insulin 0.1 IU/kg (Novo Rapid, Novo Nordisk, Switzerland) were initiated. Abdominal distension increased due to inability to drain the uroabdomen as the omentum repeatedly occluded the abdominal drain. Plasma electrolytes, glucose and lactate were controlled after four hours (Na+: 113 mmol/l, K+: 5.9 mmol/l; Cl- 77 mmol/l, glucose: 9.4 mmol/l, lactate: 2.1 mmol/l) and it was decided to perform the surgery despite the electrolyte imbalances. The foal was premedicated with butorphanol 0.05 mg/kg IV (Morphasol, Dr. E. Graeub, Switzerland) and diazepam 0.1 mg/kg IV (Valium, Roche, Switzerland) and general anaesthesia was induced with ketamine 1 mg/kg IV (Narketan, Vetoquinol, Switzerland) and propofol 1.5 mg/kg IV (Propofol, Fresenius Kabi, Germany). The trachea was intubated with a 12 mm cuffed silicone endotracheal tube which was connected to a circle system anaesthesia machine (Fabius, Dräger Medical, Germany). Anaesthesia monitoring (multiparameter analyzer, Datex Ohmeda S5, GE Healthcare, USA) consisted of a 3-lead base apex ECG lead II derivation, hemoglobin saturation by pulse oximetry, end-tidal carbon dioxide ($ETCO_2$) and inspired fraction of oxygen (FiO_2) with gas analyzer and invasive and non-invasive blood pressure. Blood pressure was monitored with an inflatable cuff placed at the base of the front limb and with an invasive arterial 22-gauge catheter placed in the facial artery. Fluid therapy administered during anaesthesia was based of saline solution 0.9% (10 ml/kg/hr) supplemented with glucose 5% (glucose: 0.5 g/kg/hr). Anaesthesia was maintained with isoflurane (Attane Isoflurane, Provet, Switzerland) in oxygen with a fresh gas flow set a 2 L/min. The foal was breathing spontaneously and the first recorded pulse oximetry measurement indicated an oxygen saturation of 78% (FiO_2 0.87). Thus, five minutes after connection to the anaesthesia machine, controlled mandatory ventilation with high peak inspiratory pressure (PIP: 40 cmH_2O) and positive end-expiratory pressure (PEEP: 5 cmH_2O) was initiated. An arterial blood gas analysis was performed revealing following values: pH: 7.27; PaO_2: 3.2 kPa, 61.9 mmHg; $PaCO_2$: 6 kPa, 45.2 mmHg; HCO3-: 19.7 mmol/l; TCO2: 21.1 mmol/l; BE: −5.8; Lactate: 2.6 mmol/l; Na+: 113 mmol/l; K+: 4.9 mmol/l; Cl-: 81: mmol/l. One puff of nebulized salbutamol (100 mcg; Ventolin, GlaxoSmithKline AG, Switzerland) was delivered via endotracheal tube. Because of mild hypotension (invasive mean arterial pressure of 60 mmHg) dobutamine (Dobutrex, Teva Pharma, Switzerland) at 0.6 mcg/kg/min has been initiated. A normal sinus rhythm of 90 beats/minute was recorded before surgical incision. A midline abdominal incision was performed and approximately 10–12 liters of intraabdominal fluids were released by free flow over approximately thirty seconds. Cardiac dysrhythmia with long periods of absent atrioventricular conduction (see **Figure 1**) developed. P-P and P-R intervals did appear to be slightly irregular but each QRS complex was always preceded by a P-wave. QRS complexes did not appear wide and bizarre. Progressive decrease of the $ETCO_2$ (from 6 kPa; 45 mmHg to 2.9 kPa; 22 mmHg) values were observed. Periods of advanced atrioventricular blocks were characterized by the absence of pulse oximeter and invasive blood pressure waves. After development of

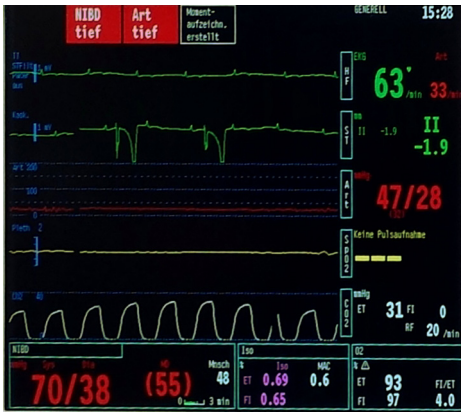

FIGURE 1 | Monitor screen capture taken during anaesthesia of a foal undergoing surgical bladder repair. Advanced 2nd or 3rd degree atrioventricular blocks with intermittent ventricular contractions were observed. The pulse oximetry and invasive blood pressure measurement correlate with the top line of the electrocardiogram (ECG) and illustrate absent pulse pressure waves when ventricular rhythm was not recorded. The bottom line of the ECG was recorded before the top line.

AV blocks, dobutamine administration was stopped and atropine 0.02 mg/kg IV (Atropinsulfat, Amino, Switzerland) was given. Because no improvements in the rhythm was observed, four additional doses of atropine were injected (0.01–0.02 mg/kg IV), but none was successful. Thereafter, a prolonged period of ventricular asystole occurred (approximately 30 s), intravenous epinephrine 0.01 mg/kg was administered, the isoflurane vaporizer was turned off, the foal placed in lateral recumbency and chest compressions (approximately 120/minute) were initiated. A sinus tachycardia at 130 beats/minute was observed. Normocapnia was restored within 30 s of cardiopulmonary resuscitation (CPR). Electrolytes concentrations (Na+: 116 mmol/l, K+: 6.3 mmol/l; Cl- 89 mmol/l) and arterial blood gas analysis (PaO2: 29.6 kPa, 222 mmHg; PaCO2: 7.8 kPa, 58.7 mmHg) were measured shortly after CPR. No more cardiac dysrhythmias were observed, surgery was completed within 100 min and total anaesthesia time was 160 min. Efforts to keep normothermia during anaesthesia included: use of a medical forced-air warming device, abdominal flushing with fluids at body temperature and administration of warm IV fluid therapy during anaesthesia. The lowest temperature was measured at the end of anaesthesia (37.4°C). The foal exhibited signs of excitement (paddling, shaking) during recovery which resolved after 10 min of manual restraint. The day after surgery, blood work was repeated, showing the following values (Na +128 mmol/l, K + 3.5 mmol/l, Cl- 109 mmol/l, iCa ++ 1.54 mmol/l, glucose 9.0 mmol/l, lactate 1.9 mmol/l). The postoperative period was uneventful and the foal was discharged three days later. Eighteen months later the owner reported that the foal had been healthy since discharge. Written signed owner consent had been obtained for publication of the present case.

DISCUSSION

Atrioventricular blocks are classified in first, second or third degree. First degree AV block is defined as a prolongation of PR interval (>500 ms in the adult horse). This implies that all atrial electrical

signals are conducted to the ventricle despite being delayed. Second degree AV block is characterised by the intermittent absence of electrical conduction from the atria to the ventricles which result in P waves not followed by QRS complexes. This rhythm can be physiological and is often recorded in horses at rest. This type of block is further classified in Mobitz type I (Wenkebach phenomenon) or Mobitz type II. Type I is characterised by a progressive lengthening of the PR-Interval which is succinctly followed by a single isolated P wave. Type II is independent of the PR Interval which remains identical for all the complexes. Second degree AV block can also have severe hemodynamic consequences if succint P-waves are not conducted. It is then called "advanced" or "high-grade" 2nd degree AV block. Third degree AV block is defined by the absence of atrioventricular conduction. Atrial and ventricular electrical activities are dissociated and a ventricular escape rhythm often develops (1, 2).

The choice of discontinuing the continuous rate infusion of dobutamine was based on its possible arrhythmogenic properties (3). However, if the anaesthetist wishes to increase cardiac conduction and contractility, the right decision would be to increase the dose of administration. After careful consideration, the authors do believe that increasing the dose of dobutamine might remain a valid choice. Dopamine does also have arrhythmogenic properties and the use of a dose of ≥5 μg/kg/min has been suggested to treat advanced 2nd or 3rd AV blocks in foals (4, 5). At this specific dose, the effect on β1 and β2 receptors predominate and lead to increase in heart rate, cardiac output and myocardial contraction (6). This increase might be responsible for improvement in conduction and elimination of AV blocks (4). Intravenous epinephrine has had the potential to convert ventricular asystole to "rapid sinus rhythm" (7) and should be considered as emergency drug whenever atropine fails to convert advanced AV block into sinus rhythm. Epinephrine is derived from dopamine and both molecules are linked in their mechanism of action. At low doses (0.01 mg/kg), epinephrine principally acts on β1 and β2 receptors (6) and the same mechanism of action as dopamine might explain its success in the treatment of advanced AV blocks. According to their findings, the authors speculate that epinephrine and its biosynthetic precursor pathway molecules (dopamine, norepinephrine) might successfully treat advanced AV blocks when IV administrations of atropine is ineffective (7). Norepinephrine has been suggested as a suitable drug during cardiac arrest or CPR in clinical cases and experimental models (8, 9). Atropine as first treatment for advanced AV blocks needs to be considered; but whenever the drug fail to convert advanced AV block into sinus rhythm, administration of norepinephrine or its derivatives should be considered promptly.

The rhythm observed in this colt may be better defined as high grade 2nd degree AV block as ventricular activity was triggered after P waves and the QRS complexes remained of normal morphology. However, 3rd degree AV block remains a valid differential diagnosis for the observed rhythm. A definitive classification of the dysrhythmia could have been obtained with continuous ECG recording including several leads derivation. Unfortunately, valid record of the observed rhythm is not available, precluding a definitive classification. We are unaware of a duration of second degree AV block or the number of non-conducted P waves being part of the distinction between 2nd and 3rd degree AV block.

Advanced heart blocks during general anaesthesia of foals with or without uroperitoneum have been reported (4, 7, 10). Electrolyte imbalance such as hyperkalemia, hyponatremia and hypochloremia usually associated with ruptured urinary bladder do appear to precipitate cardiac arrhythmia. Much has been written about importance of hyperkalemia in the foal with uroperitoneum (11–13). The rise of extracellular plasma level reduces the resting potential across the cell membrane. An initial increase in tissue excitability is usually observed with mild hyperkalemia and followed by decreased excitability as plasma potassium level rises further. This leads to a reduction in conduction velocity at the sinus node, intraatrial and AV node. An additional increase in parasympathetic tone can further reduce conduction of the AV node and might induce complete AV blocks (14). Purkinje fibers seem to be even more sensitive to hyperkalemia than AV or sinus node, therefore precipitating the occurrence of AV blocks (15). Hyperkalemia should be treated promptly whenever diagnosed and fluid therapy should be initiated. The choice of NaCl 0.9% has been driven by the lower sodium and chloride venous content of the foal. Fluid therapy can be supplemented with glucose 2.5–5% to promote insulin production and consequent intracellular uptake of potassium ions. Insulin itself can be directly administered. Other treatment options include the administration of sodium bicarbonate administration (1–2 mEq/kg slow IV over 15 min). Bicarbonate stimulates the extracellular release of hydrogen ions and stimulates the intracellular uptake of potassium ions. This exchange maintains electroneutrality and consequently lowers serum potassium level (16). Calcium-gluconate (4 mg/kg slow IV over 10–20 min) can also be administered (17). It does not lower potassium plasma concentrations but calcium offers an indirect cardioprotective effect by increasing threshold voltage, restoring the normal resting membrane potential previously increased by hyperkalemia. The use of β2-adrenergic agonist drugs such as nebulised salbutamol or injected terbutaline have also been used successfully to decrease hyperkalemia (18, 19). The mechanism of action is thought to be linked to the stimulation of the Na^+/K^+-ATPase. This case illustrates the difficulty in normalizing potassium plasma concentrations despite implementation of the above-mentioned treatments. In this case, it would have been wise to prolong the pre-operatory efforts of electrolyte stabilization and abdominal drainage. It is important to consider that the absence of hyperkalemia in foals with uroperitoneum does not exclude the occurrence of anaesthetic complications in the form of AV block or conduction block (13).

Sudden decrease of intraabdominal pressure when urine is drained rapidly has the potential to induce cardiovascular collapse. A vasovagal reflex may have been triggered by the release of urine by free flow from the abdomen. Decreased venous return to the heart may have been generated by massive inspiratory pressure through vena cava compression and sudden venous blood pooling in the mesenteric vasculature. This might have been the main trigger for advanced atrioventricular block in this case. Similar cardiovascular consequences (3rd degree AV block) have been reported after hot peritoneal lavage (20); the authors suggested that the peritoneal lavage had triggered a vasovagal reflex. It has been suggested to drain urine slowly to avoid atrioventricular block and arrhythmias (7, 11) and this would likely have been beneficial in the case reported here. The potential causes include dorsal recumbency, heat applied to the foal to prevent hypothermia, pulling on abdominal organs or intraabdominal pressure changes.

Atropine is the treatment of choice for many bradyarrhythmias such as vagally mediated bradycardia or bradyasystolic cardiac arrest (21). Atropine has been successful to treat 3rd degree AV block (20) but does not always seem effective to treat advanced AV block as illustrated in the present case. Paradoxical bradycardia or hypothermia are potential causes for the lack of efficacy of atropine. Those reasons do not to apply to this specific case and the explanation for treatment failure of atropine in patients encountering advanced AV-blocks remains unknown.

Another proarrhythmic factor that could have contributed to AV block in the present case was hypoxemia (22). To maintain an adequate level of saturated haemoglobin with oxygen, recruitment of collapsed alveoli by applying higher PIP together with PEEP and increasing the inspired fraction of oxygen was attempted. Unfortunately, those manoeuvres are likely detrimental to coronary perfusion which is essential to maintain adequate oxygen delivery to the heart and prevent myocardial hypoxia. Those manoeuvres have minor benefits as long as a high volume of intraabdominal fluids are exerting pressure on the diaphragm consequently compressing the lungs. An effective therapy will be the release of intraabdominal pressure. The anaesthetist and surgeon should coordinate this step and balance the slow release of intraabdominal fluids to enable lung expansion and prevent cardiovascular consequences related to the rapid release of intraabdominal pressure.

The analgesic protocol may have been suboptimal. The prolonged period of intraabdominal pressure could have contributed to increased sympathetic activity. When intraabdominal pressure due to uroperitoneum was released, the sympathetic stimuli has suddenly been released and might have triggered a reduction of nociception which potentiated the arrhythmogenesis.

The pathophysiology of cardiovascular complications during anaesthesia of the foal with uroperitoneum is likely to be multifactorial. The potential causes mentioned and the intrinsically immature sympathetic nervous system of neonates might induce detrimental cardiovascular consequences and promote life threatening cardiac arrhythmias.

After recovery, the discussion of whether the observed cardiac dysrhythmia could be called "cardiac arrest" was raised. According to the American Heart Association scientific statement, cardiac arrest is defined as "the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation" (23). This suggests that the electrical activity without the presence of a pulse pressure could be called "cardiac arrest". No arterial pressure waves were detected during prolonged advanced AV block and $ETCO_2$ progressively decreased. Team training and preparation, uninterrupted chest compressions ("push hard, push fast") at a rate of 100–120/minutes, ventilation provided by short breaths at a rate of 10–20/min and the administration of low-dose epinephrine (0.01 mg/kg IV or 0.1 mg/kg intratracheal) are considered key points for successful resuscitation during cardiac arrest. Those guidelines are the actual recommendations regarding CPR in the neonatal foal (24). Providing advanced life support through CPR is essential to rapidly restore return of spontaneous in case of cardiac arrest. Considering that cardiac mechanical activity was absent in the present foal and that CPR enabled restoration of normal sinus rhythm and adequate cardiovascular functions, it seems reasonable to call the observed clinical scenario "cardiac arrest", consequence of advanced AV block. Advanced second AV blocks might be "the first step" to cardiac arrest because they might have dramatic cardiovascular consequences and should be considered and treated as cardiac arrest. It is interesting to note that Richardson and Kohn (10) observed severe cardiac arrhythmias in 9 foals undergoing halothane anaesthesia for uroperitoneum repair. They described 6 of these foals as having "3rd degree AV or cardiac arrest" while the authors would suggest advanced 3rd degree AV block is a cardiac arrest.

Another terminology discussion was pertaining to the term asystole. "Asystole" (from Greek: "a" =privative prefix, "systole" =contraction) has been defined as "the complete lack of electrical activity in the heart" (25) and is colloquially called "flat-line". Jacobs et al. (23) stated that "although a specific definition of asystole is desirable, no consensus agreement was reached on either a specific duration (e.g., 30 s) or heart rate (e.g., <5 bpm) to define asystole versus bradycardia/pulseless electrical activity". Etymologically speaking asystole refers to lack of mechanical activity. Lack of electrical activity always leads to lack of mechanical activity but the reverse is not always true. These definitions are centred on electrical or mechanical ventricular activity and AV blocks are difficult to fit here *sensu stricto* due to the presence of electrical and likely mechanical atrial activity in these cases.

CONCLUSION

Based on this clinical scenario, we do believe that advanced AV block is a severe cardiovascular dysrhythmia that, according to the revised definitions, could be called and treated as cardiac arrest. Foals with uroperitoneum can encounter severe disturbances in cardiovascular homeostasis through advanced AV block which might be life threatening. Consequently, the anaesthesiologist should work with the internist and surgeon in the preoperative and operative management and be ready to provide advanced life support any time severe arrhythmias occur. Treatment toward the cause of the blocks should be favoured. This will prevent cardiac arrest or asystole and decrease morbidity and mortality.

ETHICS STATEMENT

Signed owner consent was obtained for publication.

AUTHOR CONTRIBUTIONS

VM was responsible for the anaesthetic management of the foal. He wrote the manuscript and revised the definitions presented in the paper. AM took part to the anesthetic management of the foal. He recorded all datas and participated to the redaction of the manuscript. NF was responsible for the medical management of the case and for the pre-and post-operative care. She participated the redaction of the manuscript. CN was responsible for the medical management of the case. He participated to the redaction of the manuscript and revised the definitions presented in the paper.

REFERENCES

1. Pariaut R, Reynolds C, Bednarski RM, Muir WW, Pariaut R, Reynolds C et al Bradyarrhytmias and conduction disturbances. In: Silverstein DC, Hopper K, editors. *Small Animal Critical Care*. 2nd ed. St. Louis: Saunders Elsevier (2014). p. 246–9.
2. Marr CM, Reef VB. Dysrhythmias: assessment and medical management. In: Marr CM, Bowen M, editors. *Cardiology of the Horse*. 2nd ed.↑ Philadelphia: Saunders Elsevier (2010). p. 159–78.
3. Bednarski RM, Muir WW. Arrhythmogenicity of dopamine, dobutamine, and epinephrine in thiamylal-halothane anesthetized dogs. *Am J Vet Res* (1983) 44(12):2341–3.
4. Whitton DL, Trim CM. Use of dopamine hydrochloride during general anesthesia in the treatment of advanced atrioventricular heart block in four foals. *J Am Vet Med Assoc* (1985) 187(12):1357–61.
5. Trim C., M, Shepard M. K. Horses with colics. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary Anesthesia and Analgesia*. 5th ed. New Jersey, United States: Wiley Blackwell (2015). p. 867–85.
6. Murrell JC. Adrenergic Agents. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary Anesthesia and Analgesia*. 5th ed. New Jersey, United States: Wiley Blackwell (2015). p. 183–95.
7. Haga HA, Risberg Å, Strand E. Resuscitation of an anaesthetised foal with uroperitoneum and ventricular asystole. *Equine Vet Educ* (2011) 23(10):502–7. doi: 10.1111/j.2042-3292.2011.00233.x
8. Mion G, Rousseau JM, Selcer D, Samama CM. Cardiac arrest: should we consider norepinephrine instead of epinephrine? *Am J Emerg Med* (2014) 32(12):1560.e1–e2. doi: 10.1016/j.ajem.2014.05.046
9. Lindner KH, Ahnefeld FW, Schuermann W, Bowdler IM. Epinephrine and norepinephrine in cardiopulmonary resuscitation. Effects on myocardial oxygen delivery and consumption. *Chest* (1990) 97(6):1458–62.
10. Richardson DW, Kohn CW. Uroperitoneum in the foal. *J Am Vet Med Assoc* (1983) 182(3):267–71.
11. Love EJ. Anaesthesia in foals with uroperitoneum. *Equine Vet Educ* (2011) 23(10):508–11. doi: 10.1111/j.2042-3292.2011.00258.x
12. Wilkins PA, Dunkel B. Rupture of the urinary bladder. In: Paradis MR, editor. *Equine neonatal medicine*. Philadelphia: Elsevier Saunders (2006). p. 237–45.
13. Dunkel B, Palmer JE, Olson KN, Boston RC, Wilkins PA. Uroperitoneum in 32 foals: influence of intravenous fluid therapy, infection, and sepsis. *J Vet Intern Med* (2005) 19(6):889–93. doi: 10.1111/j.1939-1676.2005.tb02783.x
14. Muir WW. Cardiovascular physiology. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary Anesthesia and Analgesia*. 5th ed. New Jersey, United States: Wiley Blackwell (2015). p. 417–72.
15. Kim NH, Oh SK, Jeong JW. Hyperkalaemia induced complete atrioventricular block with a narrow QRS complex. *Heart* (2005) 91(1):e5. doi: 10.1136/hrt.2004.046524
16. Riordan LL, Schaer M. Potassium disorders. In: Silverstein DC, Hopper K, editors. *Small Animal Critical Care*. 2nd ed. St. Louis: Saunders Elsevier (2014). p. 269–73.
17. Jesty SA. Cardiovascular System. In: Orsini JA, Divers TJ, editors. *Equine emergencies, treatment and procedures*. 4th ed. St. Louis: Saunders Elsevier (2014). p. 124–56.
18. Mahoney BA, Smith WA, Lo DS, Tsoi K, Tonelli M, Clase CM. Emergency interventions for hyperkalaemia. *Cochrane Database Syst Rev* (2005) 18(2):CD003235. doi: 10.1002/14651858.CD003235.pub2
19. Langdon Fielding C. Potassium homeostasis and derangements. In: Langdon Fielding C, Gary Magdesian K, editors. *Equine Fluid Therapy*. New Jersey, United States: Wiley Blackwell (2015). p. 27–44.
20. Nannarone S, Vuerich M, Moriconi F, Moens Y. Hot peritoneal lavage fluid as a possible cause of vasovagal reflex during two different surgeries for bladder repair in a foal. *J Equine Vet* (2016) 36:5–9. doi: 10.1016/j.jevs.2015.10.006
21. Lerche P. Anticholinergics. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary Anesthesia and Analgesia*. 5th ed. New Jersey, United States: Wiley Blackwell (2015). p. 178–82.
22. Berne RM, Belardinelli L. Effects of hypoxia and ischaemia on coronary vascular resistance, A-V node conduction and S-A node excitation. *Acta Med Scand Suppl* (1985) 694:9–19. doi: 10.1111/j.0954-6820.1985.tb08795.x
23. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation* (2004) 110(21):3385–97. doi: 10.1161/01.CIR.0000147236.85306.15
24. Jokisalo JM, Corley KT. CPR in the neonatal foal: has RECOVER changed our approach? *Vet Clin North Am Equine Pract* (2014) 30(2):301–16. doi: 10.1016/j.cveq.2014.04.010
25. Ehrlich A, Schroeder CL. Chapter 5: The cardiovascular System. In: Seeley, M M, Bellegarde M, editors. *Medical Terminology for Health Profession*. 7th ed. USA: Delmar, Cengage learning (2013). p. 146.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewers TM, AB-S and handling Editor declared their shared affiliation.

frontiers in Veterinary Science

CASE REPORT
published: 22 June 2018
doi: 10.3389/fvets.2018.00138

Successful Cardiopulmonary Resuscitation in a Sevoflurane Anaesthetized Horse That Suffered Cardiac Arrest at Recovery

Clara Conde Ruiz[1]* *and Stéphane Junot*[1,2]

[1] Service d'Anesthésie, VetAgro Sup, Université de Lyon, Marcy L'Etoile, France, [2] Unité APCSe, Agressions Pulmonaires et Circulatoires dans le sepsis, VetAgro Sup, Université de Lyon, Marcy L'Etoile, France

A 17-year-old mare undergoing dental surgery suffered a cardiac arrest while being transferred from the surgical theatre to the recovery box. This complication was diagnosed early, thus allowing a prompt start to the cardiopulmonary resuscitation maneuvers. External thoracic compressions, intermittent positive pressure ventilation, and adrenaline administration were at the core of this successful resuscitation. Although it was not possible to confirm the cause of cardiac arrest in this horse, a Bezold-Jarisch reflex due to potential decrease on venous return because of postural change and drug interactions was hypothesized. Based on this report, it appears advisable to smoothly change the position of anaesthetized patient; furthermore, the administration of drugs affecting cardiovascular hemodynamics or sympatho-vagal balance to animals while changing their recumbency should be avoided.

Keywords: horse, cardiac arrest, CPR, bezold jarisch, complications, anaesthesia

OPEN ACCESS

Edited by:
Keila Ida,
University of Liège, Belgium

Reviewed by:
Miguel Gozalo Marcilla,
Faculty of Veterinary Medicine of Botucatu, Brazil
Patrick Michael Burns,
University of Bristol, United Kingdom

***Correspondence:**
Clara Conde Ruiz
cconderuiz@gmail.com

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *14 December 2017*
Accepted: *04 June 2018*
Published: *22 June 2018*

Citation:
Conde Ruiz C and Junot S (2018) Successful Cardiopulmonary Resuscitation in a Sevoflurane Anaesthetized Horse That Suffered Cardiac Arrest at Recovery. Front. Vet. Sci. 5:138. doi: 10.3389/fvets.2018.00138

INTRODUCTION

A perioperative mortality rate from 0.12 to 0.9% has been reported in non-colic horses (1, 2). Despite the advances and improvements in equine anaesthesia, mortality rate remains still high (3). A third of these fatalities is due to cardiac arrest, as reported in sick and healthy horses (1). Severe debilitating diseases and anaesthetic drugs-related factors have been described as leading causes of cardiac arrest in horses (1). The occurrence of cardiac reflexes following change of hemodynamic conditions may also lead to this complication.

Peri-anaesthetic cardiac arrest, despite being uncommon, carries a poor outcome in horses (1, 2, 4), mainly because of the difficulties performing cardiopulmonary resuscitation (CPR) maneuvers in this specie. An early detection of the complication and a trained staff are key-points for the potential success of CPR. The present case aimed to describe the successful detection and treatment of a cardiac arrest occurring after a postural change during the recovery phase of anaesthesia in a horse.

BACKGROUND

Written informed consent was obtained from the owner for the publication of this case report. A 17-year-old Hanoverian mare, 550 kg, was admitted to the Equine Hospital for surgical removal of a fractured tooth (tooth #308, modified Triadan Tooth Numbering System of equine dental nomenclature). Preoperative physical examination, electrocardiography (ECG) and blood tests

were unremarkable. Therefore, the American Society of Anaesthesiologists (ASA) physical status was classified as two. Due to the complexity of the surgical procedure, the mare was scheduled for tooth removal under general anaesthesia the following day.

Food was withheld for 12 h with free access to water. In the day of surgery, a 14-gauge catheter was inserted percutaneously into the left jugular vein.

Acepromazine (Calmivet®, Vetoquinol, France) 0.04 mg kg^{-1} was administered intramuscularly (IM), phenylbutazone (Phenylarthrite®, Vétoquinol, France) 2.2 mg kg^{-1} and trimethoprim-sulfadoxine (Borgal®, Virbac, France) 15 mg kg^{-1} were administered intravenously (IV) 1 h before anaesthesia. In the induction box, the patient was sedated with romifidine (Sedivet®, Boehringer Ingelheim, France) 0.04 mg kg^{-1} IV followed 5 min later by morphine (Morphine Clorhydrate Aguettant®, Aguettant, France) 0.1 mg kg^{-1} IV. Anaesthesia was induced with diazepam (Valium®, Roche, France) 0.05 mg kg^{-1} and ketamine (Imalgène1000®, Merial, France), 2.2 mg kg^{-1} IV, given in separate syringes. Endotracheal intubation was performed with a 26 mm internal diameter silicone tube and the patient hoisted to the theatre and positioned in right lateral recumbency.

Once in theatre, the horse was connected to a circle breathing system and anaesthesia was maintained with sevoflurane (Sevoflo®, Axience, France) in 100% oxygen. The inspired fraction of sevoflurane was titrated to effect to maintain an adequate depth of anaesthesia based on clinical signs (palpebral reflexes, position of the eye, absence of nystagmus). A 20-gauge cannula was placed in the left metatarsal artery for invasive blood pressure (IBP) monitoring and regular arterial blood sampling for blood gas analyses. Vital signs monitoring was performed with a multivariable monitor (Datex S/5, GE Healthcare, UK) and consisted in continuous ECG, heart rate (HR), oxygen saturation (SpO_2), inspired and expired fraction of carbon dioxide ($P_{E'}CO_2$), inhaled and end-tidal concentration of oxygen and sevoflurane and IBP. Ringer Lactate (Ringer Lactate Aguettant®, Aguettant Laboratories, France) was infused at 10 mL kg^{-1} $hour^{-1}$. Dobutamine (Dobutamine Panpharma®, Panpharma, France) IV was administered at 2–10 μg kg^{-1} min^{-1} to effect, to maintain mean arterial pressure (MAP) above 70 mmHg. Intermittent positive pressure ventilation (IPPV) was provided using a volume cycled - pressure controlled ventilator (Stephan Respirator-GT; F. Stephan GmbH, Germany), and settings were adapted to maintain a $P_{E'}CO_2$ between 4.6 and 6.0 kPa (35 and 45 mmHg). Additional analgesia was provided with lidocaine (Lurocaine®, Vétoquinol SA) 1.5 mg kg^{-1} IV administered over a 20-min period, followed by a constant rate infusion (CRI) (50 μg kg^{-1} min^{-1}).

Trepanation for removal of the tooth #308 was performed, followed by a cleaning and a curettage of the dentary alveoli into which a silicone temporary prosthesis was placed.

Anaesthesia lasted 130 min, with a surgery duration of 75 min. No surgical complications were reported. Except for a period of 10 min after induction in which MAP values were around 60 mmHg, no other events or abnormalities on the ECG, HR or MAP were observed during anaesthesia. Ninety minutes after induction, morphine 0.1 mg kg^{-1} IM was administered, and the lidocaine CRI was stopped 20 min before the end of anaesthesia. Ten minutes later, the horse was weaned from the ventilator. At the end of the surgical procedure, 5 min before the end of anaesthesia, the intra-arterial catheter was removed, fluids were stopped but the IV catheter was kept for recovery. The vaporizer and oxygen were switched off; the horse was disconnected from the monitoring devices and from the breathing system but remained orotracheally intubated. While the horse was attached to a hoist and positioned on dorsal recumbency, a romifidine 0.02 mg kg^{-1} IV bolus was given, and the horse moved thereafter to the recovery box. Once there, the horse was positioned on right lateral recumbency on a padded floor, with the anaesthetist at its head to check vital signs and avoid premature attempts of rising. The time from the end of anaesthesia to this point was approximately 2 min. Despite the horse was breathing spontaneously before its transfer, apnoea was noticed when positioned in the recovery box. At physical examination, pulse was absent, mucous membranes were greyish, and pupils mydriatic. Cardiac auscultation confirmed the absence of cardiac beats. The time was noted, and thoracic compressions were immediately started by an operator jumping with his knees on the mare's thorax. Three persons (weighting 60, 80, and > 90 kg, respectively) rotated every 2 min to perform the external massage. The third heavier operator performed massage by rhythmically and energetically sitting on the horse's thorax. Meanwhile, 6 mg of adrenaline (Adrenaline Aguettant®, Aguettant, France) was administered IV, followed by 5 mL of heparinised saline. Mechanical ventilation was provided with a demand valve at a rate of 10 breaths min^{-1}, with 100 % oxygen and Ringer Lactate was administered at 10 mL kg^{-1} $hour^{-1}$. Vital parameters were continuously monitored by mandibular pulse palpation, eye reflexes evaluation. While the third operator was performing the external massage, mandibular pulse was detectable and synchronous to the thoracic compressions. A multiparameter monitor was then connected for ECG, HR, and non-invasive blood pressure measurements, with a cuff on the left metacarpal bone. However, due to the movements on the patient, monitoring assessment was difficult. Five minutes after the start of CPR, the anaesthetist detected a stronger mandibular pulse, asynchronous to the external massage. Thoracic compressions were stopped, and the anaesthetist confirmed the presence of normal QRS complexes on the ECG, whereas the horse was still apnoeic. Mechanical ventilation was continued with the demand valve with a respiratory rate of 6 breaths min^{-1}. The mare was initially tachycardic (HR of 60 beats min^{-1}), with a sinus rhythm, and MAP of 80 mmHg. Within the next 10 min, HR decreased to 37 beats min^{-1} and MAP dropped to 50 mmHg with a poor pulse quality. Dobutamine CRI was thus administered to effect at 0.5 to 2 μg $kg^{-1}min^{-1}$ IV for 5 min, until MAP reached 70 mmHg, and stopped thereafter. Ten minutes after the return of spontaneous circulation, spontaneous breathing reappeared. Afterwards, IPPV was stopped but oxygen supplementation was continued using a flow-by method, with an oxygen supply tubing positioned in the endotracheal tube and an oxygen flow set at 12 L min^{-1}. At this time, pupillary reflex was present, but not palpebral reflex. Capillary refill time

was less than 2 sec and SpO_2 100%, but mucous membranes remained pale pink and sweating was present. An arterial blood gas analysis was carried out and revealed a non-compensated respiratory acidosis (pH 7.3; arterial pressure of carbon dioxide ($PaCO_2$) 67 mmHg; bicarbonate, 29 mmol L^{-1}; anion gap 14 mmol L^{-1}, base excess 0 mmol L^{-1}). Palpebral reflex and nystagmus were noticed 15 min after the return to spontaneous circulation. Ten minutes later, reflexes became stronger and the horse started presenting some movements, which were controlled by two operators at the head to avoid premature standing. The endotracheal tube was secured to the horse's mouth and all equipment was removed from the box to prepare for the recovery, which was assisted with ropes. The mare stood up at the first attempt 1 h after the start of CPR, and remained quiet thereafter, although trembling. The patient was then extubated and kept in the recovery box for close observation. Two hours later, the mare was transferred to the hospitalization box and received phenylbutazone 4.4 mg kg^{-1} IV and omeprazole (Gastrogard, Merial, France) 2.2 mg kg^{-1}, orally. Venous blood sample analysis revealed a lactate into the normal range (1.3 mmol L^{-1}) and mild increased creatinine kinase (751 IU L^{-1}). Neurological examination was normal thereafter: the horse was alert with normal pupillary reflexes, no apparent blindness, deafness or ataxia.

The postoperative period was uneventful. Two days after anaesthesia, a cardiac ultrasound was performed, which did not reveal any abnormality. Due to the favorable outcome, the patient was discharged from the hospital 1 week later.

DISCUSSION

This case reports the successful resuscitation of a 17-year-old, 550 kg mare undergoing tooth removal under general anaesthesia that suffered cardiac arrest while transferred to the recovery box.

Cardiac arrest is a complication of equine anaesthesia that has been poorly studied. Risk factors regarding perioperative mortality include an increased ASA physical status, age, surgery type, prolonged duration of anaesthesia and emergency procedure (1). In the present case, it was debatable if a 17 years old horse could be considered as geriatric. If so, the patient could have presented a decreased ability to respond to circulatory changes or stress and, therefore, at a higher risk to anaesthetic complications (5). However, despite its age, the mare was considered overall healthy with no detected systemic abnormalities and no exercise intolerance; vital signs remained remarkably stable during anaesthesia. Therefore, in this case, the occurrence of the cardiac arrest was difficult to predict but, fortunately, its early detection allowed the prompt start of CPR maneuvers.

Cardiopulmonary resuscitation aims to restore spontaneous circulation and breathing and avoid irreversible hypoxic damages to organs. The probability of success for CPR in adult horses is considered as poor (6). The size of the animal and the physical effort required to provide cardiac massage render this procedure complicated to perform. In addition, the lack of advanced monitoring during recovery may delay the detection of cardiac arrest and worsen the outcome.

Although cardiac arrest involves one third of equine perioperative mortality (1), there is a lack in literature regarding its occurrence and treatment in adult horses. Successful CPR after direct cardiac massage in a pony and a horse was reported by De Moor et al. (7), however, both animals died in post resuscitation period. Hubbell et al. (8) evaluated the effects of thoracic compression rate on cardiac output in horses with induced cardiac arrest. They reported that thoracic compressions at a rate of 80 compressions min^{-1} allowed a better cardiac output, in comparison with lower rates. Moreover, cardiac output was higher when the operator was heavy. In this last study, horses were on right lateral recumbency and the operator delivered a blow to the chest wall immediately posterior to the left elbow with his knees. In the present case, thoracic compressions were performed in a similar way. Despite the aim was to perform 80 compressions min^{-1}, this rate seemed very difficult to achieve in practice and the rate observed in our case was probably closer to 40 to 60 compressions min^{-1}. The third operator was the heaviest and most experienced surgeon; instead of compressing the horse's thorax with his knees, he used his whole core body by sitting on it. A better pulse quality was subjectively achieved with this way of performing the external massage, but it could also have been attributed to the heavier weight of the operator.

In addition to these physical maneuvers, adrenaline was administered to the horse. This drug is recommended for asystole in horses (6) and small animals (9). Adrenaline is a synthetic catecholamine with strong α_1- and β_1-, and moderate β_2-adrenergic receptor activity which produces vasoconstriction and an increase in HR and contractility (10). In the present case, a single low dose (0.01 mg kg^{-1}) IV was used. Despite it was difficult to evaluate which part of the resuscitation maneuvers contributed to the return of spontaneous circulation, it was probably the combination of both, thoracic compressions and adrenaline that contributed to the successful CPR.

In addition to the external massage, the basic life support consists in ventilation. As previously described (8, 11), IPPV using a demand valve was performed early during CPR, at a rate of 6–10 breaths min^{-1}. Even though we cannot be certain of the minute ventilation provided, it probably allowed sufficient oxygenation of the animal, as no clinical signs of hypoxic brain damage were noticed thereafter.

In this case, the lack of close monitoring during the horse transfer made difficult to determine the precise moment and the real cause of the cardiac arrest. It was unlikely to be related to the animal health status, although individual idiosyncrasy could not be excluded, but may have been due to the surgical procedure, the occurrence of cardiovascular reflex or drug effect. Firstly, there was a potential risk of embolism associated with bleeding. However, no bleeding was noticed, nor was any sudden variation of $P_{E'}CO_2$ during the procedure. Second, a cardiac reflex following a postural change could be considered in this case. Severe cardiovascular depression in similar circumstances has been reported in a dog (12) and in humans (13, 14). In this case, the horse experienced a rapid postural change for its transfer to the recovery box. This could have produced a compression of

the caudal vena cava by abdominal viscera, leading to a decreased venous return for a few seconds, the so-called Bezold- Jarisch reflex (BJR). The BJR is a complex neuro-cardiogenic reflex mediated by ventricular receptors sensitive to chemical and / or mechanical stimuli in response to a decreased ventricular filling (15), that is not necessarily related to a hypovolaemic state. The afferent pathway is vagally mediated and terminate at the nucleus tractus solitary in the central nervous system (16). The efferent response produces an increased parasympathetic tone, leading to bradycardia, vasodilation and apnoea (17). In addition to a postural change, an interaction of a variety of anaesthetic drugs may trigger this reflex (18).

Therefore, the drugs used in the present case may also have participated to the observed complication. After its use for premedication without noticeable adverse effect, romifidine 0.02 mg kg^{-1} IV was administered at the time the horse was attached to the hoist. In our practice, this drug is routinely administered at the end of anaesthesia to improve the quality of recovery of horses (19). As an α_2-agonist, romifidine produces an initial increase in blood pressure with a subsequent bradycardia; second degree atrioventricular blocks and a decrease in stroke volume are commonly reported (20). Despite cardiovascular effects of romifidine may be dose dependent, to the authors' knowledge there are no studies that evaluated the cardiovascular effect of low dose of romifidine in anaesthetized horses. Even though it seems unlikely that romifidine alone would have been responsible for this complication, we cannot exclude a role in the development of the cardiac arrest.

Among the other drugs administered, acepromazine, a phenothiazine derivate and α_1-adrenoreceptor antagonist, was used in the premedication. In addition to hypotension (21, 22), phenothiazine derivates have been associated in humans to a decrease in myocardial contractility (23) however, this has not been reported in horses. Conversely, it has been associated to a protective cardiac effect and a decreased anaesthetic mortality (1). Even though it may have a prolonged effect on blood pressure, it was unlikely to have promoted the cardiac arrest as blood pressure was overall well maintained during anaesthesia in this case. Sevoflurane was used for maintenance of anaesthesia. In healthy horses, it produces a dose dependent decrease in MAP, cardiac index and systemic vascular resistance (SVR) (24). This decrease in SVR could have contributed to worsen the potential decrease in venous return hypothesized in this case. Similarly, lidocaine, a local anaesthetic commonly used in equine anaesthesia, may produce bradycardia and hypotension at high doses (25) and may have participated to the altered cardiovascular response to the postural change, even though it was stopped 20 min before the end of anaesthesia. Dobutamine, a β_1- adrenoreceptor agonist with inotropic properties, commonly used for treating hypotension in anaesthetized horses, was also associated with the occurrence of BJR in a dog (26). As it was sparely used in this case and particularly not at the time of recovery, it was unlikely that it had any influence on the onset of the reported complication. Finally, fatal reactions to trimethoprim-sulfadoxine have been reported in anaesthetized horses (27, 28). However, in this case, trimethoprim-sulfadoxine was administered 1 h before anaesthesia, which made it unlikely as a cause of the adverse event observed.

Based on the chronology of events, we hypothesized that the postural change combined with the cardiovascular effects of the different anaesthetic drugs used triggered the occurrence of a cardiac arrest, due to a possible BJR. However, the absence of monitoring during the transfer of the animal rendered difficult to confirm this assumption. The early detection of the complication and the presence of trained staff allowed a successful outcome. The present case also underlined that the equine patient is at high risk during the recovery period not only regarding the risk of trauma but also regarding the risk of cardiovascular and respiratory instability.

CONCLUDING REMARKS

The early detection of cardiac arrest and start of CPR maneuvers permitted the successful resuscitation of a 17-year-old mare that suffered cardiac arrest during her transfer to the recovery box.

In the light of this report, a continuous palpation of the peripheral pulse should be performed during the horse transfer to the recovery box. It seems advisable to administer drugs with a potential depressive cardiovascular effect in a time frame that does not overlap with postural changes.

AUTHOR CONTRIBUTIONS

CC and SJ participated in the development of the case and wrote or contributed to the writing of the manuscript.

ACKNOWLEDGMENTS

Authors would like to thank Professor Michael Schramme for his assistance in the development of this case report.

REFERENCES

1. Johnston G, Eastment J, Wood J, Taylor P. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of Phases 1 and 2. *Vet Anaesth Analg.* (2002) 29:159–70. doi: 10.1046/j.1467-2995.2002.00106.x
2. Bidwell LA, Bramlage LR, Rood WA. Equine perioperative fatalities associated with general anaesthesia at a private practice -a retrospective case series. *Vet Anaesth Analg.* (2007) 34:23–30. doi: 10.1111/j.1467-2995.2005.00283.x
3. Dugdale AH, Taylor PM. Equine anaesthesia-associated mortality: where are we now? *Vet Anaesth Analg* (2016) 43:242–55. doi: 10.1111/vaa.12372
4. Dugdale AH, Obhari J, Cripps PJ. Twenty years later: a single-centre, repeat retrospective analysis of equine perioperative mortality and investigation of recovery quality. *Vet Anaesth Analg.* (2016) 43:171–8. doi: 10.1111/vaa.12285
5. Cheitlin MD. Cardiovascular physiology -changes with aging. *AJGC* (2003) 12:9–13. doi: 10.1111/j.1076-7460.2003.01751.x
6. Muir WW, Hubbelll JAE. Cardiopulmonary resuscitation. In: Muir WW, Hubbell JAE, editors. *Equine Anesthesia: Monitoring and Emergence Therapy*. 2nd edn. St Louis, MO: Saunders Elsevier, (2009). p. 418–29.
7. De Moor A, Verschooten F, Desmet P, Muylle E, Steenhaut M. Intrathoracic cardiac resuscitation in the horse. *Equine Vet J.* (1972) 4:31–3. doi: 10.1111/j.2042-3306.1972.tb03874.x

8. Hubbell JAE, Muir WW, Gaynor JS. Cardiovascular effects of thoracic compression in horses subjected to euthanasia. *Equine Vet J.* (1993) 25:282–4. doi: 10.1111/j.2042-3306.1993.tb02964.x
9. Rozanski EA, Rush JE, Buckley GJ, Fletcher DJ, Boller M, RECOVER Advanced Life Support Domain Worksheet Authors. RECOVER evidence and knowledge gap on veterinary CPR. Part 4: advance life support. *J Vet Emerg Crit Care (San Antonio)* (2012) 22(Suppl.1):S44–64. doi: 10.1111/j.1476-4431.2012.00755.x
10. Schauvliege S, Gasthuys F. Drugs for cardiovascular support in anaesthetized horses. *Vet Clin Equine* (2013) 29:19–49. doi: 10.1016/j.cveq.2012.11.011
11. McGoldrick TM, Bowen IM, Clarke KW. Sudden cardiac arrest in an anaesthetised horse associated with low venous oxygen tensions. *Vet Rec.* (1998) 142:610–1. doi: 10.1136/vr.142.22.610
12. McMillan MW, Aprea F, Leece EA. Potential bezold jarisch reflex secondary to a 180° postural change in an anaesthetized dog. *Vet Anaesth Analg.* (2012) 39:561–2. doi: 10.1111/j.1467-2995.2012.00759.x
13. Brigden W, Howarth S, Sharpey-Schafer EP. Postural changes in the peripheral blood flow of normal subjects with observations on vasovagal fainting reactions as a result of tilting, the lordotic posture, pregnancy and spinal anaesthesia. *Clin Sci.* (1950) 9:79–91.
14. Hee Kim Y, Jun Kim D, Young Kim W. Bezold-Jarisch reflex caused by postural change. *J Anesth.* (2015) 29:158. doi: 10.1007/s00540-014-1880-0
15. Allyn MD. The bezold jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the Heart. *J Am Coll Cardiol.* (1983) 1:190–102.
16. Kashishana K, Kawada T, Yanagiya Y, Uemura K, Inagaki M, Takaki H et al. Bezold-Jarisch reflex attenuates dynamic gain of baroreflex neural arc. *Am J Physiol Heart Circ Physiol.* (2003) 285:833–40. doi: 10.1152/ajpheart.01082.2002
17. Thoren P. Role of cardiac vagal C-fibers in cardiovascular control. *Rev Physiol Biochem Pharmacol.* (1979) 86:1–94. doi: 10.1007/BFb0031531
18. Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br J Anaesth.* (2001) 86:859–68. doi: 10.1093/bja/86.6.859
19. Woodhouse KJ, Brosnan RJ, Nguyen KQ, Moniz GW, Galuppo LD. Effects of postanesthetic sedation with romifidine or xylazine on quality of recovery from isoflurane anaesthesia in horses. *J Am Vet Med Assoc.* (2013) 242:533–9. doi: 10.2460/javma.242.4.533
20. Buhl R, Ersbøll AK, Larsen NH, Eriksen L, Koch J. The effects of detomidine, romifidine or acepromazine on echocardiographic measurements and cardiac function in normal horses. *Vet Anaesth Analg.* (2007) 34:1–8. doi: 10.1111/j.1467-2995.2005.00269.x
21. Parry BW, Anderson GA, Gay CC. Hypotension in the horse induced by acepromazine maleate. *Aus Vet J.* (1982) 59:148–59. doi: 10.1111/j.1751-0813.1982.tb02761.x
22. Pequito M, Amory H, De Moffarts B, et al. Evaluation of acepromazine-induced hemodynamic alterations and reversal with norepinephrine infusion in standing horses. *Can Vet J* (2013) 54:150–56.
23. Landzberg JS, parker JD, Gauthier DF, Busoni V, Serteyn D, Sandersen C. Effects of myocardial alpha 1-adrenergic receptor stimulation and blockade on contractility in humans. *Circulation* (1991) 84:1608–14. doi: 10.1161/01.CIR.84.4.1608
24. Steffey EP, Mama KR, Galey FD, Puschner B, Woliner MJ. Effects of sevoflurane dose and mode of ventilation on cardiopulmonary function and blood biochemical variables in horses. *Vet Res.* (2005) 66:606–14. doi: 10.2460/ajvr.2005.66.606
25. Rioja E. Local anaesthetics. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *"Lumb and Jones" Veterinary Anaesthesia and Analgesia.* 5th ed. Ames, IA: JonWiley Sons (2015). p. 345.
26. Hoffmeister EH, Keenan K, Egger CM. Dobutamine-induced bradycardia in a dog. *Vet Anest Analg.* (2005) 32:107–11. doi: 10.1111/j.1467-2995.2004.00151.x
27. Dick IGC, White SK. Possible potenciated sulphonamide-associated fatality in an anaesthetised horse. *Vet Rec.* (1987) 19:288. doi: 10.1136/vr.121.12.288-a
28. Van Duijkeren E, Vulto AG, Van Miert ASJPAM. Trimethoprim/sulfonamide combination in the horse a review. *J Vet Pharmacol Therap.* (1994) 17:64–73. doi: 10.1111/j.1365-2885.1994.tb00524.x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

REVIEW
published: 31 August 2018
doi: 10.3389/fvets.2018.00204

The ASA Physical Status Classification: What Is the Evidence for Recommending Its Use in Veterinary Anesthesia?—A Systematic Review

Karine Portier[1,2] *and Keila Kazue Ida*[3]*

[1] Univ Lyon, VetAgro Sup, GREAT, Marcy l'Etoile, France, [2] Univ Lyon, CarMeN Laboratory, INSERM, INRA, INSA Lyon, Université Claude Bernard Lyon 1, Bron, France, [3] Anesthésiologie et Réanimation Vétérinaires, Département de Clinique des Animaux de Compagnie et des Équidés, Université de Liège, Liège, Belgium

Background: The effectiveness of the American Society of Anesthesiologists (ASA) Physical Status (PS) classification to identify the animals at a greater risk of anesthesia-related death and complications is controversial. In this systematic review, we aimed to analyze studies associating the ASA PS scores with the outcome of anesthesia and to verify whether there was any evidence for recommending the use of the ASA PS in veterinary patients.

Methods: Research articles found through a systematic literature search were assessed for eligibility, and data were extracted and analyzed using random-effects analysis.

Results: A total of 15 observational prospective and retrospective studies including 258,298 dogs, cats, rabbits, and pigs were included. The analysis found consistency between the studies showing that dogs, cats and rabbits with an ASA-PS ≥III had 3.26 times (95% CI = 3.04–3.49), 4.83 times (95% CI = 3.10–7.53), and 11.31 times (95% CI = 2.70–47.39), respectively, the risk of anesthesia-related death within 24 h (dogs) and 72 h (cats and rabbits) after anesthesia compared with those with an ASA PS <III. In addition, the analysis showed that dogs and cats with ASA PS ≥III had 2.34 times the risk of developing severe hypothermia during anesthesia (95% CI = 1.82–3.01).

Conclusions: The simple and practical ASA PS was shown to be a valuable prognostic tool and can be recommended to identify an increased risk of anesthetic mortality until 24–72 h after anesthesia, and a greater risk of development severe intraoperative hypothermia.

Keywords: mortality, fatal outcome, risk, dogs, cats, horses, rabbits, complications

OPEN ACCESS

Edited by:
Sebastiaan A. Van Nimwegen, Utrecht University, Netherlands

Reviewed by:
Hugo Van Oostrom, University of Bristol, United Kingdom
Maria Fahie, Western University of Health Sciences, United States

***Correspondence:**
Keila Kazue Ida
keila.ida@ulg.ac.be

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *11 February 2018*
Accepted: *07 August 2018*
Published: *31 August 2018*

Citation:
Portier K and Ida KK (2018) The ASA Physical Status Classification: What Is the Evidence for Recommending Its Use in Veterinary Anesthesia?—A Systematic Review. Front. Vet. Sci. 5:204. doi: 10.3389/fvets.2018.00204

INTRODUCTION

The American Society of Anesthesiologists (ASA) physical status (PS) consists of a classification system to assess a patient's physical status. The higher ASA PS appears to be related to a worse outcome of anesthesia. Its creation dates from 1941, when Saklad et al. were requested by the ASA to build a system that would allow retrieving statistical data in anesthesia (1). Their first task was

to specify arbitrary definitions of numerous variables in order to establish standard terms and a common language. Initially, they intended to develop a tool to objectively assign an operative risk and establish a prognostic. However, in such approach, the statistical treatment was impossible due to the numerous variables associated with the different establishments and clinicians. They concluded that the term "operative risk" could not be used and it was more adequate to classify the patients according to their physical status only. They stated that "no attempt should be made to prognosticate the effect of a surgical procedure upon a patient of a given physical status," since few variables were considered to favor the standardization of the definitions and the use of a common terminology for the statistical analysis.

At that time, there were different ways of assessing the patients' physical status, such as by assigning a number, a letter or, more explicit, a word (good, moderate, severe). An attempt to create a new method of standardization was proposed using six classes of "physical status" (**Figure 1**). The classes 1, 2, 3, and 4 consisted of systemic disturbances, which were graded into "none, definite, severe, extreme" with 5–10 examples each (1). The classes 5 and 6 consisted of the emergencies that would otherwise be graded in classes 1 or 2, and classes 3 or 4, respectively. A class 7 was added later to represent the moribund patients that were likely to die within 24 h with or without surgery.

The correlation between the incidence of mortality related to anesthesia and the physical status of the patient was shown for the first time in 1961 by Dripps et al. (2) in a study entitled "The role of anesthesia in surgical mortality." In this study, the Arabic numbers from the classification of Saklad were modified to roman numbers, and the classes 5 and 6 were replaced by an "E" for "emergency" that could be added to each of the ASA classes. In addition, the grades "none, definitive, severe and extreme systemic disturbance" were replaced by "normal healthy, mild, severe, and incapacitating systemic disease" but these new definitions were not accompanied by examples. These modifications were accepted by the ASA in 1962 (3) and were published in the journal Anesthesiology in 1963 (4).

In 1978, the first study on the inter-anesthetists' variability concluded that the ASA PS classification was useful but was lacking scientific definition (5). Indeed, the terms used to define each class were subjective and inaccurate, and the qualitative adjectives, such as "mild, moderate, severe" implied a personal interpretation (6, 7). Additionally, the definitions based on the severity of the disease could also be controversial (8).

This subjectivity led to the last update of the classification system approved by the ASA House of Delegates (9) on October 15th 2014 (**Figure 2**). Most of the definitions were not modified, except for class V, in which the definition was changed from "a moribund patient who is not expected to survive for 24 h with or without surgery" to "a moribund patient who is not expected to survive for 24 h without operation." Moreover, examples were added for each ASA PS class. For instance, smokers, alcoholics, pregnant women, and obese patients were included in classes II and III and an ASA VI category was added to include patients with brain-death and whose organs were being removed for donor purposes.

ASA	Definition	Example
1	No organic pathology or patients in whom the pathological process is localized and **does not cause any systemic disturbance** or abnormality.	Fractures with no shock, blood loss, emboli or systemic signs of injury; congenital deformities; localized infections; osseous deformities; uncomplicated hernias. Any type of operation may fall in this class since only the patient's physical condition is considered.
2	A moderate but **definite systemic disturbance**, caused either by the condition that is to be treated by surgical intervention or which is caused by other existing pathological processes.	Mild diabetes, functional capacity I or IIa; psychotic patients unable to care for themselves, mild acidosis, anemia moderate, septic or acute pharyngitis, chronic sinusitis with postnasal discharge, acute sinusitis, minor or superficial infections that cause a systemic reaction, nontoxic adenoma of thyroid that causes but partial respiratory obstruction, mild thyrotoxicosis, acute osteomyelitis, chronic osteomyelitis, pulmonary tuberculosis with involvement of pulmonary tissue insufficient to embarrass activity and without other symptoms
3	**Severe systemic disturbance** from any cause. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgement.	Complicated or severe diabetes; functional capacity IIb; combinations of heart disease and respiratory disease or others that impair normal functions severely; complete intestinal obstruction that has existed long enough to cause serious physiological disturbances; pulmonary tuberculosis that, because of the extent of the lesion or treatment, has reduced vital capacity sufficiently to cause tachycardia or dyspnea; patients debilitated by prolonged illness with weakness of all or several systems; severe trauma from accident resulting in shock, which may be improved by treatment; pulmonary abscess.
4	**Extreme systemic disorders**, which have already become an eminent threat to life regardless of the type of treatment. Because of their duration or nature there has already been damage to the organism that is irreversible. This class is intended to include only patients that are in an extremely poor physical state. There may not be much occasion to use this classification, but it should serve a purpose in separating the patient in very poor condition from others.	Functional capacity III – cardiac decompensation; severe trauma with irreparable damage; complete intestinal obstruction of long duration in a patient who is already debilitated; a combination of cardiovascular -renal disease with marked renal impairment; patients who must have anesthesia to arrest a secondary hemorrhage where the patient is in poor condition associated with marked loss of blood.
5	**Emergencies** that would otherwise be graded in Class 1 or Class 2	
6	**Emergencies** that would otherwise be graded as Class 3 or Class 4	
7	**Moribund patients** likely to die within 24 hours with or without surgery	

FIGURE 1 | American Society of Anesthesiologists (ASA) grading of patients for surgical procedures according to Saklad (1).

The actual version of the ASA PS classification was never validated in human medicine, although several studies showed the correlation between ASA PS and the risk of death (10–12) and complications associated with anesthesia.

ASA PS	Definition	Examples
I	Normal healthy patient	Healthy; non -smoking, no or minimal alcohol use
II	Patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI =40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or seve re valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
VI	A declared brain -dead patient whose organs are being removed for donor purposes	
E	Denotes Emergency surgery; an emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part	

FIGURE 2 | Current American Society of Anesthesiologists Physical Status (ASA PS) classification with definitions published in 1963 (4) and examples accepted in 2014 (9). BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; PCA, patient-controlled analgesia; MI, myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack; CAD, coronary artery disease; DIC, disseminated intravascular coagulation; ARD, airway respiratory disease.

Such complications included the postoperative morbidity of patients after hip replacement surgeries, transurethral prostatectomy, cholecystectomy (13), and elective cranial neurosurgery (14); the incidence of infection, delayed wound healing, and deep vein thrombosis after plastic surgery (15) and; other major complications, such as atrial fibrillation, hypotension, and hypertension (16). In addition, high ASA PS scores were significantly correlated with long hospital and intensive care unit stays, high complication rates, and increased frequency of follow-ups (13). The ASA PS classification was equal to an index of physiological capacity to predict postoperative cardiovascular, respiratory, renal and infectious complications after major abdominal surgery (17). Intraoperative variables, such as duration of the surgery, duration of the assisted ventilation, and blood loss were also associated with the ASA PS score assigned preoperatively (18).

In veterinary medicine, to the authors' knowledge, one of the first prospective publications mentioning the association between the ASA PS classification and the anesthesia-related risk of death was from Clarke and Hall (19). Since then, several studies associating the ASA PS to anesthesia-related risk of death were published for dogs and cats (20–34), rabbits (24, 35), pigs (36), and horses (37, 38) with different outcomes and definitions. However, whether veterinary patients with a high ASA PS score are at an increased risk of death and development of complications associated with anesthesia remains unknown.

In this systematic review, we compared the studies assessing the ASA PS with the outcome of anesthesia in domestic animals,

aiming to verify whether there was evidence that the ASA PS was actually effective to identify patients at a higher risk of anesthesia-related death or at a higher risk of developing any complication associated with anesthesia.

METHODS

Online Database Search Strategy

In order to find the studies assessing the anesthesia-related death and complications, an online database search was performed. In the online search, the terms (ASA or American-Society-of-Anesthesiologists) and (anesthesia or anaesthesia) and (death or mortality or risk or morbidity or complication or outcome) and (veterinary or animal) were entered in Pubmed, Google Scholar, Scopus, and VetMed Resources on April 1st 2018. In VetMed Resource, the results were filtered by "journal article," "English language," "death rate," "morbidity," and "clinical aspects." One paper was hand searched from the reference section of other papers and books.

The outcome variables included anesthesia-related mortality and complications in any domestic animal species. The anesthesia-related mortality was defined as death where anesthesia could not be excluded as a potential cause. The anesthesia-related complications were defined as any clinical alteration where anesthesia could not be excluded as a potential cause.

Only published research articles in peer-reviewed journals providing the outcome (which could be death or any other complication associated with anesthesia) according to the ASA PS score were included in the study. Studies in any domestic animal species or specific study population of domestic animals were considered for inclusion. The studies were grouped by outcome, i.e., mortality and complications, and then by animal species and specific group populations. The patients were assessed according to their ASA PS scores, which could be ASA PS <III, defined as healthy patients or with mild diseases only, without substantive functional limitations, or ASA PS ≥III, defined as sick patients with one or more moderate to severe diseases and substantive functional limitations (4, 9). The division of the ASA PS scores into two groups aimed to facilitate the analysis and was based in previous large studies assessing anesthesia-related mortality in veterinary patients (19, 24).

Risk of Bias Assessment

The risk of bias was evaluated for each article using a 9-point Newcastle-Ottawa scale (**Figure 3**) to assess the quality of non-randomized studies included in systematic reviews and meta-analyses (39). In this scale, each study was assigned a maximum of 4 points for quality of selection, 2 points for comparability, and 3 points for quality of outcome and adequacy of follow-up. The sum of the points from each category consisted of the Newcastle-Ottawa score, which indicated a low, moderate, and high risk of bias for 7–9, 4–6, and 1–3 points, respectively (40).

Study Heterogeneity

To verify the consistency of the findings of the studies assessing the same outcome in the same animal species, the Cochrane's Q and the I^2 heterogeneity tests were calculated. The Cochran's Q indicated whether the variations between the results were genuine ($P < 0.05$ = heterogeneity) or attributable to chance ($P > 0.05$ = homogeneity). The proportion of the inconsistency (heterogeneity) was expressed by the I^2 statistic between 0 and 100% [I^2 = 100% x (Cochran's Q–degree of freedom)/Cochran's Q]. Negative values for I^2 were considered equal to 0% (41).

Statistical Analyses

A 2 × 2 table for binary outcomes (**Figure 4**) was extracted from each study. From this table, the relative risk (RR) and the 95% confidence interval (CI) were calculated for each study according to the following equation: RR = [A/(A+B)]/[C/(C+D)]. The experimental group was defined as patients ASA PS ≥III and the control group was defined as patients ASA PS <III. A RR < 1.0 (plotted to the left of the line 1.0 in the graphs) indicated that in that study, patients with ASA PS ≥III were at a lower risk of anesthesia-related morbidity or mortality compared with ASA PS <III. A RR > 1.0 (plotted to the right of the line 1.0 in the graphs) indicated that in that study, patients with ASA PS ≥III were at a higher risk of anesthesia-related morbidity or mortality compared to patients with ASA PS <III. A RR = 1.0 indicated there was no difference in risk of anesthesia-related morbidity or mortality for patients assigned either ASA PS <III or ASA PS ≥III. The random-effects statistical model, which allows for differences in the treatment effect from study to study, was used for this analysis (42). The RR, the Cochran's Q, and the I^2 were calculated using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Studies Included in the Analysis

A total of 233 studies were retrieved using the online research database strategy (65 from Pubmed, 14 from Google Scholar, 5 from Scopus, and 148 from VetMed Resources) and by hand searching the literature (1 study). From these, 162 were excluded because, based on the abstract, they were not relevant to our study, 25 studies were excluded because of the inclusion of patients with only a specific ASA PS, 18 were excluded because of no full data provision to calculate the RR and incidence of mortality or complication, and 14 studies were excluded because of no assessment of the anesthetic-related mortality and complication according to the ASA PS (**Figure 5**).

A total of 14 studies with 241,509 patients (131,024 dogs; 102,064 cats; 8,394 rabbits; and 27 pigs) from 236 clinics (1 from USA, 1 from France, 18 from Japan, 42 from Spain, and 174 from UK) assessed from 1984 to 2016 met the inclusion criteria (**Table 1**). Studies in other animal species, such as horses and birds, did not comply with the inclusion criteria.

There were 12 studies assessing mortality and 3 studies assessing complications included in the analysis (1 study assessed both mortality and complications) (**Figure 5**). Mortality was assessed according to the animal species (7 studies in dogs, 6 studies in cats, 2 studies in rabbits), and

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort:
a) truly representative of the average anesthetized -animals in the community ❋
b) somewhat representative of the average anesthetized -animals in the community ❋
c) selected group of anesthetized animals
d) no descr iption of the derivation of the cohort

2) Selection of the non -exposed cohort:
a) drawn from the same community as the exposed cohort ❋
b) drawn from a different source
c) no description of the derivation of the non -exposed cohort

3) Ascertainment of exposure:
a) secure record (eg. anesthetic records) ❋
b) structured interview ❋
c) written self -report
d) no description

4) Demonstration that the ASA PS score was assigned prior to anesthesia:
a) yes ❋
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis:
a) study controls for age ❋
b) study controls for duration of anesthesia ❋

Outcome

1) Assessment of outcome:
a) independent blind assessment ❋
b) record linkage ❋
c) self-report
d) no description

2) Was follow -up long enough for outcomes to occur:
a) follow -up =24 hours after surgery ❋
b) follow -up <24 hours after surgery

3) Adequacy of follow -up of cohorts:
a) complete follow -up - all subjects accounted for ❋
b) subjects lost to follow up unlikely to introduce bias - small number lost follow up, or description provided of those lost ❋
c) lost follow up rate and no description of those lost
d) no statement

FIGURE 3 | Newcastle-Ottawa scale for assessment of quality of non-randomized studies included in the analysis.

according to specific populations (i.e., dogs undergoing thoracic surgery, cats undergoing ureteral surgery). Complications included the development of hypothermia, hyperthermia, and hypotension.

All studies had a low risk of bias, except the ones of Clarke and Hall (19) and Lee et al. (35), which had a moderate risk of bias. The study of Clarke and Hall (19) mentioned that animals died during or shortly after surgery but they did not specify the exact length of follow-up. Lee et al. (35) assigned the ASA PS score retrospectively from the animal records.

All studies excluded animals that died due to euthanasia from the analysis, except for the studies of Clarke and Hall (19), Brodbelt et al. (24), and Lee et al. (35).

The studies from Brodbelt et al. (23, 25) had supplementary data of the study of Brodbelt et al. (24) and were included in the analysis only to assess the risk of bias of the latter.

	ASA PS ≥III	ASA PS <III
Death	ASA PS ≥III that died (A) True positives	ASA PS <III that died (B) False positives
Survival	ASA PS ≥III that survived (C) False negatives	ASA PS <III that survived (D) True negatives

FIGURE 4 | The 2 × 2 table for binary outcomes used for assessing the relative risk and the 95% confidence interval in the present study.

Anesthesia-Related Mortality in Dogs

Six studies assessing the anesthesia-related death in dogs were included in the analysis (**Table 1** and **Figure 6**). All studies, except for Brodbelt et al. (24), excluded euthanized dogs from the analysis because deaths were not associated with anesthesia.

The overall mortality rate associated with anesthesia shown in the studies analyzed decreased from 0.23 to 0.17% between 1976–1978 and 2002–2004 (19, 24). This was mainly because of a decrease in the mortality rate of ASA PS III-V from 3.12 to 1.33%, although the proportion of deaths in ASA PS I-II also decreased from 0.11 to 0.05%.

All studies found a significant greater risk of anesthesia-related death in dogs with ASA PS ≥III compared to dogs with ASA PS <III. Overall the combined results of the studies showed that dogs with ASA PS ≥III had 4.73 times the risk of death due to causes associated with anesthesia compared to dogs with ASA PS <III (95% IC = 2.87 to 7.81; $P < 0.001$). However, there was a significant inconsistency of 98.5% ($Q = 337.0$; $P < 0.0001$; $I^2 = 98.5\%$) between the findings of all studies, which was further investigated by analyzing the studies according to their length of follow-up.

Further investigation revealed 0% heterogeneity between the studies of Bille et al. (26) and Bille et al. (30), which assessed death until the end of anesthesia ($Q = 0.48$; $df = 1$; $P = 0.49$), and between these studies and the study of Gil and Redondo (29), which assessed death until 24 h after anesthesia ($Q = 0.49$; $df = 2$; $P = 0.78$). They found that dogs with ASA PS ≥III had 3.26 times the risk of anesthesia-related death until the end of anesthesia (95% CI = 3.03 to 3.51; $P < 0.001$) and until 24 h after anesthesia (95% CI = 3.04 to 3.45; $P < 0.001$) compared to dogs with ASA PS <III.

When prolonging the length of follow-up to 48 h after anesthesia, the studies of Brodbelt et al. (24) and Itami et al. (33) found that dogs ASA PS ≥III had 8.95 times (95% IC = 7.97–10.04; $P < 0.0001$) and 2.71 times (95% IC = 2.09–3.51; $P < 0.0001$) the risk of anesthesia-related death, respectively, although there was 98.6% inconsistency ($Q = 72.5$; $df = 1$; $P < 0.0001$) between the findings of these studies.

The study of Clarke and Hall (19) found the highest risk of 14.14 times for anesthesia-associated death in dogs with ASA PS ≥III compared to dogs with ASA PS <III (95% CI = 10.68 to 18.71; $P < 0.0001$), although the length of follow-up was not provided in the article.

Anesthesia-Related Mortality in Cats

The 5 studies assessing the anesthesia-related mortality on cats included in the analysis were presented in **Table 1** and **Figure 7**.

The overall mortality rate associated with anesthesia shown in the studies analyzed decreased from 0.29% (19) to 0.24% (24) between 1976–1978 and 2002–2004, mainly because of a decrease in the mortality rate of ASA PS III-V from 3.33 to 1.4%, although the proportion of deaths in ASA PS I-II also decreased from 0.18 to 0.11%. Animals dying due to euthanasia were excluded from the analysis on 3 (26, 28, 30) out of 5 studies in cats.

All studies showed a significant greater risk of anesthesia-related death in cats with ASA PS ≥III compared with ASA PS <III. The studies of Bille et al. (26) and Bille et al. (30) found that cats with ASA PS ≥III had 3.24 times (95% CI = 1.60 to 6.55; $P = 0.001$) the risk of anesthesia-related death until the end of anesthesia than cats ASA PS <III, although there was a significant 88.35% inconsistency between these results ($Q = 8.58$; $df = 1$; $P = 0.0034$). The studies of Brodbelt et al. (24) and Redondo et al. (28) found that cats ASA PS ≥III had 6.42 times (95% CI = 5.58–7.38; $P < 0.0001$) and 2.99 times (95% CI = 1.63–5.49; $P = 0.0004$) the risk of anesthesia-associated death until 48 and 72 h after anesthesia, respectively, compared to cats with ASA PS <III, although a significant heterogeneity was found between the results of these studies ($Q = 72.5$; $df = 1$; $P < 0.0001$; $I^2 = 98.6\%$). Clarke and Hall (19) found that cats ASA PS ≥III had 11.3 times (95% = CI 8.31–15.3; $P < 0.0001$) the risk of death due to causes associated with anesthesia compared to cats with ASA PS <III, although no length of follow-up was provided in the study.

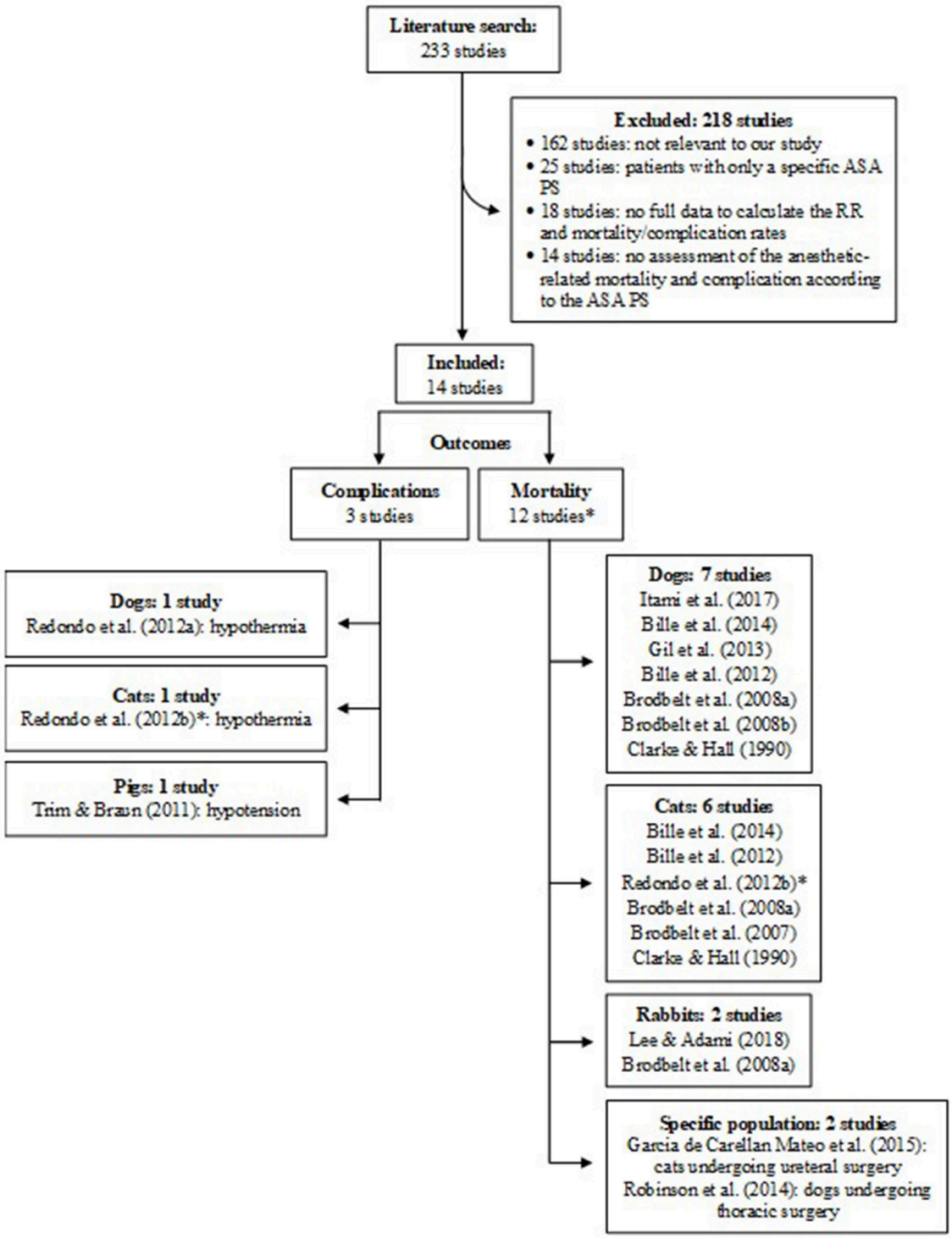

FIGURE 5 | Flow diagram of studies included in the analysis. *The study of Redondo et al. (28) was counted twice because it assessed both complication and mortality. RR, relative risk; ASA PS, American Society of Anesthesiologists physical status.

The overall RR for the 5 studies combined showed that cats with ASA PS ≥III had 4.83 times (95% CI = 3.10–7.53; $P < 0.001$) greater risk of anesthesia-related mortality compared to cats with ASA-PS <III. No significant inconsistency was detected between the results of these studies ($I^2 = 24.34\%$; $Q = 5.2865$; df 4; $P = 0.2591$; **Figure 7**).

TABLE 1 | Study design and population, number of patients included in the study, overall mortality, period of the study, number of clinics, and country of the studies included in the review.

Studies	Study design	Population	*n* included (overall mortality)	Period of the study	*n* clinics	Country
MORTALITY IN DOGS						
Itami et al. (33)	Observational prospective cohort	Dogs anesthetized for surgical or diagnostic procedures	4,323 (0.65%)	Apr 2010–Mar 2011	18	Japan
Bille et al. (30)	Observational prospective cohort	Dogs undergoing general anesthesia	1,783 (0.62%)	Apr 2008–Apr 2010	1	France
Gil and Redondo (29)	Observational prospective cohort	Dogs undergoing anesthesia	2,012 (1.29%)	Feb 2007–Mar 2008	39	Spain
Bille et al. (26)	Observational prospective cohort	Dogs and cats undergoing general anesthesia	2,252 (1.51%)	Apr 2008–Apr 2010	1	France
Brodbelt et al. (24, 25)	Observational prospective cohort	Dog undergoing anesthesia and sedation	98,036 (0.17%)[a]	Jun 2002–Jun 2004	117	UK
Clarke and Hall (19)	Observational prospective cohort	Dogs undergoing anesthesia	20,814[a] (0.23%)	1984–1986	53	UK
MORTALITY IN CATS						
Bille et al. (30)	Observational prospective cohort	Dogs undergoing general anesthesia	902 (1.11%)	Apr 2008–Apr 2010	1	France
Bille et al. (26)	Observational prospective cohort	Dogs undergoing general anesthesia	1,294 (1.08%)	Apr 2008–Apr 2010	1	France
Redondo et al. (28)	Retrospective	Cats undergoing anesthesia	275 (2.2%)	Not available	1	UK
Brodbelt et al. (23, 24)	Observational prospective cohort	Cats undergoing anesthesia and sedation	79,178 (0.24%)[a]	Jun 2002–Jun 2004	117	UK
Clarke and Hall (19)	Observational prospective cohort	Cats undergoing anesthesia	20,103 (0.29%)[a]	1984–1986	53	UK
MORTALITY IN RABBITS						
Lee et al. (35)	Retrospective	Anesthetized and sedated pet rabbits	185 (18.5%)[a]	2009–2016	1	UK
Brodbelt et al. (24)	Observational prospective cohort	Rabbits undergoing anesthesia and sedation	8,209 (1.39%)[a]	Jun 2002–Jun 2004	117	UK
MORTALITY IN SPECIFIC POPULATION						
Garcia de Carellan Mateo et al. (32)	Retrospective cohort	Cats anesthetized for ureteral surgery	37 (18.9%)	Mar 2010–Mar 2013	1	UK
Robinson et al. (31)	Retrospective	Dogs undergoing thoracic surgery	279 (2.2%)—at 24 h 266 (3.6%)—at discharge	Jun 2002–Jun 2011	1	UK
COMPLICATIONS						
Redondo et al. (27)	Retrospective	Dogs undergoing anesthesia	1,525	Not available	2	Spain
Redondo et al. (28)	Retrospective	Cats undergoing anesthesia	275	Not available	1	Spain
Trim and Braun (36)	Retrospective	Pigs undergoing anesthesia	27	May 1999–Jun 2006	1	USA

[a] *Including euthanized patients.*

Anesthesia-Related Mortality in Rabbits

Two studies assessing the mortality associated with anesthesia on rabbits were included in the analysis (**Table 1** and **Figure 8**).

In the study of Brodbelt et al. (24), the rabbits with ASA PS ≥III had 6.64 times the risk of anesthesia-related death until 48 h after anesthesia compared to rabbits with ASA PS <III (95% CI = 5.19–8.51; $P < 0.0001$).

The study of Lee et al. (35) found that rabbits with ASA-PS ≥III had 30.6 times the risk of anesthesia-associated death until 72 h after anesthesia compared to rabbits with ASA PS <III (95% CI = 5.74–163.1; $P = 0.0001$). In this study, the ASA PS scores were assigned retrospectively from the patient's records, which contributed to a moderate risk of bias.

Overall, the findings of these studies combined showed that rabbits with ASA PS ≥III had 11.31 times the risk of death-associated with anesthesia compared to rabbits with ASA PS <III (95% CI = 2.70–47.39; $P = 0.001$). There was no

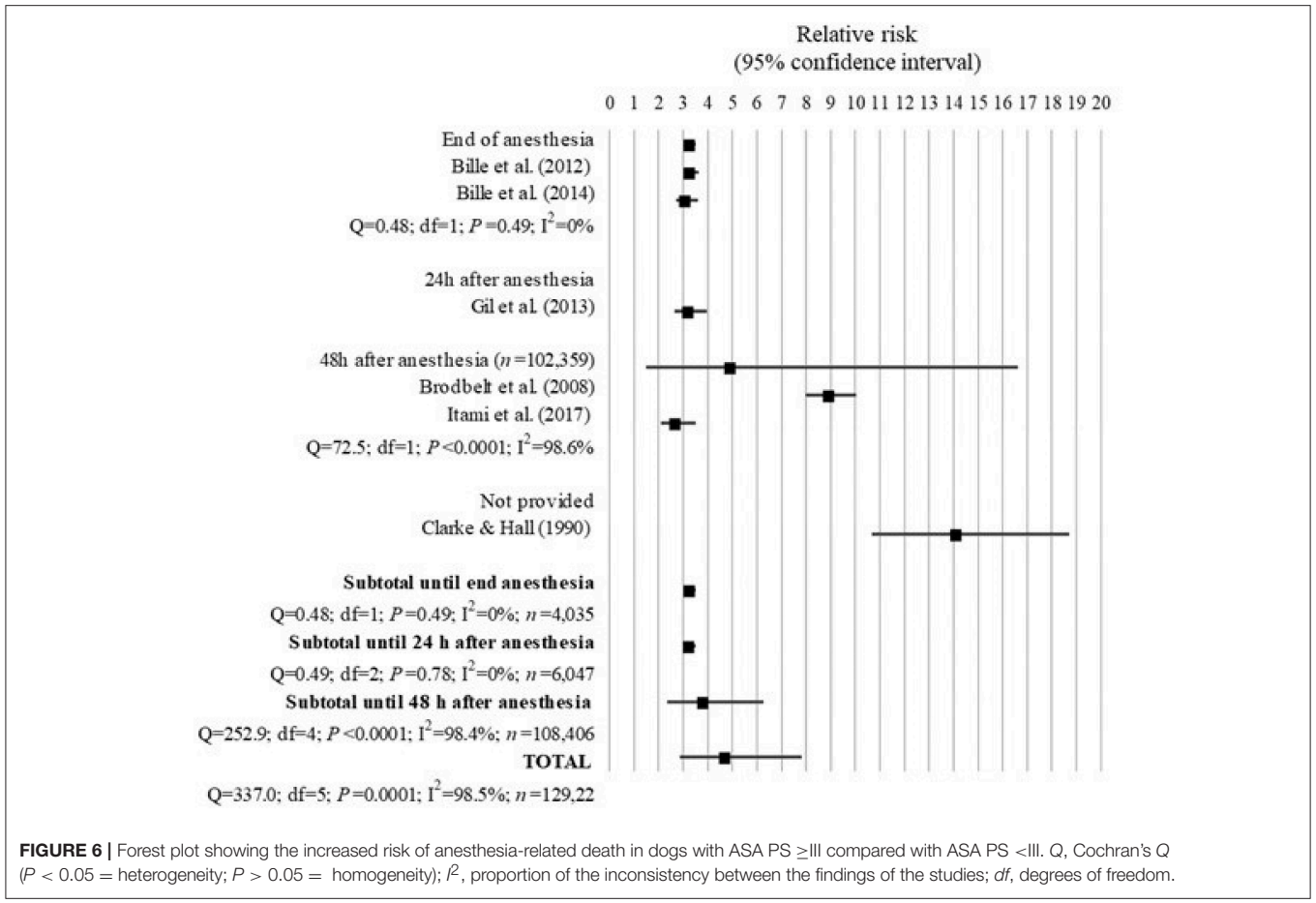

FIGURE 6 | Forest plot showing the increased risk of anesthesia-related death in dogs with ASA PS ≥III compared with ASA PS <III. *Q*, Cochran's *Q* ($P < 0.05$ = heterogeneity; $P > 0.05$ = homogeneity); I^2, proportion of the inconsistency between the findings of the studies; *df*, degrees of freedom.

significant heterogeneity between the findings of these studies ($Q = 3.16$; $df = 1$; $P = 0.07$; $I^2 = 68.35\%$), regardless of the differences in the length of follow-up of 48 h (24) and 72 h after anesthesia (35).

Anesthesia-Related Mortality in Specific Populations

There were 2 studies included in the analysis that assessed the risk of death on specific populations, which were dogs undergoing thoracic surgery and cats undergoing ureteral surgery (**Table 1** and **Figure 9**).

In the study of Robinson et al. (31), dogs ASA PS ≥III undergoing thoracic surgery had 1.19 times the risk of anesthesia-related death compared to those with ASA PS <III (95% CI = 1.04 to 1.36; $P = 0.01$). Within the study, although the risk of death was significant when assessed until discharge (RR = 1.21; 85% CI = 1.05–1.40; $P = 0.0079$) but not when assessed until 24 h after anesthesia (RR = 1.06; 95% CI = 0.74–1.52; $P = 0.7603$), no significant heterogeneity was found between the findings of the study ($Q = 0.55$; $df = 1$; $P = 0.46$; $I^2 = 0\%$).

In the study of Garcia de Carellan Mateo et al. (32), cats ASA PS ≥III undergoing ureteral surgery had 16.43 times the risk of anesthesia-related mortality compared to cats with ASA PS <III (95% CI = 2.46–16.81; $P = 0.0001$).

COMPLICATIONS

Three studies describing anesthesia-related complications were included in the analysis (**Figure 10**). All studies used a retrospective design. The complications consisted of: hypothermia, which was stratified in three levels [i.e., slight (36.5–38.49°C), moderate (34.0–36.49°C), and severe (<34°C)], and hyperthermia (>39.5°C) in dogs and cats at the end of anesthesia; and arterial hypotension (MAP ≤65 mmHg or SAP ≤85 mmHg) in Vietnamese potbellied pigs at discharge.

In dogs, the study of Redondo et al. (27) found that the risk of developing hyperthermia (RR = 1.00; 95% CI = 0.50–1.87; $P = 0.9195$) and hypothermia (RR = 1.39; 95% CI = 0.90–2.15; $P = 0.14$) was not significantly different between patients with ASA PS ≥III compared to patients with ASA PS <III. However, when stratifying hypothermia in three levels, dogs with ASA PS ≥III had 1.24 times (95% CI = 1.03–1.50; $P = 0.0252$) and 2.33 times (95% CI = 1.72–3.15; $P < 0.0001$) the risk of developing moderate and severe hypothermia associated with anesthesia, respectively, compared to dogs with ASA PS <III.

In cats, similar to dogs, the study of Redondo et al. (28) showed no significant difference in the risk for developing hyperthermia (RR = 0.71; 95% CI = 0.06–8.97) and hypothermia (RR = 1.04; 95% CI = 0.25–4.38; $P = 0.95$) between cats with

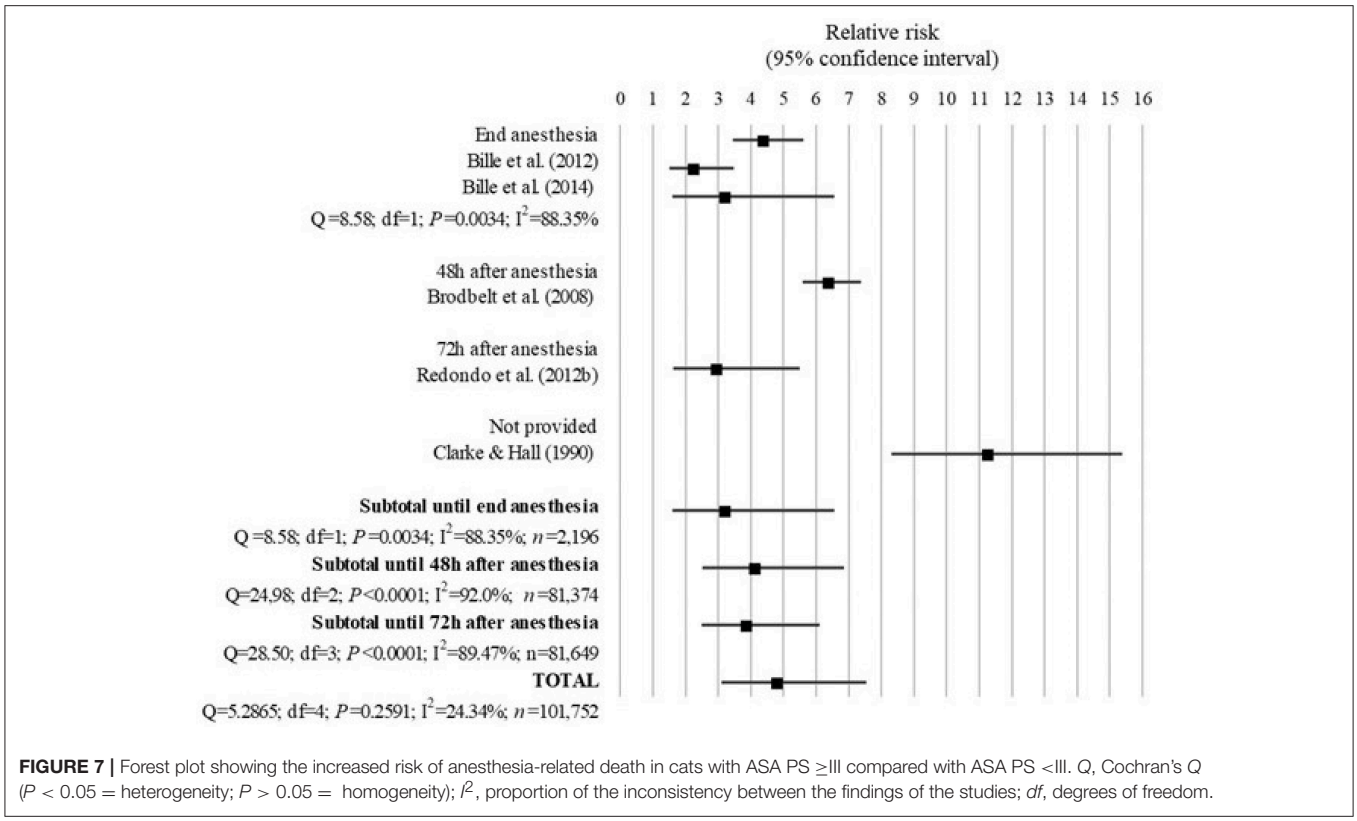

FIGURE 7 | Forest plot showing the increased risk of anesthesia-related death in cats with ASA PS ≥III compared with ASA PS <III. *Q*, Cochran's *Q* ($P < 0.05$ = heterogeneity; $P > 0.05$ = homogeneity); I^2, proportion of the inconsistency between the findings of the studies; *df*, degrees of freedom.

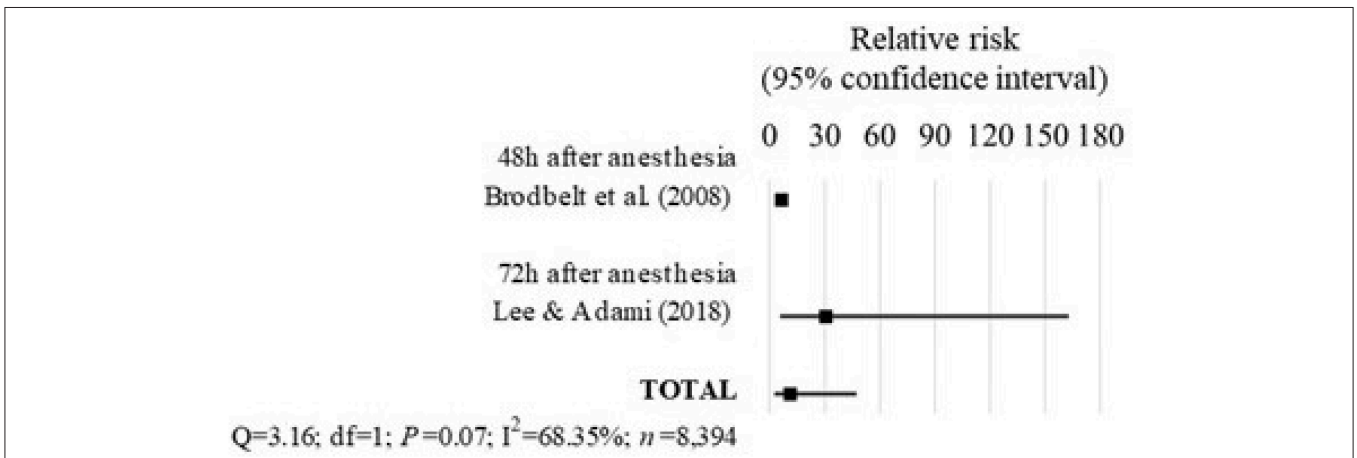

FIGURE 8 | Forest plot showing the increased risk of anesthesia-related death in rabbits with ASA PS ≥III compared with ASA PS <III. *Q*, Cochran's *Q* ($P < 0.05$ = heterogeneity; $P > 0.05$ = homogeneity); I^2, proportion of the inconsistency between the findings of the studies; *df*, degrees of freedom.

ASA PS ≥III compared to cats with ASA PS <III. However, when stratifying hypothermia in three levels, cats with ASA PS ≥III had a 76% reduction in the risk of developing anesthesia-related slight hypothermia compared to cats with ASA PS <III (RR = 0.24; 95% CI = 0.14–0.42; $P < 0.0001$). In addition, cats with ASA PS ≥III had 1.93 times and 2.37 times the risk of developing moderate (RR = 1.93; 95% CI = 1.24–3.00; $P = 0.0036$) and severe hypothermia (RR = 2.37; 95% CI = 1.51–3.73; $P = 0.0002$) than cats with ASA PS <III.

The analysis of the results of the studies (27, 28) combined found that dogs and cats ASA PS ≥III had 2.34 times the risk of developing severe hypothermia compared to patients with ASA PS <III (95% CI = 1.82–3.01; $P < 0.001$). No significant inconsistency was found between the results of the studies ($Q = 0.006$; $df = 1$; $P < 0.9391$; $I^2 = 0\%$).

The findings of Trim and Braun (36) indicated that the risk of anesthesia-related hypotension was not significantly different

between pigs with ASA PS ≥III and pigs with ASA PS <III (RR = 1.27; 95% CI = 0.54–2.96; $P = 0.5864$).

DISCUSSION

This meta-analysis shows that for dogs, cats and rabbits with ASA PS ≥III the risk of anesthesia-related mortality up to 24 h (dogs) and up to 72 h (cats and rabbits) after anesthesia is higher than for dogs, cats and rabbits with ASA PS <III. In dogs, this increased risk is not consistent between the studies when the period of follow up is longer than 24 h. In addition, there was also evidence found to support that dogs and cats with ASA PS ≥III have an increased risk of developing severe hypothermia associated with anesthesia.

The present study indicates that part of the anesthesia-related deaths actually occurs after anesthesia and that, therefore, more attention should be given to this longer post-anesthetic period. Originally, the ASA PS classification was created in order to analyze data statistically and not to calculate operational risk (1). It was believed that the only cause of anesthetic mortality that could be correlated with the physical status of the patient was drug overdose (43) and human error (44). The increased risk of death during anesthesia could be attributed to the fact that animals with an ASA PS ≥III could not tolerate many anesthetic drugs due to their impaired functional organ systems. They could not compensate the cardiopulmonary alterations induced by the anesthetic drugs and, therefore, would be more likely to die during anesthesia. Sick animals could tolerate only a limited range of drugs, since the severe systemic disease could impair organ function that could not compensate for the hemodynamic alterations induced by the anesthetic drugs and death would be

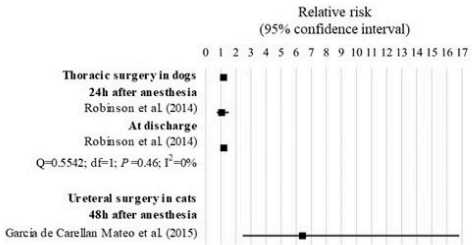

FIGURE 9 | Forest plot showing the increased risk of anesthesia-related death in specific populations with ASA PS ≥III compared with ASA PS <III. *Q*, Cochran's *Q* ($P < 0.05$ = heterogeneity; $P > 0.05$ = homogeneity); I^2, proportion of the inconsistency between the findings of the studies; *df*, degrees of freedom.

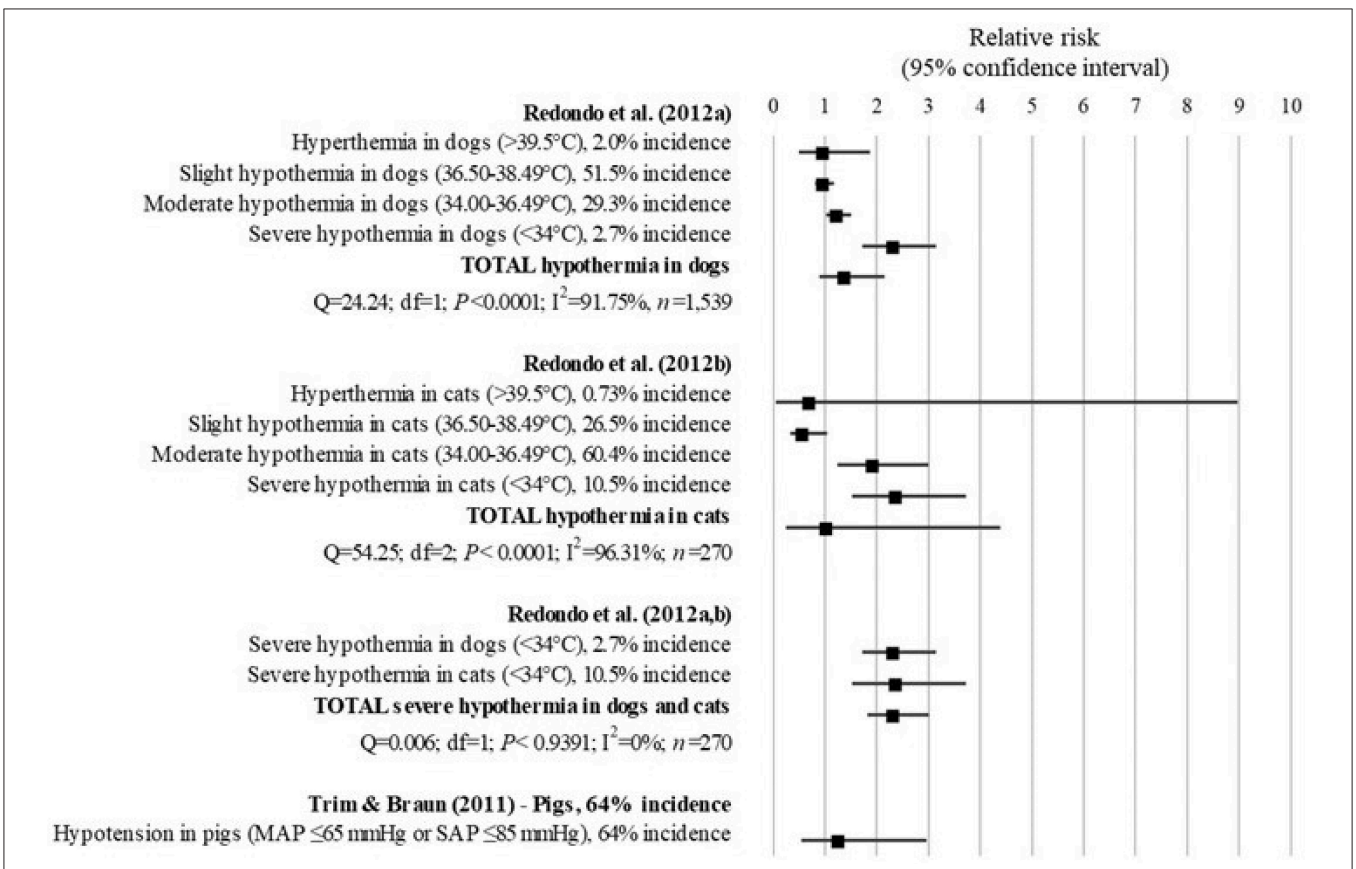

FIGURE 10 | Forest plot showing the increased risk of developing complications associated with anesthesia in patients with ASA PS ≥III compared with ASA PS <III. *Q*, Cochran's *Q* ($P < 0.05$ = heterogeneity; $P > 0.05$ = homogeneity); I^2, proportion of the inconsistency between the findings of the studies; *df*, degrees of freedom.

more likely to occur during anesthesia (24). In addition, these findings could suggest that stabilization of the patients prior to anesthesia in order to decrease the ASA PS category of the animal may be useful to decrease the risk of death. The surprising finding in the present study was that the increased risk of anesthesia-related death of patients with an ASA PS ≥III is significant during anesthesia until up to 24 h after the end of anesthesia in dogs and up to 72 h after the end of anesthesia in cats and rabbits. It suggests that death apparently does not occur only during anesthesia and, therefore, cannot necessarily be directly related to the use of certain anesthetic drugs. Other factors must be playing a role, of which the most likely one is progression of the underlying disease. Stress due to the disease, pain, and unfamiliar surroundings, can lead to anorexia, reduced gut motility, gastric ulceration, and immunosuppression, which could also contribute to the postanesthetic death. Other potential reasons could explain the higher risk of anesthesia-related death up to 24 h and up to 72 h after the end of anesthesia. Differences between studies in regards to the definition of anesthesia-related death, inclusion of sedated patients, and exclusion of those euthanized, and to the subjectivity of the ASA PS classification could have influenced these results. These features could also explain the significant inconsistency between the results of the studies assessing death after 24 h of the end of anesthesia in dogs.

The variation in the definition of anesthesia-related death among studies could have influenced the mortality rate in each ASA PS class. It could be difficult to distinguish the cases of mortality associated with anesthesia from those associated with the disease of the patient. In addition, terms as perioperative, postoperative, and perianeshetic death were often confused and used interchangeably throughout the studies with anesthesia-related risk of death without clear reference to their possible differences in meaning. Bille et al. (26, 30) and Clarke and Hall (19) included all deaths from medical or surgical complications and no attempt was made to classify the cause of death. In some studies, it was not clear whether ASA-associated risk of perioperative death could be interpreted as anesthesia-related. In the attempt to overcome this limitation, anesthesia-related death was defined as that where anesthesia could not be excluded as a potential cause, instead of only those where it was possible to ensure its association. In the studies of Itami et al. (33), Gil and Redondo (29), and Redondo et al. (28), it was possible to infer from the description of the causes of death, that they were associated with anesthesia or anesthesia could not be excluded as a potential cause of death. The studies of Robinson et al. (31) and Garcia de Carellan Mateo et al. (32) were analyzed separately because all deaths were included in the analysis (not only those anesthesia-related), and they were assessed in a specific population of dogs undergoing thoracic surgery and cats undergoing ureteral surgery, respectively. In rabbits, both studies of Lee et al. (35) and Brodbelt et al. (24) defined anesthesia-related death as any death that could not be explained totally by pre-existing medical or surgical complications, indicating that ASA-associated risk of perianesthetic death could be interpreted as anesthesia-related in this species.

In addition to the definition of anesthesia-related death, other potential explanations for differences among findings of the studies could be that two of them included sedated animals and six studies excluded deaths due to euthanasia from the analysis. All studies in rabbits included sedated animals (24, 35), indicating that rabbits with an ASA PS ≥III are at an increased risk of death associated not only with anesthesia, but also with sedation, compared with rabbits ASA PS <III. In dogs and cats, there was only one study (24) that included sedated animals, which could have had a minor impact in the differences among the findings included in the present analysis. In addition, the exclusion of euthanized animals could be associated with differences in the findings of the studies whenever anesthesia contributed to the negative outcome. However, all studies provided the reason for euthanasia and they did not seem to be associated with anesthesia.

The subjectivity of the ASA PS classification could have influenced the findings of the studies included in the present analysis. This subjectivity could be attributed to the vague definition of the ASA PS classes, especially before examples were published in the version of the ASA PS classification from 2014 (9). For instance, a healthy obese patient was cited as an example of an ASA PS II patient, while a morbid obese patient was cited as an example of an ASA PS III patient. However, Brodsky and Ingrande (45) stated that the physical status of a patient could not be based on his/her body mass index and that the obese population was heterogeneous. They specified that the presence of pathologies was independent of the bodyweight of the patient, and that it was the presence of fat infiltration that increases the risk of organic failure.

The subjectivity could lead to a high inter-observer and maybe intra-observer variability. In human medicine, some studies demonstrated a high inter-observer variability associated with pregnancy (46), smoking, the nature of surgery, airway complications, and acute injuries (47). The variability of the ASA PS scores was not correlated with the gender, age, expertise, working environment, or any demographic variable, and no difference between scores assigned by different groups of anesthetists was observed (47). In veterinary anesthesia, McMillan and Brearley (7) found a moderate variability among ASA PS scores given for 16 theoretical cases of small animals with different physical and pathological status by 144 anesthetists (specialist veterinarians, residents, interns, generalists and nurses). When studying real and non-hypothetical small animal cases in a university study, Mair and Wise (48) found homogeneity between ASA PS scores assigned by anesthetists and veterinary students. However, the inter-observer variability increased with the severity of the cases. In the present study, the Cochran's Q was calculated to verify the consistency of the findings of the studies in terms of whether they had the same outcome or not. The potential differences that could have contributed to the deviations remained unclear. In addition, the Newcastle-Ottawa scale was used to assess the quality of non-randomized studies included in the analysis and, therefore, the risk of bias. Finally, the ASA PS classes were grouped in I-II vs. III-V, which was described to improve the homogeneity of the responses in pediatric (49) and veterinary anesthesia (7).

The fact that the ASA PS score is a number does not make it an objective tool and, therefore, improvements in the classification were proposed to reduce inter/intra-observer variability. Some authors proposed the addition of a class of patients with moderate systemic disease between ASA PS II and ASA PS III (50). The lack of option for moderate systemic disease allowed the use of the ASA PS III as a cut-off to distinguish healthy from sick patients as previously described (19, 24), and to reach a binary answer to whether ASA PS was effective or not to identify patients at a greater risk of death or a specific complication. The simplification from a 5-point scale (ASA I-V) into a merged 2-point scale (ASA<III and ASA≥III), despite necessary to run the meta-analysis, could have resulted in some information loss.

It is debatable whether a patient with an ASA PS ≥III could also be associated with an increased risk of outcomes other than death. In human medicine, patients ASA PS class III-V had an increased cost of hospitalization (51). Accordingly, in veterinary medicine, a study with 235 dogs undergoing general anesthesia indicated that the ASA PS status was the only factor associated with the duration of ICU care (the higher ASA PS, the longer ICU stay), which, in turn, was a feature associated with an increase in the cost of hospitalization (34). In addition, the ASA PS classification could identify an increased frequency and severity of perioperative complications in human patients (52), dogs and cats (21, 22); a long ICU stay in dogs (34), and a poor recovery quality from anesthesia in horses (37, 38). Dogs ASA III, IV and V, were 3.4, 7.1, and 18.8 times, respectively, more likely to develop severe perianesthetic complications than those ASA I-II (21). Cats having an ASA status of III-V were nearly 4 times as likely to develop severe perianesthetic complications, such as cardiopulmonary arrest (22). In the present study, the risk of severe hypothermia in dogs and cats, and hypotension in pigs were anesthesia-related, but only the risk of hypothermia was associated with the preoperative ASA PS. The lack of association between the risk of hypotension associated with anesthesia and ASA PS in pigs may be associated with the small number of pigs included in the analysis ($n = 27$) (36). However, prospective studies with a large population would be necessary to confirm whether this is a true effect or type II error.

The search for evidence on whether the ASA PS classification can be recommended in veterinary anesthesia is a challenging task. The differences among studies (i.e., the length of follow up, definitions, inclusion and exclusion criteria, and subjectivity of the classification system) could have influenced the final analysis. However, some of these features cannot be controlled when assessing the risk of anesthesia-related death in patients with a high ASA PS. Indeed, randomized controlled trials, which presence greatly increases the quality of evidence (53), are not feasible. All prospective studies included in the present review were clinical observational cohort studies, which were not randomized and blinded, and did not control for mortality. In a clinical setting, patients were naturally randomized and mortality was not under control of the researcher. In addition, an independent blind assessment by assigning an ASA PS score without knowing whether the patient had a systemic disease is not possible. Usually cohort studies are not associated with a high quality of evidence because although they can show an association between an intervention and an outcome, they cannot prove a cause-effect relationship. However, it was never expected that an inadequate ASA PS score assigned preoperatively would cause anesthesia-related death. In order to answer our initial question, it was enough to know whether there was an association between the ASA PS score and the outcome.

Veterinary practitioners have obligations to inform owners of the potential foreseeable and serious risks their animal might be subjected to during a surgery. This review found evidence that dogs, cats, and rabbits with an ASA PS ≥III had an increased risk of anesthesia-related death and development of severe intraoperative hypothermia compared with those with an ASA PS <III. Nevertheless, the classification still needs to be refined to decrease inter and intra-raters variability. The outcome of anesthesia depends sometimes on other factors than the ASA PS status.

AUTHOR CONTRIBUTIONS

KP contributed to the conception of the work, data acquisition and interpretation, drafted and revised the work, and approved the final version. KI contributed to the data acquisition and interpretation, drafted and revised the work, and approved the final version.

REFERENCES

1. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* (1941) 5:281–4. doi: 10.1097/00000542-194105000-00004
2. Dripps R, Lamont A, Eckenhoff J. The role of anesthesia in surgical mortality. *JAMA* (1961) 178:261–6. doi: 10.1001/jama.1961.03040420001001
3. Ament R. Origin of the ASA classification. *Anesthesiology* (1979) 51:179. doi: 10.1097/00000542-197908000-00023
4. Driupps RD. New classification of physical status. *Anesthesiology* (1963) 24:111.
5. Owens W, Felts J, Spitznagel E. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology* (1978) 49:239–43. doi: 10.1097/00000542-197810000-00003
6. Mak PHK, Campbell RCH, Irwin MG, American Society of Anesthesiologists. The ASA physical status classification: inter-observer consistency. *Anaesth Intensive Care* (2002) 30:633–40.
7. McMillan M, Brearley J. Assessment of the variation in American Society of Anaesthesiologists Physical Status Classification assignment in small animal anaesthesia. *Vet Anaesth Analg.* (2013) 40:229–36. doi: 10.1111/vaa.12007
8. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J Anaesth.* (2011) 55:111–5. doi: 10.4103/0019-5049.79879
9. ASA House of Delegates. *ASA Physical Status Classification System* (2014). Available online at: http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system

10. Vacanti C, VanHouten R, Hill R. A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. *Anesth Analg.* (1970) 49:564–6. doi: 10.1213/00000539-197007000-00010
11. Marx G, Mateo C, Orkin L. Computer analysis of postanesthetic deaths. *Anesthesiology* (1973) 39:54–8. doi: 10.1097/00000542-197307000-00010
12. Koch J, McLellan B, Wortzman D, Bertram S, Szalai J. Is the ASA physical status classification adequate in predicting mortality in blunt trauma? *Anesthesiology* (1987) 67:A482. doi: 10.1097/00000542-198709001-00482
13. Cullen D, Apolone G, Greenfield S, Guadagnoli E, Cleary P. ASA Physical Status and age predict morbidity after three surgical procedures. *Ann Surg.* (1994) 220:3–9. doi: 10.1097/00000658-199407000-00002
14. Reponen E, Tuominen H, Korja M. Evidence for the use of preoperative risk assessment scores in elective cranial neurosurgery: a systematic review of the literature. *Anesth Analg.* (2014) 119:420–32. doi: 10.1213/ANE.0000000000000234
15. Miller T, Jeong H, Davis K, Matthew A, Lysikowski J, Cho M, et al. Evaluation of the American Society of Anesthesiologists Physical Status classification system in risk assessment for plastic and reconstructive surgery patients. *Aesthet Surg J.* (2014) 34:448–56. doi: 10.1177/1090820X14525394
16. Forrest J, Rehder K, Cahalan M, Goldsmith C. Multicenter study of general anesthesia. III Predictors of severe perioperative adverse outcomes. *Anesthesiology* (1992) 76:3–15. doi: 10.1097/00000542-199201000-00002
17. Hightower C, Riedel B, Feig B, Morris G, Ensor JJ, Woodruff V, et al. A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: physiological capacity compared with the ASA physical status classification system. *Br J Anaesth.* (2010) 104:465–71. doi: 10.1093/bja/aeq034
18. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth.* (1996) 77:217–22. doi: 10.1093/bja/77.2.217
19. Clarke K, Hall L. A survey of anaesthesia in small animal practice: AVA/BSAVA report. *Vet Anaesth Analg.* (1990) 17:4–10. doi: 10.1111/j.1467-2995.1990.tb00380.x
20. Dyson D, Maxie M, Schnurr D. Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. *J Am Anim Hosp Assoc.* (1998) 34:325–35. doi: 10.5326/15473317-34-4-325
21. Hosgood G, Scholl D. Evalution of age as a risk factor for perianesthetic morbidity and mortality in the dog. *J Vet Emerg Crit Care* (1998) 8:222–36. doi: 10.1111/j.1476-4431.1998.tb00128.x
22. Hosgood G, Scholl D. Evaluation of age and American Society of Anesthesiologists (ASA) physical status as risk factors for perianesthetic morbidity and mortality in the cat. *J Vet Emerg Crit Care* (2002) 12:9–15. doi: 10.1046/j.1534-6935.2002.00002.x
23. Brodbelt D, Pfeiffer D, Young L, Wood J. Risk factors for anaesthetic-related death in cats: results from the confidential enquiry into perioperative small animal fatalities (CEPSAF). *Br J Anaesth.* (2007) 99:617–23. doi: 10.1093/bja/aem229
24. Brodbelt D, Blissitt K, Hammond R, Neath P, Young L, Pfeiffer D, et al. The risk of death: the confidential enquiry into perioperative small animal fatalities. *Vet Anaesth Analg.* (2008) 35:365–73. doi: 10.1111/j.1467-2995.2008.00397.x
25. Brodbelt D, Pfeiffer D, Young L, Wood J. Results of the Confidential Enquiry into Perioperative Small Animal Fatalities regarding risk factors for anaesthetic-related death in dogs. *J Am Vet Med Assoc.* (2008) 233:1096–104. doi: 10.2460/javma.233.7.1096
26. Bille C, Auvigne V, Libermann S, Bomassi E, Durieux P, Rattez E. Risk of anaesthetic mortality in dogs and cats: an observational cohort study of 3546 cases. *Vet Anaesth Analg.* (2012) 39:59–68. doi: 10.1111/j.1467-2995.2011.00686.x
27. Redondo JI, Suesta P, Serra I, Soler C, Soler G, Gil L, et al. Retrospective study of the prevalence of postanaesthetic hypothermia in dogs. *Vet Rec.* (2012) 171:374. doi: 10.1136/vr.100476
28. Redondo JI, Suesta P, Gil L, Soler G, Serra I, Soler C. Retrospective study of the prevalence of postanaesthetic hypothermia in cats. *Vet Rec.* (2012) 170:206. doi: 10.1136/vr.100184
29. Gil L, Redondo J. Canine anaesthetic death in Spain: a multicentre prospective cohort study of 2012 cases. *Vet Anaesth Analg.* (2013) 40:e57–67. doi: 10.1111/vaa.12059
30. Bille C, Auvigne V, Bomassi E, Durieux P, Libermann S, Rattez E. An evidence-based medicine approach to small animal anaesthetic mortality in a referral practice: the influence of initiating three recommendations on subsequent anaesthetic deaths. *Vet Anaesth Analg.* (2014) 41:249–58. doi: 10.1111/vaa.12116
31. Robinson R, Chang YM, Seymour CJ, Pelligand L. Predictors of outcome in dogs undergoing thoracic surgery (2002-2011). *Vet Anaesth Analg.* (2014) 41:259–68. doi: 10.1111/vaa.12112
32. Garcia de Carellan Mateo A, Brodbelt D, Kulendra N, Alibhai H. Retrospective study of the perioperative management and complications of ureteral obstruction in 37 cats. *Vet Anaesth Analg.* (2015) 42:570–9. doi: 10.1111/vaa.12250
33. Itami T, Aida H, Asakawa M, Fujii Y, Iizuka T, Imai A, et al. Association between preoperative characteristics and risk of anaesthesia-related death in dogs in small-animal referral hospitals in Japan. *Vet Anaesth Analg.* (2017) 44:461–72. doi: 10.1016/j.vaa.2016.08.007
34. Smith M, Barletta M, Young C, Hofmeister E. Retrospective study of intra-anesthetic predictors of prolonged hospitalization, increased cost of care and mortality for canine patients at a veterinary teaching hospital. *Vet Anaesth Analg.* (2017) 44:1321–31. doi: 10.1016/j.vaa.2017.04.007
35. Lee HW, Machin H, Adami C. Peri-anaesthetic mortality and nonfatal gastrointestinal complications in pet rabbits: a retrospective study on 210 cases. *Vet Anaesth Analg.* (2018) 45:520–28. doi: 10.1016/j.vaa.2018.01.010
36. Trim CM, Braun C. Anesthetic agents and complications in Vietnamese potbellied pigs: 27 cases (1999-2006). *J Am Vet Med Assoc.* (2011) 239:114–21. doi: 10.2460/javma.239.1.114.
37. Dugdale A, Obhrai J, Cripps P. Twenty years later: a single-centre, repeat retrospective analysis of equine perioperative mortality and investigation of recovery quality. *Vet Anaesth Analg.* (2016) 43:171–8. doi: 10.1111/vaa.12285
38. Niimura Del Barrio MC, David F, Hughes JML, Clifford D, Wilderjans H, Bennett R. A retrospective report (2003-2013) of the complications associated with the use of a one-man (head and tail) rope recovery system in horses following general anaesthesia. *Ir Vet J.* (2018) 71:6. doi: 10.1186/s13620-018-0117-1
39. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality If Nonrandomized Studies in Meta-Analyses* (2012). Available online at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
40. Zhou Y, Li W, Herath C, Xia J, Hu B, Song F, et al. Off-Hour admission and mortality risk for 28 specific diseases: a systematic review and meta-analysis of 251 cohorts. *J Am Heart Assoc.* (2016) 5:e003102. doi: 10.1161/JAHA.115.003102
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557.
42. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* (2011) 342:d549. doi: 10.1136/bmj.d549.
43. Keats A. The ASA Classification of Physical Status-A recapitulation. *Anesthesiology* (1978) 49:233–6. doi: 10.1097/00000542-197810000-00001
44. Fink R. Interpretation of data. *Anesthesiology* (1979) 5:179. doi: 10.1097/00000542-197908000-00024
45. Brodsky J, Ingrande J. Obesity and ASA physical status. *ASA Monitor*. (2015) 79:76.
46. Barbeito A, Schultz J, Muir H, Dwane P, Olufolabi A, Breen T, et al. ASA physical status classification. A pregnant pause. *Anesthesiology* (2002) 96(Suppl. 1):96. doi: 10.1097/00000542-200204001-00118
47. Aronson CWL, McAuliffe MS, Miller K. Variability in the American Society of Anesthesiologists physical status classification scale. *AANA J.* (2003) 71:265–74.
48. Mair A, Wise I. A comparison of anaesthetist and student awarded classifications of American Society of Anesthesiologists (ASA) Physical Status scores in small animal anaesthesia. *Vet Anaesth Analg.* (2014) 41:A66.
49. Jacqueline R, Malviya S, Burke C, Reynolds P. An assessment of interrater reliability of the ASA physical status classification in pediatric surgical patients. *Paediatr Anaesth.* (2006) 16:928–31. doi: 10.1111/j.1460-9592.2006.01911.x

50. Pratt, S. Clinical forum revisited: The "P" value. In: *The Society for Obstetric Anesthesia and Perinatology (SOAP) Newsletter.* Phoenix, AZ (2003). p. 9–11.
51. Coalson D, Apfelbaum J. Correlation between two physical status measures and the ASA physical status score. *Anesthesiology* (1990) 73:A1253. doi: 10.1097/00000542-199009001-01253
52. Saubermann A, Lagasse R. Prediction of rate and severity of adverse perioperative outcomes: "normal accidents" revisited. *Mt Sinai J Med.* (2012) 79:46–55. doi: 10.1002/msj.21295
53. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* (2004) 328:1490. doi: 10.1136/bmj.328.7454.1490

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

CASE REPORT
published: 01 October 2018
doi: 10.3389/fvets.2018.00235

Prolonged Recovery From General Anesthesia Possibly Related to Persistent Hypoxemia in a Draft Horse

Julien Dupont, Didier Serteyn and Charlotte Sandersen*

Department of Clinical Sciences, Anesthesiology and Equine Surgery, Faculty of Veterinary Medicine, University of Liege, Liège, Belgium

Horses are susceptible to developing large areas of pulmonary atelectasis during recumbency and anesthesia. The subsequent pulmonary shunt is responsible for significant impairment of oxygenation. Since ventilation perfusion mismatch persists into the post-operative period, hypoxemia remains an important concern in the recovery stall. This case report describes the diagnosis and supportive therapy of persistent hypoxemia in a 914 kg draft horse after isoflurane anesthesia. It highlights how challenging it can be to deal with hypoxemia after disconnection from the anesthesia machine and how life-threatening it can become if refractory to treatment. Furthermore, it stresses the point on the interactions between hypoxemia and other factors, such as residual drug effects and hypothermia, that should also be considered in the case of delayed recovery from general anesthesia.

Keywords: horse, anesthesia, recovery, hypoxemia, estimated shunt fraction, hypothermia, residual drug effects

OPEN ACCESS

Edited by:
Karine Portier,
Université de Lyon, France

Reviewed by:
Bruna Santangelo,
VetAgro Sup, France
Regula Bettschart,
Universität Zürich, Switzerland

****Correspondence:***
Julien Dupont
julien.dupont@ulg.ac.be

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *26 June 2018*
Accepted: *10 September 2018*
Published: *01 October 2018*

Citation:
Dupont J, Serteyn D and Sandersen C (2018) Prolonged Recovery From General Anesthesia Possibly Related to Persistent Hypoxemia in a Draft Horse. Front. Vet. Sci. 5:235. doi: 10.3389/fvets.2018.00235

INTRODUCTION

A 9-year-old Boulonnais gelding weighing 914 kg was referred to the Equine Clinic of the University of Liege for transpalpebral enucleation of the left eye under general anesthesia. Preoperative laboratory values including total protein, packed cell volume (PCV), total hemoglobin (tHb), total and differential white blood cell count, serum creatinine, total and conjugated bilirubin, and gamma glutamyl transpeptidase were within normal limits. Physical examination was unnoticeable unless a mild tachypnoea (24 breaths/min), the patient was graded II according to the American Society of Anesthesiologists physical status.

Food, but not water, was withheld for 10 h prior to surgery. Vitamin E acetate and sodium selenite pentahydrate (VMD, Belgium; 6500 mg and 130 mg respectively), were administered IM twice, the day before and the morning of the surgery. A 12-gauge intravenous catheter was placed in the left jugular vein. Procaine penicillin (Kela, Belgium; 19.2 M UI IM), gentamicin (Franklin Pharmaceuticals, Ireland; 6 g IV), and acepromazine (Kela, Belgium; 90 mg IM) were administered 120 min before induction. Flunixin meglumine (Ecuphar, Belgium; 950 mg IV) immediately followed by xylazine (Prodivet Pharmaceuticals, Belgium; 480 mg IV) were administered as preanaesthetic medication. Anesthesia was induced with midazolam (Mylan, Belgium; 55 mg IV) and ketamine (Ecuphar, Belgium; 2 g IV) and the trachea was intubated with a 30 mm cuffed endotracheal tube (ETT) as soon as the patient was recumbent. The horse was positioned in right lateral recumbency on a padded surface and conducted to the operating room where he was connected to a rebreathing circuit.

A 20-gauge catheter was placed in the left dorsal metatarsal artery for continuous direct arterial pressure measurement and repeated arterial blood sampling. Invasive arterial blood pressure, pulse oximetry, electrocardiogram, inspired and expired percentages of oxygen and isoflurane, inspired and expired carbon dioxide partial pressures, airway pressure, and flow-volume loops were continuously recorded using a multiparameter monitor (Tafonius, Vetronics, UK). Arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), pH, PCV, plasma electrolytes, arterial saturation of hemoglobin (SaO_2), tHb, oxyhemoglobin (O_2Hb), carboxyhemoglobin, and methemoglobin were measured with co-oxymetry (Cobas b 123, Roche, Belgium).

Isoflurane (Zoetis, Belgium) was delivered in 100% oxygen and its end-tidal percentage was maintained between 0.9 and 1.3%. Intermittent positive pressure ventilation (IPPV) was provided during the whole procedure (Tafonius) to maintain end-tidal carbon dioxide partial pressure between 35 and 45 mmHg (respiratory rate: 6–8 breaths/min, tidal volume: 9.5–10 L, I:E ratio = 1:2 and maximum peak inspiratory pressure: 35 cmH_2O). Retrobulbar nerve block was performed with 100 mg lidocaine (AstraZeneca, Belgium) and 100 mg mepivacaine (AstraZeneca, Belgium) and auriculopalpebral nerve block with 20 mg lidocaine. Ketamine was administered three times as IV bolus (300 mg) to increase the anesthetic depth and morphine (Sterop, Belgium; 90 mg) was injected IV to control pain 82 min after induction. Partial intravenous anesthesia using ketamine (1 mg/kg/h) and midazolam (0.02 mg/kg/h) was added 25 min after induction, lasted for 95 min to be finished 80 min before the end of anesthesia. Lactated Ringer's solution (Dechra, UK) was infused during anesthesia at a rate of 5.6 ml/kg/h. Standard transpalpebral enucleation of the left eye was completed within 150 min and the total anesthesia time was 200 min.

Heart rate was comprised between 35 and 45 beats/min. Systolic, mean and diastolic arterial blood pressures ranged between 85 and 120, 65 and 95, and 50 and 85 mmHg, respectively. The first arterial blood gas revealed mild hypoxemia (PaO_2 64 mmHg). Salbutamol (Sandoz, Belgium; 1.9 mg) was administered through the ETT with a metered-dose inhaler 37 min after induction. However, the second arterial blood sample showed only a small improvement (PaO_2 73 mmHg). Therefore, an alveolar recruitment maneuver (ARM) was performed 47 min after induction. Practically, it consisted in interrupting IPPV during inspiratory phase and applying a continuous positive airway pressure (CPAP) of 50 cmH_2O during 45 s. Afterwards, IPPV was resumed and a positive end-expiratory pressure (PEEP) of 10 cmH_2O was maintained until the end of the procedure. Ulterior arterial blood samples showed a progressive improvement and hypoxemia was solved (PaO_2 80, 103, 153, and 203 mmHg at 3, 34, 61, and 90 min post-recruitment maneuver, respectively). Data from blood gas analysis are displayed in **Table 1**.

At the end of surgery, the horse was placed in right lateral recumbency in a rubber floored and heavily padded recovery stall. The ETT was secured and oxygen (15 L/min) was administered through it. The horse became extremely agitated 5 min after isoflurane discontinuation and needed to be sedated nine times with xylazine (total dose: 930 mg IV) and butorphanol (Ecuphar, Austria; 20 mg IV) to avoid self-inflicted traumas. The trachea was extubated 70 min after the end of anesthesia. Because of snoring, 10 ml of a solution of 0.5% phenylephrine (Bausch and Lomb, Belgium) was instilled in each nostril, a 16 mm nasopharyngeal tube was inserted through the left nostril and oxygen therapy was continued. He removed the nasopharyngeal tube during one of his violent uncoordinated movements but, because he was not snoring anymore, the oxygen hose (15 L/min) was placed directly in the nose to the pharynx and maintained in place whenever it was possible. Following the nine unsuccessful attempts to sedate the horse with xylazine, and as he was still not standing at that time, acepromazine was administered (50 mg IV), providing light but longer sedation (**Figure 1**).

Supportive therapy was started in the recovery stall as the recovery period exceeded 180 min. It consisted in fluid therapy with lactated Ringer's solution (11 ml/kg/h) supplemented with calcium gluconate (Dechra, Belgium), magnesium sulfate (Sterop, Belgium), and potassium chloride (Braun, Germany). Alternatively, sodium chloride 0.9% (Aguettant, Belgium) was infused according to plasma electrolytes measurement (sodium 137.2 mmol/l; chloride 98.6 mmol/l). Furthermore, nutrition support was provided with glucose 50% (Baxter, Belgium; 2mg/kg/min). Inotropic support with dobutamine (Mylan, Belgium; 1 μg/kg/min) was also added as the pulse was weak. Analgesia was provided with morphine (90 mg IM) TID and flunixin meglumine (950 mg IV) BID. The horse was also given a single dose of dexamethasone (Eurovet, Holland; 92 mg IV) 285 min after isoflurane discontinuation. Regular physical examinations were performed: the pulse became stronger after fluid therapy and inotropic support were initiated. Mucosa were pink and refill capillary time was prolonged up to 4 s. He presented tachycardia (50–64 beats/min) with arrhythmias and mild tachypnoea (22–28 breaths/min). Hypothermia, up to 33.4°C, was efficiently treated by covering him with blankets. Furthermore, he showed nystagmus and an obtunded pupillary light reflex. As the recovery period abnormally prolonged, concern was raised about generalized post-anaesthetic myopathy. However, the soft and non-painful muscle palpation, the normal gross appearance of urine and serum creatine kinase levels (**Table 1**) did not advocate for this condition.

A sling was put on the horse 8.5 h after entering the recovery stall, in addition to head and tail ropes, which were attached from the beginning, to lift him up with the hoist. Unfortunately, we did not manage to get him to standing position after having tried several times. Because he was very agitated and heavy, we also failed to change recumbency and he spent 14.5 h (including surgery) in right lateral recumbency. At 11 h after anesthesia, he managed to get and stay intermittently in sternal recumbency. Twenty-nine hours after the end of anesthesia, the horse finally stood up without any assistance. The right front leg was painful and he could not bear any weight on it, he kept standing for 90 min before lying down again. The horse finally stood up 5 h later and he was moved out of the recovery stall. The likely

TABLE 1 | Peripheral arterial and venous blood samples analyzed during anesthesia (A), when recumbent during recovery (R) and after standing (S).

Time	A/R/S	Patm	FiO_2	pH	Hba	PaO_2	SaO_2	$PaCO_2$	PvO_2	SvO_2	$PvCO_2$	Lact	CK	PAO_2	F-$shunt_e$
31 min	A	742.6	0.66	7.396	10.5	64.3	94.2	49.3	/	/	/	/	/	397.5	35
42 min (after salbutamol)	A	742.7	0.71	7.380	9.3	73.0	96.0	44.9	/	/	/	/	/	437.8	32
50 min (after ARM)	A	742.8	0.80	7.379	9.9	79.7	96.6	49.8	/	/	/	/	/	494.4	33
1 h 21 min	A	742.7	0.82	7.361	10.5	103.3	98.0	51.0	/	/	/	/	/	506.7	31
1 h 48 min	A	742.7	0.84	7.364	9.8	153.1	98.8	52.0	/	/	/	/	/	519.4	27
2 h 17 min	A	742.8	0.85	7.384	9.7	203.4	98.9	51.7	/	/	/	/	/	526.8	25
5 h 42 min	R	742.0	0.30	7.501	/	40.5	/	36.4	/	/	/	/	/	163.0	/
5 h 46 min	R	741.8	0.30	7.441	/	/	/	/	20.7	40.2	47.7	4.2	787	/	/
10 h 38 min	R	741.8	0.30	7.401	13.2	48.1	84.9	46.0	/	/	/	3.2	/	150.9	46
13 h 27 min	R	742.0	0.30	7.377	12.8	57.2	91.0	44.1	/	/	/	/	/	153.4	35
21 h 36 min	R	740.7	0.21	7.340	/	/	/	/	25.5	43.0	51.4	2.8	/	/	/
23 h 15 min	R	740.9	0.21	7.386	13.4	46.7	85.8	39.8	/	/	/	/	/	96.0	44
27 h 27 min	R	740.8	0.30	7.401	/	61.6	/	34.1	/	/	/	/	13,000	165.5	/
34 h 44 min	R (after S)	741.8	0.21	7.424	11.3	49.0	89.0	41.2	/	/	/	3.8	/	94.4	34
45 h 59 min	S	743.4	0.21	7.454	11.8	38.1	78.6	41.2	/	/	/	0.9	3,788	94.7	51

Patm, atmospheric pressure (mmHg); FiO_2, inspired oxygen fraction (mmHg); Hba, arterial hemoglobin concentration (g/dl); PaO_2, arterial oxygen partial pressure (mmHg); SaO_2, arterial hemoglobin oxygen saturation (%); $PaCO_2$, arterial carbon dioxide partial pressure (mmHg); PvO_2, venous oxygen partial pressure (mmHg); SvO_2, venous hemoglobin oxygen saturation (%); $PvCO_2$, venous carbon dioxide partial pressure (mmHg); Lact, lactates (mmol/L); CK, creatine kinase (UI/L); PAO_2, alveolar oxygen partial pressure (mmHg); F-$shunt_e$, estimated shunt fraction (%); ARM, alveolar recruitment maneuver.

$$PAO_2 = FiO_2{}^*(PAtm - PH_2O)] - (PaCO_2/0.8).$$

$$F - shunt_e = \left\{ \frac{[(1,36{}^*Hba{}^*(1 - SaO_2)) + (0,0031{}^*(PAO_2 - PaO_2))]}{[1,36{}^*Hba{}^*(1 - SaO_2)) + (0,0031{}^*(PAO_2 - PaO_2)) + 3,5]} \right\} {}^*100.$$

radial neuropathy and/or triceps myopathy were treated by administering acepromazine (46 mg IM) TID, morphine (90 mg IM) TID, ketamine (460 mg IM) QID and flunixin meglumine (950 mg IV) BID. Low molecular weight heparin (Sanofi, Belgium; 150 mg) was administered SC SID and supportive hoof bandages were placed on both front legs to prevent laminitis. Moreover, the horse presented paralysis and distortion of the nose and lips to the right side, most likely due to paralysis of the buccal branch of the right facial nerve, which spontaneously returned to normal upon discharge. Furthermore, the horse developed a surgical wound dehiscence due to infection, which successfully healed after a second surgery under standing sedation.

BACKGROUND

Perioperative Respiratory Complications

Horses are susceptible to quickly developing large areas of atelectasis and a consequent large pulmonary shunt causing significant impairment of gas exchange during recumbency and anesthesia (1–4). Pulmonary shunt has been estimated at 1% in standing horses, extending to 19%, and 33% in anesthetized laterally and dorsally recumbent horses, respectively (5, 6).

Compression atelectasis is the major type of atelectasis in anesthetized horses (6). Recumbency changes distribution of ventilation by reducing lung volume and altering the pleural pressure gradient to such an extent that the peripheral airways close in the dependent regions of the lung where closing volume exceeds functional residual capacity (2, 5). Body weight and body shape both influence PaO_2 and alveolar arterial oxygen gradient (Aa gradient). Indeed, light-weight animals which are tall with large thoracic circumference and flat belly better maintain oxygenation (7–9).

Moreover, characteristics of the pulmonary artery in the caudodorsal regions of the lung alter the hypoxic vasoconstrictive response to alveolar hypoxia, leading to preferential caudodorsal lung perfusion and larger ventilation perfusion mismatch regardless of the posture (3, 10, 11). In addition, most anesthetics, and particularly inhalants, deeply reduce or even abolish hypoxic vasoconstriction and flow redistribution (12).

Consequently, there can be prolonged periods of hypoxemia during general anesthesia in horses (4, 13–16).

Since ventilation perfusion (V/Q) mismatch persists into the postoperative period (17), hypoxemia remains an important concern in the early recovery period, especially when breathing room air reduces the inspired oxygen fraction (FiO2), requiring vigilant monitoring and oxygen supplementation (18). Nasotracheal insufflation of oxygen at a flow rate of at least 15 L/min immediately after disconnection from the anesthesia machine efficiently improves PaO_2 and relieves hypoxemia in the recovering horse (18). Furthermore, horses auto-recruit

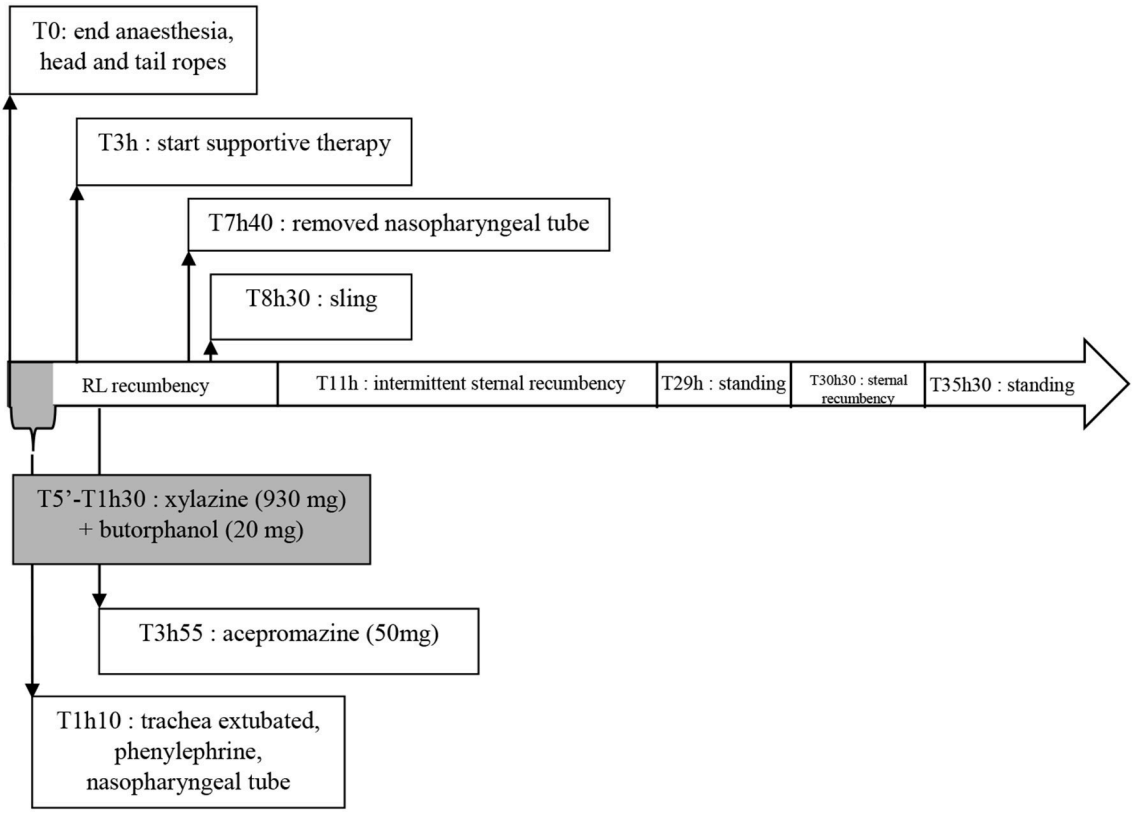

FIGURE 1 | Time line of the main events that happened during recovery. RL, right lateral.

their lungs by inspiratory breath holding following recovery from general anesthesia, possibly reflecting a compensatory mechanism to counteract persistent atelectasis (19).

Residual Drug Effects

Ketamine infusion is commonly used to balance inhalational anesthesia and midazolam infusion is frequently added to reduce the central excitatory effects of ketamine (20). Nevertheless, common concerns are often raised about their negative influence on recovery quality after prolonged infusion and the difficulty to predict the pharmacokinetics and pharmacodynamics of drugs combinations.

The pharmacokinetics of midazolam has only been described in conscious horses (21). Redistribution is responsible for the termination of its clinical effect and accumulation in peripheral compartment is highly probable.

Two studies described the pharmacokinetics of racemic ketamine after infusion in conscious horses (22, 23). They both mentioned that the pharmacokinetics of ketamine after infusion was different from those described after single bolus. Moreover, both studies stressed the point that premedication or concurrent administration of inhalants or other anesthetics were known to influence the pharmacokinetics of ketamine. Ketamine undergoes rapid metabolism to norketamine, whose redistribution and metabolism are slower than for parent drug. Nevertheless, the contribution of ketamine's metabolite to its pharmacological effects is unknown in the horse.

Intraoperative administration of ketamine has been shown to be a significant predictor of faster recovery time, indicating that these horses were kept at a lighter plane of anesthesia, and consequently had less isoflurane accumulation (24).

Inadvertent Perioperative Hypothermia

Several studies reported that hypothermia prolong time to standing in horses (24–26).

Drug metabolism relies on enzymatic reactions that may be altered by hypothermia. Hypothermia can therefore prolong recovery time (27).

DISCUSSION

Perioperative Respiratory Complications

Assessment of Oxygenation

Diagnostic tools

Usually, clinical assessment is sufficient to monitor most recoveries. However, different indices have been described to assess oxygenation. Venous admixture (Qs/Qt) is the most accurate but requires mixed venous blood collected from the pulmonary artery. Estimated shunt fraction (F-shunt$_e$) is a

content-based index that is calculated from peripheral arterial blood and has the best agreement with Qs/Qt (28).

Perioperative hypoxemia and atelectasis

Arterial blood gas analysis revealed mild hypoxemia at the beginning of the anesthesia period (PaO_2 64 mmHg). Inhalation of salbutamol and ARM followed by PEEP reverted hypoxemia (PaO_2 up to 203 mmHg at the end of the anesthesia period). During anesthesia, F-$shunt_e$ lay between 25 and 35%. In the recovery stall, PaO_2 was between 41 and 62 mmHg, corresponding to mild to moderate hypoxemia, and F-$shunt_e$ lay between 34 and 46% (**Table 1**). These calculated values of shunt percentage were largely superior to the expected value of 19% in anesthetized laterally recumbent horses (5, 6), suggesting a large pulmonary shunt responsible for hypoxemia in that horse. Moreover, PaO_2 10 h after standing was 38 mmHg, corresponding to severe hypoxemia and F-$shunt_e$ was 51%.

Prevention and Treatment of Hypoxemia

Oxygen supplementation

These measurements showed that, despite oxygen insufflation immediately after disconnection from the anesthesia machine, hypoxemia developed during recovery. Administering oxygen in ETT creates a combination of room air and oxygen leading to FiO_2 between 30 and 70% (29). The further distal in the airway oxygen is delivered, the greater the increase in FiO_2 for a particular oxygen flow rate (29). However, the horse could not bear the nasopharyngeal tube and was sometimes so agitated that the anesthetist did not manage to maintain the oxygen hose in his nose continuously, preventing from proper oxygen insufflation. Furthermore, the degree of improvement in PaO_2 depends on the increment in FiO_2 and on the degree of V/Q mismatch (29). Nevertheless, increasing FiO_2 during anesthesia is generally unsuccessful in correcting hypoxemia since much of the impairment in gas exchange results directly from shunt (30). Unfortunately, we did not measure the real FiO_2 during recovery and considered 30% for F-$shunt_e$ calculation, which might be a potential source of imprecision.

Lung recruitment

Open lung concept consists in, first, applying a high PIP to reinflate atelectatic lungs, which is also referred as ARM, and, second, maintaining a PEEP to prevent re-collapse. Indeed, once a critical amount of atelectasis is present in the equine lung, it is difficult to recruit that portion of the lung using traditional ventilation strategies (29) and PIP of up to 80 cmH_2O and PEEP of up to 30 cmH_2O are required (31–36). Two strategies are commonly used: either a stepwise incremental and decremental PIP and PEEP titration; or a sustained high-pressure maneuver followed by a predetermined PEEP. Although high airway pressures inevitably induce cardiovascular and pulmonary side effects, the first technique may present two main advantages: first, by allowing the cardiovascular system to better adapt to higher intrathoracic pressures; and second, by using the lowest PEEP required to keep recruited alveoli open (32, 34, 35, 37, 38). Optimal PEEP for each patient is best titrated by monitoring PaO_2 or the compliance of the dependent lung assessed by electrical impedance tomography (35). Despite that the sustained high-pressure ARM followed by predetermined PEEP used in this case resulted in reduction of pulmonary shunt and resolution of hypoxemia, these improvements did not extend in the recovery period. These observations suggested re-collapse as soon as positive airway pressure is lost, which is conflicting with studies reporting applications of modified open lung concept techniques. It is technically difficult to provide PEEP after disconnection, but, in theory, it may have limited de-recruitment (32, 33, 36, 37).

Auto-recruitment

It has been reported that horses auto-recruit their lungs by inspiratory breath holding until 5 h after standing (19). Nevertheless, this seemed not to be the case for this horse because pulmonary shunt and hypoxemia worsened after standing for 10 h. The reason why he did not manage to recruit his lungs is not clear. Obviously, the horse did not present a clinical picture compatible with a severe lung pathology such as pulmonary edema, pneumothorax, or pulmonary embolism. However, gene expression quantification has shown that mechanical ventilation, either IPPV (PIP of 20 cmH_2O) or stepwise ARM combined with PEEP (PIP of up to 60 cmH_2O and PEEP of 20 cmH_2O), might be responsible for an early inflammatory state in the lungs. Indeed, these ventilation strategies both increased markers possibly associated with lung injuries without being related to any histological lesion nor any modification of total and differential cell counts in bronchoalveolar lavage fluid (39). Therefore, we cannot exclude that the ventilation strategy applied to this horse, and combining IPPV (PIP of up to 35 cmH_2O) and sustained high-pressure ARM followed by predetermined PEEP (CPAP of 50 cmH_2O and PEEP of 10 cmH_2O), might not have caused alterations in the lungs that prevent from auto-recruitment.

Moreover, the higher weight of that draft horse might have played a role as for example prolonged atelectasis has been demonstrated in morbidly obese patients (40).

Body weight

As body weight and body shape both influence PaO_2 and Aa gradient (7–9), body weight might have played a role in the development of atelectasis, compression atelectasis being the major type of atelectasis in anesthetized horses (6).

Duration of anesthesia

Duration of anesthesia is known to influence the incidence of episodes of hypoxemia in humans (41, 42). The total anesthesia time was 200 min, which is much more than usual for transpalpebral enucleation and might have contributed to hypoxemia.

Anaesthetics

Anaesthetics may alter cardiorespiratory function and therefore negatively influence gas exchange. However, morphine and butorphanol have not produced clinically significant cardiorespiratory impairments, maintaining PaO_2 (43, 44). Similarly, acepromazine has improved arterial oxygenation by reducing V/Q disturbance and fall in PaO_2 associated with general anesthesia (45).

Hypoxemia-Related Postoperative Complications

Delayed recovery

Inhalants attenuate autoregulation of cerebral blood flow (46). Inhalants and hypoxemia can be involved in brain injury and consequent altered cognition (47), potentially explaining nystagmus and obtunded pupillary light reflex. They might therefore affect recovery quality. However, hypoxemia is aggravated by repeated attempts to stand (48). Moreover, hypoxemia reduces the strength of muscle contraction (49). In that case, reduced cardiac output, probably added to hypoxemia, led to further decrease in tissue oxygen delivery. Indeed, pulse became stronger after initiation of supportive therapy, suggesting improvement in circulatory function.

Residual Drug Effects

The use of midazolam (loading dose 0.04 mg/kg and infusion rate 0.02 mg/kg/h) and ketamine (loading dose 2.5 mg/kg and infusion rate 1 mg/kg/h) in sevoflurane-anesthetized horses has been described (50). All horses recovered satisfactorily but showed mild ataxia for 15–20 min, probably due to midazolam. As doses that we used were comparable to those described in this study; and as infusion lasted for a shorter duration (95 vs. 126–190 min) and was discontinued well before switching off inhalant (80 vs. 0 min), it is less likely that neither midazolam nor ketamine prevented our horse from standing.

Some studies described ketamine infusions in halothane-anesthetized horses (51–53), using loading doses ranging from 2.2 to 2.4 mg/kg and infusion rates from 2.0 to 2.8 mg/kg/h. All recoveries were considered acceptable and comparable of those observed with halothane only. We used comparable loading dose but our infusion rate was two to almost three times less than that described in these studies. Furthermore, the maximum infusion time was shorter (95 vs. 127 min) and it was stopped much more ealier than inhalant (80 vs. 0–15 min). Consequently, it is less likely that ketamine might have interfere with recovery in our case.

Although its pharmacological activity has not been described yet in horses, norketamine accumulation is still a concern. Its implication in the nystagmus and the obtunded pupillary light reflex that we observed can not be ruled out.

Inadvertent Perioperative Hypothermia

Hypothermia might be partly responsible for prolonged recovery. Indeed, it may play a part in midazolam and ketamine accumulation by reducing their metabolism. Moreover, by reducing baroreceptor function and cardiomyocytes contractility, hypothermia may be involved in the low cardiac output suspected in our case as well as in the cardiac arrhythmias that we noticed (54, 55). Furthermore, it may decrease central nervous system function and alter cerebral perfusion, potentially leading to the altered cognition that we observed (56). In addition, hypothermia and consequent shivering might have worsened hypoxemia by greatly increasing oxygen consumption. In our case, body temperature should have been more closely monitored during anesthesia and recovery; and hypothermia should have been aggressively treated as soon as it appeared.

CONCLUDING REMARKS

When facing complicated recovery, all the potentially contributing factors should always be contemplated. In this case, hypoxemia, residual drug effects, and hypothermia are three relevant factors that might have prolonged the period of time elapsed before the horse stood up. Indeed, although hypoxemia is a common complication in equine anesthesia and should be considered, residual drug effects and hypothermia should not be misregarded as they might have been responsible for rough recovery even without hypoxemia.

ETHICS STATEMENT

While signing the hospitalization contract, the owner is aware and accepts that data concerning his animal might be used for scientific purposes without further consent, guaranteeing confidentiality and anonimity of the owner.

AUTHOR CONTRIBUTIONS

JD, DS, and CS were involved in clinical management of the case including data treatment and interpretation. All authors were involved in the preparation of the manuscript.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Alexandra Gougnard for the precious help she brought in clinical management of the case.

REFERENCES

1. Hall LW. Disturbances of cardiopulmonary function in anesthetized horses. *Equine Vet J.* (1971) 3:95–8. doi: 10.1111/j.2042-3306.1971.tb04447.x
2. McDonnell WN, Hall LW, Jeffcott LB. Radiographic evidence of impaired pulmonary function in laterally recumbent anaesthetized horses. *Equine Vet J.* (1979) 11:24–32. doi: 10.1111/j.2042-3306.1979.tb01290.x
3. Dobson A, Gleed RD, Meyer RE, Stewart BJ. Changes in blood flow distribution in equine lungs induced by anaesthesia. *Q J Exp Physiol.* (1985) 70:283–97. doi: 10.1113/expphysiol.1985.sp002909
4. Nyman G, Funkquist B, Kvart C, Frostell C, Tokics L, Strandberg A et al. Atelectasis causes gas exchange impairment in the anaesthetised horse. *Equine Vet J.* (1990) 22:317–24. doi: 10.1111/j.2042-3306.1990.tb04280.x
5. Sorenson PR, Robinson NE. Postural effects on lung volumes and asynchronous ventilation in anaesthetized horses. *J Appl Physiol.* (1980) 48:97–103. doi: 10.1152/jappl.1980.48.1.97
6. Nyman G, Hedenstierna G. Ventilation-perfusion relationships in the anaesthetised horse. *Equine Vet J.* (1989) 21:274–81. doi: 10.1111/j.2042-3306.1989.tb02167.x
7. Moens Y, Lagerweij E, Gootjes P, Poortman J. Distribution of inspired gas to each lung in the anaesthetised horse and influence of body shape. *Equine Vet J.* (1995) 27:110–6. doi: 10.1111/j.2042-3306.1995.tb03045.x

8. Mansel JC, Clutton RE. The influence of body mass and thoracic dimensions on arterial oxygenation in anaesthetized horses and ponies. *Vet Anaesth Anal.* (2008) 35:392–9. doi: 10.1111/j.1467-2995.2008.00400.x
9. Schauvliege S. Savvast I, Gasthuys F. The effect of the inspired oxygen fraction on arterial blood oxygenation in spontaneously breathing, isoflurane anaesthetized horses: a retrospective study. *Vet Anaest Analg.* (2015) 42:280–5. doi: 10.1111/vaa.12208
10. Hlastala MP, Bernard SL, Erickson HH, Fedde MR, Gaughan EM, McMurphy R et al. Pulmonary blood flow distribution in standing horses is not dominated by gravity. *J Appl Physiol.* (1996) 81:1051–61. doi: 10.1152/jappl.1996.81.3.1051
11. Stack A, Derksen FJ, Williams KJ, Robinson NE, Jackson WF. Lung region and racing affect mechanical properties of equine pulmonary microvasculature. *J Appl Physiol.* (2014) 117:370–6. doi: 10.1152/japplphysiol.00314.2014
12. Steffey EP, Wheat JD, Meagher DM, Norrie RD, McKee J, Brown M et al. Body position and mode of ventilation influences arterial pH, oxygen, and carbon dioxide tensions in halothane- anesthetized horses. *Am J Vet Res.* (1977) 38:379–82.
13. Hall LW, Gillespie JR, Tyler WS. Alveolo-arearterial oxygen tension differences in anaesthetised horses. *Br J Anaesth.* (1968) 40:560–8. doi: 10.1093/bja/40.8.560
14. Mitchell B, Littlejohn A. The effect of anaesthesia and posture on the exchange of respiratory gases and on the heart rate. *Equine Vet J.* (1974) 6:177–8. doi: 10.1111/j.2042-3306.1974.tb03956.x
15. Stegmann GF, Littlejohn A. The effect of lateral and dorsal recumbency on cardiopulmonary function in the anaesthetised horse. *J S Afr Vet Assoc.* (1987) 58:21–7.
16. Day TK, Gaynor JS, Muir WW, Bednarski RM, Mason DE. Blood gas values during intermittent positive pressure ventilation and spontaneous ventilation in 160 anesthetized horses positioned in lateral or dorsal recumbency. *Vet Surg.* (1995) 26:266–76. doi: 10.1111/j.1532-950X.1995.tb01330.x
17. Mason DE, Muir WW, Wade A. Arterial blood gas tensions in the horse during recovery from anesthesia. *J Am Vet Med Assoc.* (1987) 190:989–94.
18. McMurphy RM, Cribb PH. Alleviation of post-anesthetic hypoxemia in the horse. *Can Vet J.* (1989) 30:37–41.
19. Mosing M, Waldmann AD, MacFarlane P, Iff S, Auer U, Bohm SH et al. Horses auto-recruit their lungs by inspiratory breath holding following recovery from general anaesthesia. *PLoS ONE* (2016) 11:e0158080. doi: 10.1371/journal.pone.0158080
20. Bettschart-Wolfensberger R. Horses. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. *Veterinary Anesthesia and Analgesia, The Fifth Edition of Lumb and Jones*. Oxford, UK: Wiley Blackwell (2015). p. 857–66.
21. Hubbell JA, Kelly EM, Aarnes TK, Bednarski RM, Lerche P, Liu Z et al. Pharmacokinetics of midazolam after intravenous administration to horses. *Equine Vet J.* (2013) 45:721–5. doi: 10.1111/evj.12049
22. Fielding CL, Brumbaugh GW, Matthews NS, Peck KE, Roussel AJ. Pharmacokinetics and clinical effects of subanesthetic continuous rate infusion of ketamine in awake horses. *Am J Vet Res.* (2006) 67:1484–90. doi: 10.2460/ajvr.67.9.1484
23. Lankveld DP, Driessen B, Soma IR, Moate PJ, Rudy J, Uboh CE et al. Pharmacodynamic effects and pharmacokinetic profile of a long-term continuous rate infusion of racemic ketamine in healthy conscious horses. *J Vet Pharmacol Therap.* (2006) 29:477–88. doi: 10.1111/j.1365-2885.2006.00794.x
24. Voulgaris DA, Hofmeister EH. Multivariate analysis of factors associated with post-anesthetic times to standing in isoflurane-anesthetized horses: 381 cases. *Vet Anaesth Analg.* (2009) 36:414–20. doi: 10.1111/j.1467-2995.2009.00472.x
25. Tomasic M. Temporal changes in core body temperature in anesthetized adult horses. *Am J Vet Res.* (1999) 60:556–62.
26. Mayerhofer I, Scherzer S, Gabler C, van den Hoven R. Hypothermia in horses induces by general anaesthesia and limiting measures. *Equine Vet Educ.* (2005) 17:53–6. doi: 10.1111/j.2042-3292.2005.tb00336.x
27. Clark-Price S. Inadvertent perianesthetic hypothermia in small animal patients. *Vet Clin Small Anim.* (2015) 45:983–94. doi: 10.1016/j.cvsm.2015.04.005
28. Araos JD, Larenza P, Boston R, De Monte V, De Marzo C, Grasso S et al. Use of oxygen content-based index, Fshunt, as an indicator of pulmonary venous admixture at various inspired oxygen fractions in anesthetized sheep. *Am J Vet Res.* (2012) 73:2013–20. doi: 10.2460/ajvr.73.12.2013
29. Kerr CL, McDonell WN. Oxygen supplementation and ventilatory support. In: Muir WW, Hubbell JAE, editors. *Equine Anesthesia: Monitoring and Emergency Therapy*. St. Louis, MI: Saunders (2009). p. 332-52.
30. Benator SR, Hewlett AM, Nunn JF. The use of iso-shunt lines for control of oxygen therapy. *Br J Anaesth.* (1973) 45:711–8. doi: 10.1093/bja/45.7.711
31. Levionnois OL, Iff I, Moens Y. Successful treatment of hypoxemia by an alveolar recruitment maneuver in a horse during general anaesthesia for colic surgery. *Pferdeheilkunde* (2006) 2:333–6. doi: 10.21836/PEM20060314
32. Bringewatt T, Hopster K, Kästner SB, Rohn K, Ohnesorge B. Influence of modified open lung concept ventilation on the cardiovascular and pulmonary function of horses during total intravenous anaesthesia. *Vet Rec.* (2010) 167:1000–6. doi: 10.1136/vr.c4172
33. Hopster K, Kästner SB, Rohn K, Ohnesorge B. Intermittent positive pressure ventilation with constant positive end-expiratory pressure and alveolar recruitment manoeuvre during inhalation anaesthesia in horses undergoing surgery for colic, and its influence on the early recovery period. *Vet Anaesth Analg.* (2011) 38:169–77. doi: 10.1111/j.1467-2995.2011.00606.x
34. Moens Y, Schrammel JP, Tusman G, Ambrisko TD, Solà J, Brunner JX et al. Variety of non-invasive continuous monitoring methodologies including electrical impedance tomography provides novel insights into the physiology of lung collapse and recruitment – case report of an anaesthetized horse. *Vet Anaesth Analg.* (2014) 41:196–204. doi: 10.1111/vaa.12098
35. Ambrisko TD, Schrammel J, Hopster K, Kästner S, Moens Y. Assessment of distribution of ventilation and regional lung compliance by electrical impedance tomography in anaesthetized horses undergoing alveolar recruitment manoeuvres. *Vet Anaesth Analg.* (2017) 44:264–72. doi: 10.1016/j.vaa.2016.03.001
36. Hopster K, Rohn K, Ohnesorge B, Kästner SB. Controlled mechanical ventilation with constant positive pressure and alveolar recruitment manouevres during anaesthesia in laterally or dorsally recumbent horses. *Vet Anaest Analg.* (2017) 44:121–6. doi: 10.1111/vaa.12390
37. Wettstein D, Moens Y, Jaeggin-Schmucker N, Böhn SH, Rothen HU, Mosing M et al. Effects of an alveolar recruitment maneuver on cardiovascular and respiratory parameters during total intravenous anesthesia in ponies. *Am J Vet Res.* (2006) 67:152–9. doi: 10.2460/ajvr.67.1.152
38. Hospter K, Wogatzki A, Geburek F, Conze P, Kästner SB. Effects of positive end-expiratory pressure titration on intestinal oxygenation and perfusion in isoflurane anaesthetised horses. *Equine Vet J.* (2016) 49:250-256. doi: 10.1111/evj.12555
39. Hopster K, Jacobson B, Hopster-Iversen C, Rohn K, Kästner SB. Histopathological changes and mRNA expression in lungs of horses after inhalation anaesthesia with different ventilation strategies. *Res Vet Sci.* (2016) 107:8–15. doi: 10.1016/j.rvsc.2016.04.008
40. Eichenberger A, Proietti S, Wicky S, Magnusson L. Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. *Anesth Analg.* (2002) 95:1788–92. doi: 10.1213/01.ANE.0000065081.21607.4C
41. Smith DC, Crul JF. Early postoperative hypoxia during transport. *Br J Anaesth.* (1988) 61:625–7.
42. Moller JT, Wittrup M, Johansen SH. Hypoxemia in the post-anesthesia care unit: an observer study. *Anesthesiology* (1990) 73:890–5. doi: 10.1097/00000542-199011000-00016
43. Hofmeister EH, Mackey EB, Trim CM. Effect of butorphanol administration on cardiovascular parameters in isoflurane-anesthetized horses-a retrospective clinical evaluation. *Vet Anaest Analg.* (2008) 35:38–44. doi: 10.1111/j.1467-2995.2007.00355.x
44. Benmasour P, Husulak ML, Bracamonte JL, Beazley SG, Withnall E, Duke-Novakovski T. Cardiopulmonary effects of an infusion of remifentanil or morphine in horses anesthetized with isoflurane and dexmedetomidine. *Vet Anaest Analg.* (2014) 41:46–56. doi: 10.1111/vaa.12149
45. Marntell S, Nyman G, Funkquist P, Hedenstierna G. Effects of acepromazine on pulmonary gas exchange and circulation during sedation and dissociative anaesthesia in horses. *Vet Anaest Analg.* (2005) 32:83–93. doi: 10.1111/j.1467-2995.2004.00178.x

46. Patel PM, Drummond JC, Lemkuil BP. Cerebral physiology and the effects of anesthetic drugs. In: Cohen NH, Eriksson LI, Fleisher LA et al, editors. *Miller's Anesthesia.* Elsevier Saunders (2015). p. 387–422.
47. Hopkins RO, Bigler ED. Pulmonary disorders. In: Tarter RE, Butters M, Beers SR, editors. *Medical Neuropsychology.* Alphen aan den Rijn: Kluwer Academic (2001). p. 25–50.
48. Auckburally A, Nyman G. Review of hypoxaemia in anaesthetized horses: predisposing factors, consequences and management. *Vet Anaesth Analg.* (2017) 44:397–408. doi: 10.1016/j.vaa.2016.06.001
49. Romer LM, Dempsey JA, Lovering A, Eldridge M. Exercise-induced arterial hypoxemia: consequences for locomotor muscle fatigue. *Adv Exp Med Biol.* (2006) 588:47–55. doi: 10.1007/978-0-387-34817-9_5
50. Kushiro T, Yamashita K, Umar MA, Maehara S, Wakaiki S, Abe R et al. Anesthetic and cardiovascular effects of balanced anesthesia using constant rate infusion of midazolam-ketamine-medetomidine-with inhalation of oxygen-sevoflurane (MKM-OS) in horses. *J Vet Med Sci.* (2005) 67:379–84. doi: 10.1292/jvms.67.379
51. Flaherty D, Nolan A, Reid J, Monteiro AM. The pharmacokinetics of ketamine after a continuous infusion under halothane anaesthesia in horses. *J Vet Anaesth.* (1998) 25:31–6. doi: 10.1111/j.1467-2995.1998.tb00166.x
52. Spadavecchia C, Stucki F, Moens Y, Schatzmann U. Anaesthesia in horses using halothane and intravenous ketamine-guaiphenesin: a clinical study. *Vet Anaesth Analg.* (2002) 29:20–8. doi: 10.1046/j.1467-2987.2001.00060.x
53. Kruger K, Stegmann GF. Partial intravenous anaesthesia in 5 horses using ketamine, lidocaine, medetomidine and halothane. *J S Afr Vet Assoc.* (2009) 80:233–6. doi: 10.4102/jsava.v80i4.214
54. Kaul SU, Beard DJ, Millar MD. Preganglionic sympathetic activity and baroreceptor responses during hypothermia. *Br J Anaesth.* (1973) 45:433–9. doi: 10.1093/bja/45.5.433
55. Maaravi Y, Weiss T. The effect of prolonged hypothermia on cardiac function in a young patient with accidental hypothermia. *Chest* (1990) 98:1019–20. doi: 10.1378/chest.98.4.1019
56. Niwa K, Takizawa S, Takagi S, Shinohara Y. Mild hypothermia disturbs cerebrovascular autoregulation in awake rats. *Brain Res.* (1998) 789:68–73. doi: 10.1016/S0006-8993(98)00013-4

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 29 May 2019
doi: 10.3389/fvets.2019.00160

Do the Manual or Computer-Controlled Flowmeters Generate Similar Isoflurane Concentrations in Tafonius?

Mathieu Raillard[1,2]*, *Olivier Levionnois*[2] *and Paul MacFarlane*[1]

[1] *Bristol Veterinary School, University of Bristol, Bristol, United Kingdom,* [2] *Section of Anaesthesiology and Pain Therapy, Department of Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern, Bern, Switzerland*

Introduction: Tafonius is an anesthesia machine with computer-controlled monitor and ventilator. We compared the isoflurane fluctuations in the circuit with manual (MF) or computer-driven (CF) flowmeters, investigated the origin of the differences and assessed whether isoflurane concentration time course followed a one-compartment model.

Material and Methods: A calibrated TEC-3 isoflurane vaporizer was used. Gas composition and flows were measured using a multiparametric monitor and a digital flowmeter. Measurements included: (1) Effects of various F_iO_2 with MF/CF on the isoflurane fraction changes in the breathing system during mechanical ventilation of a lung model; wash-in kinetic was fitted to a compartmental model; (2) Gas outflow at the common gas outlet (CGO) with MF/CF at different F_iO_2; (3) Isoflurane output of the vaporizer at various dial settings with MF/CF set at different flows without and with reduction of the CGO diameter.

Results: (1) The 3% targeted isoflurane concentration was not reached; additional time was required to reach specific concentrations with CF (lowest F_iO_2, longer time). The exponential course fitted a two-compartment model; (2) Set and measured flows were identical with MF. With CF at 0.21 F_iO_2, flow was intermittently 7.6 L min^{-1} or zero (mean total: 38% of the set flow); with CF at 1.00 F_iO_2, flow was 10.6 L min^{-1} or zero (mean: 4–5.3 L min^{-1}); with $0.21 < F_iO_2 < 1.00$, combined flow was intermittent (maximum output: 15.6 L min^{-1}); (3) With MF, isoflurane output was matching dial setting at 5 L min^{-1} but was lower at higher flows; with CF generating intermittent flows, isoflurane output was fluctuating. With the 4 mm diameter CGO, isoflurane concentration was close to dial setting with both MF and CF. With a 14 G CGO, isoflurane concentration was lower than dial setting with MF, higher with CF.

Conclusions and Clinical Relevance: Using MF or CF led to different isoflurane fraction time course in Tafonius. Flows were lower than set with CF; the TEC-3 did not compensate for high/intermittent flows and pressures; the CGO diameter influenced isoflurane output.

Keywords: anesthesia, flowmeter, horses, Tafonius, TEC 3, vaporizer, ventilator, veterinary

OPEN ACCESS

Edited by:
Karine Portier,
Université de Lyon, France

Reviewed by:
Rene Doerfelt,
Ludwig-Maximilians Universität München, Germany
Francesco Staffieri,
University of Bari Aldo Moro, Italy

***Correspondence:**
Mathieu Raillard
mathieu_raillard@yahoo.it

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *24 December 2018*
Accepted: *10 May 2019*
Published: *29 May 2019*

Citation:
Raillard M, Levionnois O and MacFarlane P (2019) Do the Manual or Computer-Controlled Flowmeters Generate Similar Isoflurane Concentrations in Tafonius? Front. Vet. Sci. 6:160. doi: 10.3389/fvets.2019.00160

INTRODUCTION

Tafonius (Hallowell EMC and Vetronic Services LTD, UK) is a large animal anesthesia machine with integral computer-controlled monitor and ventilator. Although fresh gas flow (FGF) into the breathing system is conventionally controlled by a manually-driven flowmeter (MF), a computer-driven flowmeter (CF) can be used as an alternative. This feature is particularly useful to administer oxygen-air admixtures in versions of the machine fitted with an oxygen (O_2) and nitrous oxide (N_2O) manual flowmeters but no medical air flowmeter. When using the CF, the user sets the targeted inspired oxygen fraction (F_iO_2) and the total FGF. In an attempt to deliver the desired gas mixture, oxygen (O_2) from the pipeline or cylinder supply is blended with room air pumped into the anesthetic machine. The data from the gas measurement module attached to the anesthetic machine is used by the computer to determine the required flows of air and/or O_2 into the system.

Delivery of inaccurate amounts of volatile agents during equine anesthesia can represent a serious safety concern. Insufficient volatile concentrations might lead to movements or awaking of anesthetized horses; excessive concentrations might result in cardiovascular and respiratory complications, prolonged and poor recoveries. Based on personal experience in anesthetized horses, the authors noticed that using the CF instead of the MF altered the inspired volatile agent fraction reached and on the time required to reach similar fractions. It was hypothetized that, at similar FGF settings, changes in time of volatile agent fraction in the breathing system would be different between MF and CF. The aim of this bench study was to compare the isoflurane fraction fluctuations in the Tafonius anesthetic machine when using the MF or CF and investigate the origin of the differences observed. Wash-in and wash-out kinetics of isoflurane in a breathing system have been described to follow a one-compartment model and are characterized by the time constant (1). The present study also aimed to investigate whether the isoflurane time course followed this assumption with the Tafonius anesthetic machine.

MATERIALS AND METHODS

Equipment

Tafonius 07 (Hallowell EMC and Vetronic Services LTD, UK) was used in this study. Oxygen and N_2O (but no medical air) manual flowmeters were present on this version of the machine. The machine had been serviced and calibrated the week before the experiment. A recently serviced and calibrated Datex-Ohmeda TEC-3 isoflurane vaporizer was fitted onto the backbar. Prior to each experimental procedure the anesthetic machine was connected to the hospitals piped O_2 supply and isoflurane added to the vaporizer until the fill gauge was at the recommended maximum level. The anesthetic machine was switched on, the piston zeroed and the automatic leak and compliance check ran following the manufacturer's instructions. The buffer value for the ventilator setting of the Tafonius was set at 15 L. The total volume of the breathing system was calculated to be 28 L (manufacturer's information: breathing tubes [6 L], down-pipes and area above the soda-lime [7 L], and buffer volume [15 L]).

In addition to the monitoring unit of the Tafonius, a Datex-Ohmeda S/5 anesthetic monitor was used throughout the study to measure fractions of O_2 (F_iO_2, $F_{E'}O_2$) and isoflurane (F_iISO, $F_{E'}$ISO) within the breathing system (mean sampling rate of 150 mL min^{-1}; the extracted volume was not redirected to the breathing system). Before each experiment, this monitor's gas module was calibrated using a calibration gas (Quick Cal Calibration gas, Ref: 755583-HEL [CO_2 5.00%, O_2 55.0%, N_2O 33.0%, Desflurane 2.00%] GE Healthcare, Helsinki, Finland) according to the manufacturer's recommendations.

Phase 1: Effects of Various F_iO_2 Settings on the Isoflurane Fraction in the Breathing System During Mechanical Ventilation of a Lung Model

The breathing system was connected to an artificial lung constructed from a rubber reservoir bag (with a volume of 12 L including tubing) within a closed transparent plastic cylinder. This unit was the "bag in bottle" assembly of another large animal ventilator (Dräger Large Animal ventilator; Dräger, UK). Small amount of foam padding was placed within the cylinder to reproduce lung compliance. The artificial lung was connected to the Y-piece of the breathing system. Absence of leak under pressure up to 40 cm H_2O was checked after assembling the device (manually before connection to Tafonius). Controlled mechanical ventilation was applied (tidal volume: 4 L; respiratory rate: 6 breaths per minute; I:E ratio: 1:3). Peak inspiratory pressure was 35 cm H_2O. All gas measurements were taken from the gas sampling port of the Y-piece of the breathing system through a three-way tap allowing simultaneous sampling for the monitoring unit of the Tafonius and for the Datex gas module.

Step 1a: Effect of F_iO_2 and Fresh Gas Flow (FGF) on the Rise (0–3%) of Isoflurane Fraction ($F_{E'}$ISO)

At the beginning of each step the isoflurane vaporizer was off, and both the breathing system and the artificial lung were pre-filled with the admixture of gases (O_2 and air) until the $F_{E'}O_2$ being tested remained unchanged for 15 min. The vaporizer dial was then turned on 3%, and isoflurane and O_2 partial pressures measured in the breathing system were manually recorded every minute for 90 min or until $F_{E'}$ISO remained unchanged for 15 min. The order of experiments was: *(1)* F_iO_2 1.00, MF 5 L min^{-1}; *(2)* F_iO_2 1.00, CF 5 L min^{-1}; *(3)* F_iO_2 0.21, CF 5 L min^{-1}; *(4)* F_iO_2 0.40, CF 5 L min^{-1}; *(5)* F_iO_2 0.40, CF 10 L min^{-1}; *(6)* F_iO_2 0.70, CF 5 L min^{-1}.

Step 1b: Effect of F_iO_2 on the Reduction (3–1%) of Isoflurane Fraction ($F_{E'}$ISO)

At the beginning of each test the isoflurane vaporizer dial was set on 3%, and both the breathing system and the artificial lung were pre-filled with the admixture of gases (O_2 and air) until the $F_{E'}O_2$ being tested remained unchanged for 15 min. The vaporizer dial was then turned on 1%, and isoflurane and O_2 partial pressures measured in the breathing system were manually recorded every minute for 90 min or until $F_{E'}$ISO remained unchanged for 15 min. The order of experiments was: *(1)* F_iO_2 1.00, MF 5 L min^{-1}; *(2)* F_iO_2 1.00, CF 5 L min^{-1}; *(3)* F_iO_2 0.40, CF 5 L min^{-1}; *(4)* F_iO_2 0.70, CF 5 L min^{-1}.

For steps 1a and 1b, the difference for the time required to reach a target concentration between MF (as reference) and CF (at different F_iO_2) is calculated as a mean of comparison.

Step 1c: Comparison of Isoflurane Time Course to One-Compartmental Model

The time course of the isoflurane concentration ($F_{E'}ISO$) during the previous steps was fitted to a pharmacokinetic compartmental model (Phoenix 8.1, Certara USA Inc.), and compared to the ideal behavior of a one-compartmental model for a volume of distribution of 40 L (28 L of the breathing system + 12 L of the lung simulator) and a clearance equal to the input.

Step 1d: Effect of F_iO_2 Changes on the Stability of the Isoflurane Fraction in the Breathing System Using the CF

The system was filled with O_2 (F_iO_2 1.0, MF 10 L min^{-1}) and isoflurane (set at 3% on the vaporizer) until $F_{E'}O_2$ and $F_{E'}ISO$ remained unchanged for 15 min. MF was switched off, CF turned on at 5 L min^{-1}, and $F_{E'}ISO$ recorded every minute for 15 min. Afterwards, F_iO_2 was decreased stepwise to 0.8, 0.6, and 0.4, and then re-increased to 0.6, 0.8, and 1.00. At each F_iO_2, $F_{E'}ISO$ was recorded every minute until the targeted $F_{E'}O_2$ was reached and remained unchanged for 15 min, before moving to the next step.

Phase 2: Measurements of the Gas Outflow at the Common Gas Outlet With MF or CF Set at Different F_iO_2

Gas flows were measured with a calibrated portable digital flowmeter (PFM 100 Flow Meter, manufactured by Rusz Instruments Inc. Pittsfield, Massachusetts, USA) connected at the common gas outlet (CGO). Investigated gas (O_2 or air) was selected on the digital flowmeter to allow accurate measurements.

Step 2a: Measurements of the Gas Outflow at the Common Gas Outlet With MF ($F_iO_2 = 1.0$) Across a Range of Flow Settings

The MF was set over a wide range of FGF: 0.5 and 1 L min^{-1} then up to 10 L min^{-1} by 1 L min^{-1} increments.

Step 2b: Measurements of the Gas Outflow at the Common Gas Outlet With CF Set at Different F_iO_2, Across a Range of Flow Settings

When the CF is used, both the O_2 flow and the air intake pump (for $F_iO_2 < 1.0$) are intermittent. This intermittent functioning is audible and can be recorded.

The average gas outflow generated by the CF over a range of flow settings (5, 10, 15, and 20 L min^{-1}) was calculated at $F_iO_2 = 1.0$ (only O_2) and $F_iO_2 = 0.21$ (only air). For each setting (FGF, F_iO_2), the delivered gas outflow was measured continuously over 2 min, as well as the duration of pump functioning. Combination of these two values provided the average gas outflow (L min^{-1}).

Phase 3: Measurements of the Isoflurane Output of the TEC-3 Vaporizer at Different Dial Settings (0.5–5%), With MF or CF (set at FiO2 of 0.21 or 1) and Across a Range of Flow Settings (5–20 L min^{-1})

The CGO (4 mm. internal diameter) was connected to a 22 mm scavenging corrugated hose.

Step 3a:

The scavenging corrugated hose was directed to a F/air canister for waste anesthetic gases (Hanna pharmaceuticals, UK) and the vaporizer dial was successively turned on 0.5-1-1.5-2-2.5-3-3.5-4-4.5-5% and the isoflurane output measured at *(1)* F_iO_2 1.00, MF 5–10 L min^{-1}; *(2)* F_iO_2 1.00, CF 5-10-15-20 L min^{-1}; *(3)* F_iO_2 0.21, CF 5-10-15-20 L min^{-1}. The isoflurane output ($F_{E'}ISO$) was measured by the gas analyser with the sampling line attached to a 20 G needle inserted through the corrugated hose close to the CGO.

Step 3b:

An average isoflurane output was measured by collecting the outflow for 4 min within a 30 L rubber bag instead of the absorption canister, and measuring its final isoflurane concentration. This was performed at 5 L min^{-1} with: *(1)* MF, F_iO_2 1.00; *(2)* CF, F_iO_2 1.00; *(3)* CF, F_iO_2 0.21.

These measurements were repeated with a connector reducing internal diameter by introducing and sealing a 14 G needle in the CGO before the corrugated tube.

The **figure 1** summarizes the different steps of the investigations.

STATISTICAL ANALYSIS

Each experiment was conducted only once so statistical analysis were not performed. Phoenix 8.1, Certara USA Inc. was used for the pharmacokinetics modeling. For the graphical representations of the additional time required to reach a specific isoflurane concentration at different settings, SigmaPlot for Windows 13.0, Systat Software Inc, CA, USA was used.

RESULTS

Phase 1: Effects of Various F_iO_2 Settings on the Isoflurane Fraction in the Breathing System During Mechanical Ventilation of a Lung Model

Step 1a and Step 1b

The time difference between MF and CF (at different F_iO_2) in order to reach a target concentration obtained from steps 1a and 1c is presented in **Figure 2** (SigmaPlot for Windows 13.0, Systat Software Inc, CA, USA).

Step 1c

The time course obtained with MF differed from the ideal one-compartment model ($V_d = 40$ L, $k_e = 0.125$ min^{-1}, $\tau = 8$ min, Cl = 5 L min^{-1}). The targeted isoflurane concentration (3%) was not reached requiring a higher elimination constant ($k_e =$

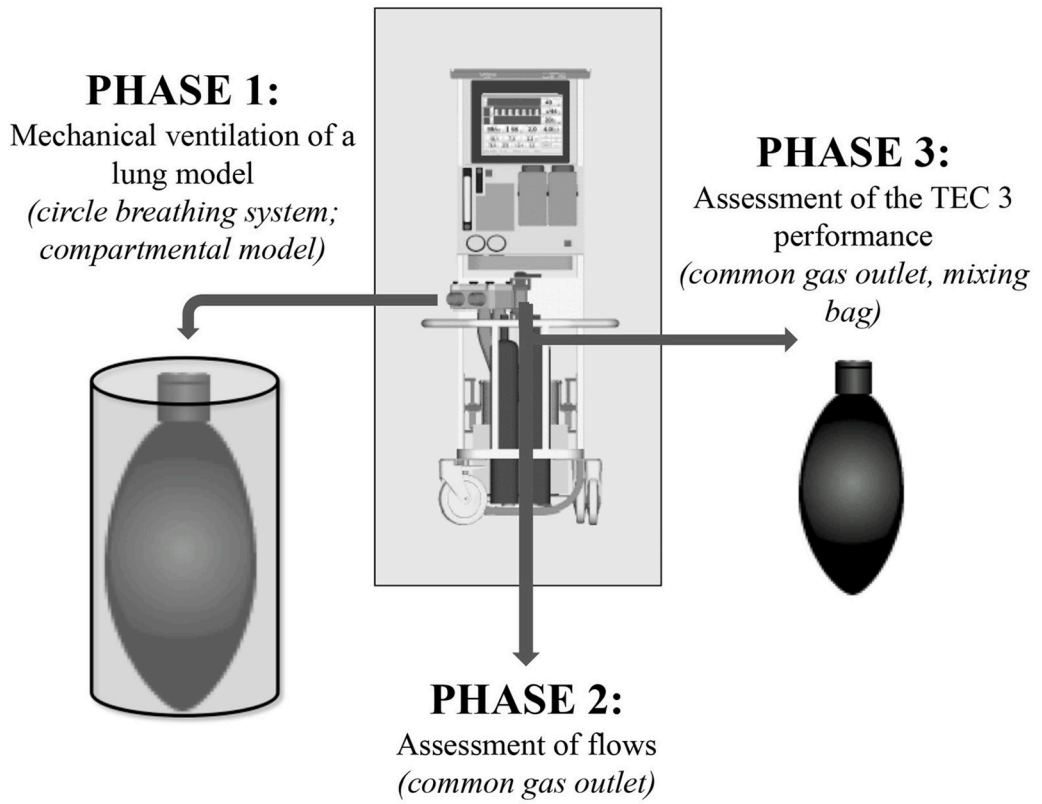

FIGURE 1 | Steps of investigation of the manual or computer-driven flowmeters' different performance on isoflurane changes in Tafonius.

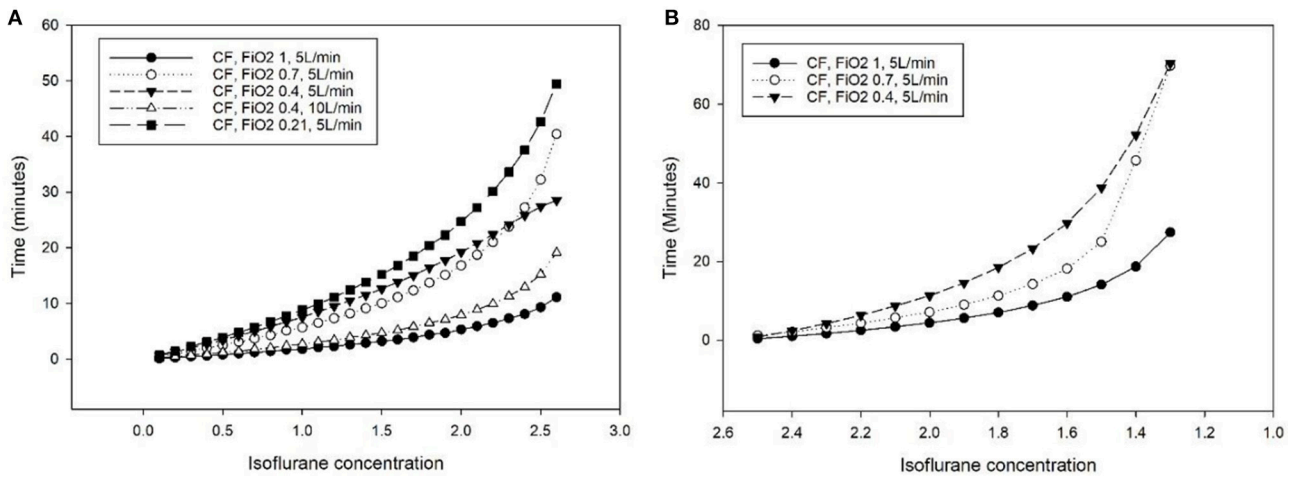

FIGURE 2 | Additional time (minutes) required to reach a specific isoflurane concentration in the breathing system of the Tafonius anesthesia machine during mechanical ventilation of a lung model (bag in a bottle) with a computer-driven flowmeter (CF) at different settings, compared to the use of a manual flowmeter at 5 L minute^{-1}. **(A)** Isoflurane increase from 0 to 3% (dial setting of a calibrated TEC 3 vaporizer). **(B)** Isoflurane decrease from 2.7 to 1%.

0.138 min^{-1}, $\tau = 7.25$ min, Cl = 5.52 L min^{-1}). The exponential course fitted better a model including two rather than one compartment (**Figure 3**).

Step 1d

Changes in F_iO_2 had no effect on the steady isoflurane partial pressure in the breathing system.

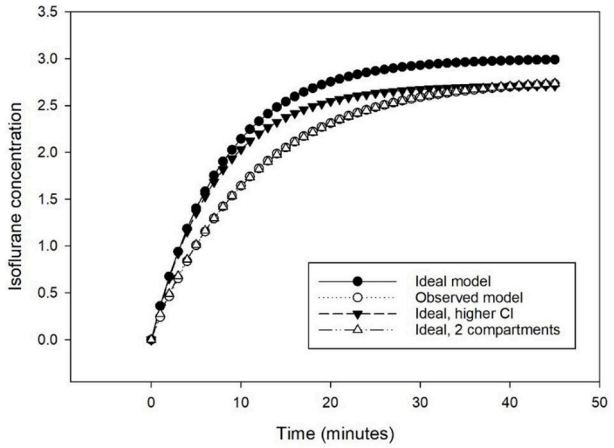

FIGURE 3 | Predicted isoflurane time course to increase from 0 to 3% at 5 L min^{-1} following a one-compartmental model of 40 L and an elimination of 5 L min^{-1} (Ideal model), with an elimination of 5.52 L min^{-1} (Ideal, higher Cl), and with a 2-compartments model of 40 L and an elimination of 5.52 L min^{-1} (Ideal, 2 compartments), compared to the observed time course (Observed model).

TABLE 1 | Calculation of the mean fresh gas flows (FGF) at the common gas outlet of the Tafonius anesthesia machine with the computer-controlled flowmeter (CF) set at different F_iO_2 and FGF based on outflow measurements, frequency, and duration of the air or O_2 intakes.

F_iO_2	FGF (L $minute^{-1}$)	Number of air/O_2 intakes over 120 s	Approximative duration (seconds) of air/O_2 intakes over 120 s	Calculated mean FGF (L $minute^{-1}$)
0.21	5	12	30	1.9
	10	12	60	3.8
	15	12	90	5.7
	20	1	120	7.6
1	5	12	45	4.0
	10	10	50	4.4
	15	12	55	4.9
	20	12	60	5.3

Phase 2: Measurements of the Gas Outflow at the Common Gas Outlet With MF or CF Set at Different F_iO_2

Step 2a: Measurements of the Gas Outflow at the Common Gas Outlet With MF ($F_iO_2 = 1.0$) Across a Range of Flow Settings

Set and measured flows were identical when the MF was used.

Step 2b: Measurements of the Gas Outflow at the Common Gas Outlet With CF set at Different F_iO_2, Across a Range of Flow Settings

With CF at F_iO_2 of 0.21 (delivering only air), the air outflow was intermittently 7.6 L min^{-1} or none. Based on recorded durations and frequencies (**Table 1**), the mean total flow was 38% of the set flow, reaching continuous flow (7.6 L min^{-1}) for a set FGF of 20 L min^{-1}.

With CF at F_iO_2 of 1.00 (delivering only O_2), the O_2 outflow was intermittently 10.6 L min^{-1} or none. Based on recorded durations and frequencies (**Table 1**), the mean total flow was between 4 and 5.3 L min^{-1}, varying mildly with the set FGF and never reaching continuous flow.

With CF at $0.21 < F_iO_2 < 1.00$ (mixing air and O_2), the combined outflow was intermittent with a maximum output of 15.6 L min^{-1}.

Phase 3: Measurements of the Isoflurane Output of the TEC-3 Vaporizer at Different Dial Settings (0.5–5%), With MF or CF (set at F_iO_2 of 0.21 or 1.0) and Across a Range of Flow Settings (5 to 20 L min^{-1})

With MF, the isoflurane output of the vaporizer was matching the dial setting at 5 L min^{-1} and 76.6% (± 0.06) of it at 10 L min^{-1}.

With CF set at 20 L min^{-1} for F_iO_2 of 0.21 (continuous FGF of 7.6 L min^{-1}), the isoflurane output of the vaporizer was 87.9% (± 0.03) of it.

For other settings of CF, the intermittent flow generated a fluctuating vaporizer output with a rapid sigmoidal increase up to a peak value, followed by a slower exponential decrease down to a basal value (**Table 2**), maintained until the next intermittent flow.

With the 4 mm diameter CGO, the average isoflurane concentration obtained after a 4-min collection in a bag (5 L min^{-1}) was close to the dial setting with both MF and CF (**Table 3**). With the reducing connector to 14 G, the average isoflurane concentration was lower than the dial setting (85%) with MF, and higher than the dial setting with CF (particularly when dialed at 1.00%).

DISCUSSION

When ventilating a lung model, it was challenging to predict the isoflurane fraction course in Tafonius' breathing system when the CF was used. The wash-in kinetics did not follow the expected one-compartment model and variations in isoflurane fraction were slower with the CF compared to the MF, particularly at lower F_iO_2. This difference was attributable to *(1)* the discrepancy between flows set on the CF and actual lower delivered flows and *(2)* to the fact that the isoflurane output of the TEC-3 vaporizer was inaccurate for flows higher than 5–7.5 L min^{-1}, for intermittent flow or for flows entering it at high pressures. Interestingly, a smaller tubing downstream the TEC-3 vaporizer worsened the accuracy of isoflurane output.

Factors governing the time course of a change in partial pressure of a volatile anesthetic in a circle breathing system are: *(1)* the volume of the system; *(2)* the FGF and the concentration of anesthetic in the gas admixture entering the system, *(3)* the extent to which circuit components absorb the anesthetic and the extent to which the anesthetic is degraded by the soda lime; *(4)* the uptake of anesthetic by the animal when connected to the breathing system; *(5)* the flow and concentration of anesthetic in the gas admixture leaving the system. The concentration of an anesthetic gas in a breathing system is expected respond to an

TABLE 2 | Peak and basal isoflurane concentration (in % of the dialed concentration) generated by the intermittent flow of the computer-driven flowmeter at different F_iO_2 and across a range of isoflurane dial setting of the vaporizer.

	F_iO_2 1.00								F_iO_2 0.21	
	5 L min^{-1}		10 L min^{-1}		15 L min^{-1}		20 L min^{-1}		5 L min^{-1}	
Isoflurane (%)	**Peak (%)**	**Basal (%)**	**Peak**	**Basal (%)**	**Peak**	**Basal (%)**	**Peak**	**Basal (%)**	**Peak**	**Basal (%)**
0.5	380	116	90		88		90		220	
1.0	200	100	86		82		86		140	
1.5	147	93	80		80		80		114	
2.0	140	95	85		85		90		110	
2.5	124	92	84		84		84		104	
3.0	114	90	87		87		87		104	
3.5	111	89	83		83		86		100	
4.0	105	88	83		83		85		98	
4.5	96	84	80		80		82		98	
5.0	100	82	78		76		78		98	

TABLE 3 | Mean isoflurane concentration obtained by a 4-min collection in a bag at different dial setting of the isoflurane vaporizer under different settings (Manual flowmeter at F_iO_2 1.00, Computer-controlled flowmeter at F_iO_2 0.21 and 1.00, fresh gas flow set at 5 L min^{-1}).

Flowmeter	**F_iO_2**	**% isoflurane vaporizer setting**	**% isoflurane measured in collection bag with 14 G**	**% isoflurane measured in collection bag with 4 mm**
MF	1.00	0.50	N/A	0.50
		1.00	0.86	1.00
		3.00	2.50	3.00
CF	0.21	0.50	N/A	0.53
		1.00	2.20	1.00
		3.00	3.30	2.70
	1.0	0.50	N/A	0.70
		1.00	2.50	1.10
		3.00	3.70	3.00

equation of a simple compartment model equation (2):

$$C(t) = Css \times \left(1 - e^{-t/\tau}\right)$$

where C(t) and Css are the time dependent and steady state concentrations of the volatile agent considered, respectively. A steady state is reached when outflow of gases equals the inflow, in ∼3 times the time constant τ (ratio between volume of the breathing system and FGF in case no animal is uptaking the anesthetic gas) (3). However, in the present study, when the volume of the system was forced at 40 L, data fitted better a two-compartment model precluding the use of the time constant to compare the different scenarios.

The 3% targeted isoflurane concentration was not reached in our study. A higher than expected elimination constant was necessary to obtain a good fit of the model with the observed data. This suggests that isoflurane and oxygen were not leaving the system in the same proportion at which they were entering it, isoflurane "elimination" being greater. Three hypotheses could be considered. First, some isoflurane could be degraded by the soda lime (4–7). Second, isoflurane could be absorbed by components of the breathing system, particularly by the rubber bellows of the lung model (8). Rubber is more permeable to anesthetic agents than other components of the breathing system and substantial absorption of isoflurane is likely to happen in clinical anesthesia conditions (8). If this were to be the case, the artificial lung would be the most important site of absorption and the amount of absorbed isoflurane in Tafonius under clinical conditions could be less than what potentially happened in the present study. Third, the dump valve function could be relevant. The dump valve is the equivalent in Tafonius to a pop-off valve in other ventilators and it is computer-controlled. It opens when the level of the piston rises to the point equal to the sum of tidal volume and buffer volume (when the FGF is continuous and greater than patient uptake and leaks, the level of the piston at the end of expiration rises breath by breath). In Tafonius, CGO and exhaust ports are at the same level and close to one another. Since gas movements in a circle breathing system are intermittent (inspiratory and expiratory valves and intermittent ventilation), the mixing of the FGF within the breathing system might not be uniform and a greater portion of the FGF could be scavenged in some circumstances. The fact that our data fitted better a two-compartment model may actually suggest non-uniform mixing of gas inflow in the breathing system. Our study focused on partial pressure of gases at the level of the Y-piece and on flows and vaporizer output at the CGO but waste gases flows and composition were not investigated.

When flows higher than 5 L min^{-1} were delivered through the vaporizer, isoflurane output was lower than dial setting, particularly at settings >2% (**Table 2**). This finding was in accordance with previous reports (9). The flows delivered when the CF was in use were intermittent and high (7.6 L min^{-1} with 0.21 FiO_2, 10.6 L min^{-1} with 1.00 FiO_2 and 15.6 L min^{-1} total combined flow). This could contribute to explain the differences in isoflurane fraction changes between MF and CF.

Although FGF and temperature are known to potentially influence the volatile output in some models of vaporizers

(10, 11), the variability in vaporizer output associated with the intermittent flows encountered when CF was used was, not anticipated. A situation that can lead to variable vaporizer output is the "pumping effect" (12). Initially observed during inspiratory phases of intermittent positive pressure ventilation, the "pumping effect" originates from an increase in the resistance in the outlet of the anesthetic machine which leads to an intermittent and variable increase in the anesthetic gas pressure transmitted back to the vaporizer. The gas present in the outlet is saturated with volatile anesthetic; when the backpressure is released, the expanding carrier gas (also saturated) exits both the inlet and the outlet of the vaporizer chamber. The gas leaving the inlet enters the bypass and adds to the vaporizer output, hence the increase of the final vapor output (12). Compared to earlier versions, various modifications have been performed in the Mark 3 to reduce the impact of the pumping effect: the volume of the vaporizing chamber has been reduced in order to minimize the effect of compression. The vapor control channel has been placed on the outlet side of the vaporizing chamber in order to make the resistance of the chamber outlet higher than that of the inlet; a small annular expansion chamber, unprovided with wicks, adjacent to the vaporizing chamber inlet and a long, narrow, annular throat, without wicks, leading down from the expansion chamber to the liquid volatile has been added to confine anesthetic vapor to regions of the chamber remote from the inlet (13). Performance of the Cyprane Fluotec Mark 3 for halothane was evaluated and compared to the TEC 2 and the pumping effect seemed eliminated (13). However, only fairly modest pressures (up to 35 cm H_2O) were investigated in the latter study. With the CF in Tafonius, O_2 bypasses the MF and likely reaches the system at higher than atmospheric pressure upstream the vaporizer. This pressure will further increase if the diameter of the tubing is decreased downstream (Haggen Poiseuille equation). Oxygen pressures reaching the vaporizer were not measured but are expected to be markedly above the usual subatmospheric pressure of usual fresh gas inlet. Plenum vaporizer are designed to work at atmospheric pressure and, likely, cannot compensate for high gas pressures. We believe that, under such conditions, an alteration of the splitting ratio in the vaporizer could also explain our findings. Performance of a TEC-3 vaporizer at different given known pressures has not been reported yet and deserves characterization when Tafonius is used in CF mode.

There are several limitations to the present study. Since each experiment was conducted only once, no statistical analysis was performed. Although there is no reason for the results to be markedly different using the same equipment in the same situation, this was not investigated. It could have been interesting to repeat the experiment on several different Tafonius but the ventilator tested was an early model and may not represent more recently constructed units. We used an infrared multi-gas analyser (Datex-Ohmeda S/5 anesthetic monitor) to measure isoflurane tension. The monitor was calibrated prior to each experiment according to the manufacturer's instructions. This is a single point calibration. Gas chromatography (often considered as the most accurate method to measure the concentration of inhaled anesthetic gases) and infrared gas analysis with the monitor we used cannot be used interchangeably as deviations between the techniques exist and performances of individual analysers differ unpredictably (14). Advantages of the infrared monitoring are practicality and limited cost: it is readily available and provides continuous data. Although our isoflurane absolute values may not be perfectly accurate because of the technique we used, we standardized the experiment so that the comparison is valid and we believe the infrared analysis and our results are of clinical relevance.

CONCLUSION

Under experimental conditions, using MF or CF led to different isoflurane fraction time course in Tafonius. The wash-in kinetics did not follow a one-compartment model and variations in isoflurane fraction were slower with the CF compared to the MF, particularly at lower F_iO_2. Actual delivered flows were lower than set with CF and the TEC-3 did not compensate for high/intermittent flows and pressures. It was therefore challenging to predict the isoflurane fraction course in Tafonius' breathing system when the CF was used. Caution is recommended when using the CF.

AUTHOR CONTRIBUTIONS

MR: study design, data collection, data analysis, interpretation, redaction of the paper. OL: mathematical modeling, data analysis, interpretation, redaction of the paper. PM: study design, data collection, data analysis, interpretation, redaction of the paper.

ACKNOWLEDGMENTS

The authors thank Keith Simpson for his technical assistance and lending them the digital flowmeter.

REFERENCES

1. Meakin GH. Time constant or half time of a breathing system? *Anaesthesia*. (2003) 58:386–7. doi: 10.1046/j.1365-2044.2003.03095_5.x
2. Bukoski A. Proper theoretical analysis of the oxygen wash-in kinetics of circle breathing systems. *Vet Anaesth Analg*. (2012) 39:185–9. doi: 10.1111/j.1467-2995.2011.00674.x
3. Baum JA. *Low Flow Anaesthesia.* Oxford: Butterworth-Heinmann (1996).
4. Eger EI, and Strum DP. The absorption and degradation of isoflurane and 1-653 by dry soda lime at various temperatures. *Anesth Analg.* (1987) 66:1312–5. doi: 10.1213/00000539-198712000-00020
5. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P. Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. *Anesth Analg.* (1995) 80:1187–93. doi: 10.1213/00000539-199506000-00021

6. Liu J, Laster MJ, Eger EI, Taheri S. Absorption and degradation of sevoflurane and isoflurane in a conventional anesthetic circuit. *Anesth Analg.* (1991) 72:785–9. doi: 10.1213/00000539-199106000-00012
7. Strum DP, Eger EI. The degradation, absorption, and solubility of volatile anesthetics in soda lime depend on water-content. *Anesth Analg.* (1994) 78:340–8. doi: 10.1213/00000539-199402000-00024
8. Targ AG, Yasuda N, Eger EI. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. *Anesth Analg.* (1989) 69:218–25. doi: 10.1213/00000539-198908000-00014
9. Steffey EP, Wolimer M, Howland D. Evaluation of an isoflurane vaporizer: the Cyprane Fortec. *Anesth Analg.* (1982) 61:457–64. doi: 10.1213/00000539-198205000-00013
10. Ambrisko TD, Klide AM. Evaluation of isoflurane and sevoflurane vaporizers over a wide range of oxygen flow rates. *Am J Vet Res.* (2006) 67:936–40. doi: 10.2460/ajvr.67.6.936
11. Ambrisko TD, Klide AM. Accuracy of isoflurane, halothane, and sevoflurane vaporizers during high oxygen flow and at maximum vaporizer dial setting. *Am J Vet Res.* (2011) 72:751–6. doi: 10.2460/ajvr.72.6.751
12. Davey AJ. *Vaporizers in Ward's Anaesthetic Equipment.* 5th Edn. Philadelphia: Elsevier Saunders (2005).
13. Paterson GM, Hulands GH, Nunn JF. Evaluation of a new halothane vaporizer: the Cyprane Fluotec Mark 3. *Brit J Anaesth.* (1969) 41:109–19. doi: 10.1093/bja/41.2.109
14. Hendrickx JFA, Lemmens HJM, Carette R, De Wolf AM, Saidman LJ. Can modern infrared analyzers replace gas chromatography to measure anesthetic vapor concentrations? *BMC Anesth.* (2008) 8:2. doi: 10.1186/1471-2253-8-2

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 22 January 2020
doi: 10.3389/fvets.2019.00514

Risk Factors of Anesthesia-Related Mortality and Morbidity in One Equine Hospital: A Retrospective Study on 1,161 Cases Undergoing Elective or Emergency Surgeries

Chiara Laurenza[1], *Lèa Ansart*[1] *and Karine Portier*[1,2]*

[1] Section of Anesthésiologie, Université de Lyon, VetAgro Sup, Marcy l'Étoile, France, [2] GREAT, Laboratoire Carmen, INSERM U1060, INRA U1235, INSA Lyon, Université Claude Bernard Lyon 1, Villeurbanne, France

A retrospective analysis was performed to determine mortality and morbidity rates for elective and emergency cases in an equine university teaching hospital. It investigated the effect of horse-, anesthetic-, timing, and clinician experience-related variables on anesthetic complications. In total, 1,161 horses undergoing general anesthesia between January 2012 and December 2016 were included in the study. Patient information and details of the anesthetic, recovery period and immediate complications were retrieved from an archival database. Statistical analysis of qualitative and quantitative factors affecting anesthetic complications was performed using an univariable and multivariable ordinal logistic regression. Odds ratio of variables primarily affecting mortality and complications were calculated. Statistical significance was set at $p < 0.05$. General anesthesia-related global mortality rate was 1.4% (95% CI [7.1–10.4]) but was only 0.96% (95% CI [0.44–1.82]) for non-colic cases. The complication rate was 17.5% ($n = 204$; 95% CI [15.2–20.0]) of which 46.9% [39.4–54.5] were neuromuscular, 22.6% [16.7–29.5] were respiratory, 15.8% [10.8–22.0] were systemic, 13.6% [8.9–19.5] were cardiovascular, 1.1% [0.1–4.0] were other complications. Ninety two percent of complications occurred during recovery. Major risk factors for mortality and complications included high weight, surgeon experience, increasing age, high ASA score, long duration of anesthesia, quality of induction, lateral recumbency, orthopedic surgery, and hypotension. In these models, colic surgery did not influence the rate of any complications.

Keywords: horse, equine, anesthesia, mortality, perioperative complications, risk factors

OPEN ACCESS

Edited by:
Yvonne A. Elce, Langford Vets Equine Centre, United Kingdom

Reviewed by:
Regula Bettschart, University of Zurich, Switzerland
Timothy Bernard Lescun, Purdue University, United States

***Correspondence:**
Karine Portier
karine.portier@vetagro-sup.fr

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *27 September 2019*
Accepted: *27 December 2019*
Published: *22 January 2020*

Citation:
Laurenza C, Ansart L and Portier K (2020) Risk Factors of Anesthesia-Related Mortality and Morbidity in One Equine Hospital: A Retrospective Study on 1,161 Cases Undergoing Elective or Emergency Surgeries. Front. Vet. Sci. 6:514. doi: 10.3389/fvets.2019.00514

INTRODUCTION

Equine anesthesia has become a routine practice in most horse hospitals. However, the anesthetic risk of mortality does not seem to have decreased over time (1). The most severe complications being fatal. In 2002, the Confidential Enquiry into Perioperative Equine Fatalities (CEPEF), a prospective observational epidemiological multicenter study, found a risk of death (up to 7 days

after anesthesia) to be 0.9% for healthy horses (2). The most recent study, performed in a single equine university teaching hospital between 2010 and 2013, published an identical mortality rate (0.9%) for elective cases (up to the return of the horse to its stable) (3). Since the mortality rate is more easily calculated, it is more often studied than the morbidity rate. Nevertheless the fact remains that the published results are extremely variable from one study to another (4).

While caution in comparing the results of such studies should remain the rule (due to differences, for example, in study design, hospitals, sample size, selection of cases, observation time, definition of the outcomes), the issue of decreasing anesthetic mortality over time has always been debated and compared across species (1). Mortality rate in healthy horses is higher than in healthy dogs (0.05%), cats (0.11%), and rabbits (0.73%) (5). The death rate in humans is more than a thousand times smaller (0.69 10^{-3}%) than in animals. In France, an investigation into millions of procedures showed that mortality was divided by 10 in 15 years between 1986 and 2000 (6). Since the mortality and morbidity rate is high in equine anesthesia compared with human anesthesia, it should be possible to make a risk analysis using smaller samples than in humans (1). The reasons for these differences in rates and trends between species are multiple. The heavy weight of the horse and its poor tolerance to depression of cardiovascular and respiratory functions could explain a higher rate of complications in this species (4). The recovery phase is described as the riskiest phase of equine anesthesia. This may be related to the anatomy and behavior of the horse and to lack of monitoring and cardiovascular support in the recovery box (2).

However, the mortality and morbidity rates related to anesthesia should not be directly correlated with safety level. There is little information on morbidity, but even if the mortality rate has not changed a lot, some progresses have been made in terms of monitoring, anesthesia equipment, training and information of equine veterinarians (7, 8). In parallel surgical procedures have become more complex and are performed on patients at higher risk (9). Therefore, it is reasonable to assume that in the near future the decrease in anesthetic mortality and morbidity will be related to an improvement in safety.

One of the best ways to improve security is to inform equine anesthesiologists and surgeons in order to guide the logic of their interventions/professional practices made in the interest of anesthetic safety. The effectiveness of guidelines to reduce anesthetic risk is controversial (1). Nevertheless, attempts to reduce the risk of anesthesia are still possible by continuing to document mortality and morbidity rates and describing any factor associated with an increased rate of death/post-operative complication. The analysis of triggering causes, favoring or simply associated with these events, is essential. Risk factors (associated with increased rate of death) mostly reported in the equine literature are American Society of Anesthesiologists (ASA) physical status, age, the type of surgery, prolonged duration of anesthesia and out-of-hour surgery (4).

The primary aim of this retrospective single-center study was to document the mortality and morbidity rate associated with elective and emergency procedures in horses undergoing general anesthesia in our clinic. The secondary aim was to investigate the intrinsic and extrinsic factors that determined anesthetic mortality and morbidity from the pre-operative clinical examination up to the end of recovery. The complications that occurred between the end of recovery and the 48 h postoperative were also described.

MATERIALS AND METHODS

The medical records of all horses (n = 1,161) that underwent general anesthesia at the Equine Teaching Hospital of Lyon for elective and emergency surgeries between January 2012 and December 2016 were collected. Patient information and details of the anesthetic management, recovery period and immediate complications within 48 h postoperatively were obtained from the anesthesia report, the surgical report and the complication report if applicable.

The information (and their categorization) recorded from these documents were as follows: details about the horse: breed (pony, sport horse, draft horse, racehorse, other), age (year), sex (male, gelding, mare), body mass (kg), pregnancy (yes/no), ASA physical status classification (1–5). The types of surgery were arthroscopy, colic, castration, skin tumor resection, orthopedic surgery (other than arthroscopy), head surgery, septic surgery, others. The distribution of surgeries in these categories is detailed in **Table 1**. The experience of the surgeon (resident vs. senior), whether anesthesia was done for elective or emergency procedure, fasting (yes/no), time of the year (first or second

TABLE 1 | Distribution of the 1,161 surgeries, performed at the Equine Teaching Hospital of Lyon between January 2012 and December 2016, in each of the eight categories defined in the study.

Surgery categories	Surgical procedures	Number of Cases
Arthroscopy	Bursoscopy, tenoscopy, intra-articular lavage	253
Colic	Colic, umbilical hernia, inguinal hernia, dystocia, cesarean section	229
Castration	Castration	199
Skin tumors resection	Sarcoids resection	135
Orthopedic surgery	Fracture, arthrodesis, angular deviation, cast change, neurectomy, osteosynthesis material removal, keratoplasty, sequestrectomy, cyst excision, periosteal elevation, surgical correction of patellar luxation	108
Head	Transarterial coil embolization, sinusotomy, ethmoid hematomas, dentistry, ophthalmic surgery, laryngeal surgery	99
Septic surgery	Wounds, foreign body and abscess debridement, umbilical infection, patent urachus	98
Others	X-Ray, computer tomography, myelography, cerebrospinal fluid puncture, cisplatin treatment, stem cells injection	40

semester), time of the week (weekend or not), time of the day (8 a.m.−8 p.m./8 p.m.−00 a.m./00 a.m.−8 a.m.) were also noted.

The conventionally used anesthesia protocol (administered to the majority of healthy horses) included tranquilization with acepromazine, premedication with an alpha 2 agonist (romifidine, detomidine, or xylazine) and an opioid (morphine or butorphanol), induction with diazepam and ketamine and maintenance with isoflurane or sevoflurane in 100% O_2. Inspiratory positive pressure ventilation (IPPV) was performed. The volume was adjusted to maintain normocapnia with a maximal positive inspiratory pressure at 35 cmH_2O. Occasionally, anesthesia was maintained by an infusion of guaiphenesin with ketamine and xylazine for short-term procedures. Dobutamine was used to maintain mean arterial blood pressure (MABP) above 70 mmHg, if necessary. Analgesia was provided with a non-steroidal anti-inflammatory drug (phenylbutazone or flunixin), an opioid (as described above) and local anesthetic (lidocaine) when possible. The analgesic protocol was sometimes complemented by constant rate infusion (CRI) of morphine and/or ketamine and/or lidocaine and/or dex/medetomidine, at the discretion of the anesthetist. Horses presented in a state of physiological shock received a protocol of resuscitation and the anesthesia was adapted to the case (for example without acepromazine).

The following anesthesia data (and categorization) were recorded from the anesthesia sheet: experience of the anesthetist (senior vs. resident), body position (dorsal vs. lateral), duration of anesthesia (from induction to entrance in the recovery box), whether dobutamine was administered during the second half of the surgery (yes/no), premedication and induction protocol (conventional vs. other), administration of a CRI (lidocaine or alpha 2 agonist or none), anesthetics used for maintenance (isoflurane or sevoflurane or injectable). Calcium plasma concentration during colic surgery (mean concentration in mEq/L), pH (mean value), PaO_2/FiO_2 ratio (mean value), invasive MABP (mean value), hypotension index [$HI = 1/12\sum(70\text{-MAP})$] (10) were also recorded.

Recoveries were performed in a rubber-padded recovery box. Intranasal phenylephrine was administered before moving the horse to the recovery box. Oxygen was administered either by a demand valve (in case of apnea) through the orotracheal tube or by insufflation through a nasopharyngeal or orotracheal tube.

The characteristics of the recovery that were recorded were as follows: whether the recovery was assisted or not, the duration (from entrance in the recovery box to standing) and the quality of recovery (with a score using dichotomous objective descriptors (11).

Cases were also classified according to the outcome of the procedure: alive, dead, or euthanized. Total mortality was defined as all cases that were euthanized or died within the period from the induction of anesthesia to the return to the hospitalization box. The dead were also divided according to the primary cause of death. We defined anesthetic mortality as all deaths considered due solely to anesthesia that unexpectedly occurred during surgery, and euthanasia due to peri-anesthetic complications. Non-anesthetic mortality was then defined as all deaths due to a cause not attributable to anesthesia, and euthanasia related to inoperable lesions.

Non-fatal complications were defined as complications that did not induce death within the recovery period. They were recorded and classified according to 4 categories: respiratory, neuromuscular, cardiovascular and systemic. The overall non-fatal complication rate for the observation period was also calculated (number of non-fatal complications related to anesthesia divided by the total number of anesthesia).

Statistical Analysis

Statistical analysis was performed using R (https://www.rstudio.com/) statistical software. Qualitative data were described using frequency distribution. Quantitative data were checked for normality of distribution using a Shapiro Wilk test. They were all normally distributed and expressed as the mean ± standard deviation (SD).

The relationships between possible risk factors and mortality or complications were tested using Pearson's chi-squared test or Fisher's test for qualitative variables and Student's *t*-test for quantitative variable. Significance level was set at $p < 0.05$ for univariate analysis.

Predictors which have been found significant at $p < 0.2$ by the univariate logistic regression were tested in a multivariable model. The Akaike information criterion (AIC) was used to estimate the relative quality of the models as a mean for model selection. The best model was also considered the one with the smallest possible number of variables. The links between explanatory variables were also studied in order to identify confounding factors, using a linear regression analysis, a correlation or a Chi-Square test.

RESULTS

The results presented here concern observation until the return to the hospitalization box immediately after recovery. The complications observed in the 48 h that followed are described in the discussion. We could not include this observation period in the statistical study because of the uncertainty of the recruitment, this period not being under the control of the anesthetists. In addition, some horses were discharged before 48 h post-surgery.

Description of the Sample

A total of 1,161 horses underwent general anesthesia at the Equine Teaching Hospital of Lyon for elective and emergency surgeries between January 2012 and December 2016.

To study the risk factors for each type of anesthetic complication those who died for surgical reasons ($n = 84$) were excluded from this count. The medical records of 438 mares, 293 geldings, 346 stallions (total 1,077) were therefore studied ($n = 236$ in 2012, $n = 214$ in 2013, $n = 224$ in 2014, $n = 214$ in 2015, $n = 188$ in 2016). They had a body mass of (median, range) 481 [38–730] kg and were aged 5 [1–35] years. The distribution by breed category was as follows: saddle horses ($n = 752$; 70%), ponies ($n = 132$; 12%), racehorses ($n = 104$; 10%), horses of undetermined breed ($n = 58$; 5%), draft horses ($n = 31$; 3%).

Horses ASA physical status was divided into 5 categories [ASA1 $n = 118$ (11%), ASA2 $n = 631$ (58%), ASA3 $n = 152$ (14%), ASA4 $n = 104$ (10%), ASA5 $n = 72$ (7%)].

Most of the surgeries were elective ($n = 802$; 74%) whereas 275 (26%) were emergency procedures. These surgeries were performed by a diplomate of the European College of Veterinary Surgery (ECVS) ($n = 662$; 61%) or a resident ($n = 369$; 34%), for 46 (5%) surgeries the qualification of the surgeon was not specified. Horses underwent arthroscopy ($n = 252$; 23%), castration ($n = 189$; 17%), colic surgery ($n = 160$; 15%), skin tumor resection ($n = 136$; 13%), surgery of the head ($n = 108$; 10%), orthopedic surgery ($n = 104$; 10%), septic surgery ($n = 94$; 9%), other type of surgery ($n = 34$; 3%).

The duration of anesthesia was (median, range) 135 [0–495] min. The duration of recoveries was (median, range) 45 [5–315] min. Recoveries were unassisted for 410 cases whereas they were assisted (head and tail ropes or Anderson sling for fractures) in 667 cases. Anesthesia was performed by a diplomate of the European College of Veterinary Anesthesia and Analgesia (ECVAA) in 343 (32%) cases and by a resident in 681 (63%) cases. The qualification of the anesthetist was not specified for 53 (5%) surgeries.

Mortality Rates

Total mortality rate was 8.6% ($n = 100/1161$; 95% CI [7.1–10.4]). Non anesthetic mortality rate was estimated at 7.2% of the total case number ($n = 84/1161$; 95% CI [5.9–9.0]). Anesthetic mortality rate was 1.4% ($n = 16/1161$; 95% CI [0.7–2.1]). A total of 932 horses underwent surgeries other than emergency abdominal surgeries. The non-colic anesthetic mortality rate was 0.96% ($n = 9/932$; 95% CI [0.44–1.82]). The anesthetic mortality rate of horses presented for colic ($n = 229$) was 3% (7/229). The rate of euthanasia due to inoperable lesion of horses anesthetized for colic was 30% (68/229). The total mortality rate for horses presented for colic was therefore 33% (75/229).

The details of the causes of mortality are presented in **Table 2**.

Factors Associated With Increased Mortality

Among the studied factors described in the material and method section, increased age ($p = 0.04$), higher ASA physical status ($p < 0.01$), colic surgeries ($p < 0.01$), orthopedic surgeries ($p = 0.01$), seniority of the surgeon ($p = 0.02$), emergencies ($p = 0.04$), longer anesthetic duration ($p < 0.001$), worst quality of recovery ($p < 0.001$) were significantly associated (univariable

TABLE 2 | Details of primary causes of anesthetic and non-anesthetic mortality of horses which were presented at the Equine Teaching Hospital of Lyon between January 2012 and December 2016 for colic and non-colic surgery.

Number of deaths	Euthanasia/Spontaneous Death	Cause of death	Death attributed to	Reason of anesthesia
68	Euthanized	Inoperable lesions	surgery	Colic surgery
3	Euthanized	Inoperable lesions	surgery	Diagnostic Imaging
2	Euthanized	Inoperable lesions	surgery	Wound debridement
2	Euthanized	Inoperable lesions	surgery	Skin tumors resection
2	Euthanized	Inoperable lesions	surgery	Fracture surgery
1	Euthanized	Inoperable lesions	surgery	Arthroscopy
1	Euthanized	Inoperable lesions	surgery	Septic arthritis
1	Euthanized	Inoperable lesions	surgery	Thoracotomy
1	Euthanized	Inoperable lesions	surgery	Articular lavage
1	Euthanized	Inoperable lesions	surgery	Dystocia
1	Euthanized	Inoperable lesions	surgery	Cisplatin treatment
1	Euthanized	Inoperable lesions	surgery	Cast placement
2	Euthanized	Failure of osteosynthesis material	anesthesia	Fracture surgery
1	Euthanized	Fracture at recovery	anesthesia	Colic surgery
1	Euthanized	Fracture at recovery	anesthesia	Fracture surgery
1	Euthanized	Severe myopathy	anesthesia	Colic surgery
1	Euthanized	Myelomacia	anesthesia	Castration
1	Euthanized	Myositis+Vestibular syndrome	anesthesia	Transarterial coil embolization
1	Euthanized	Fall	anesthesia	Fracture surgery
1	Euthanized	Severe myopathy	anesthesia	Sinusotomy
1	Euthanized	Weakness syndrome+Myopathy	anesthesia	Colic surgery
1	Euthanized	Weakness syndrome+Paralysis	anesthesia	Arthroscopy
1	Dead	Cardiorespiratory arrest at induction	anesthesia	Colic surgery
1	Dead	Cardiorespiratory arrest at recovery	anesthesia	Colic surgery
1	Dead	Cardiorespiratory arrest at recovery	anesthesia	Osteosynthesis material removal
1	Dead	Intraoperative cardiorespiratory arrest	anesthesia	Colic surgery
1	Dead	Myopathy, prolonged recovery, respiratory arrest	anesthesia	Colic surgery

TABLE 3 | Results of the multivariable model showing odds-ratio of the explanatory variables for the risk of anesthetic mortality, neuromuscular, respiratory, systemic and cardiovascular complications.

Variable	Anesthetic mortality	Neuro muscular complication	Respiratory complication	Systemic complication	Cardiovascular complication
Senior surgeon	5.49 [1.05–10.10]	2.14 [1.10–4.44]	2.58 [1.04–7.79]		
Weight/100	1.54 [1.02–2.60]	1.26 [1.00–1.63]	1.57 [1.08–2.42]		
Age			1.71 [0.91–3.06]		1.08 [1.00–1.15]
Anesthesia duration		1.35 [1.05–1.71]	1.49 [1.12–1.94]		
ASA	2.10 [1.27–3.56]			1.93 [1.42–2.61]	
PaO_2/FiO_2			0.66 [0.47–0.92]		0.52 [0.33–0.88]
Dobutamine	0.37 [0.11–1.12]				
Orthopedic surgery	9.82 [2.55–38.04]				
Arthroscopy		0.55 [0.26–1.06]			
IBP/10		1.25 [0.95–1.63]			
Induction quality		0.82 [0.73–0.93]			
Lateral recumbency					4.89 [1.78–13.45]

logistic regression) with increased mortality. Other factors had no significant effect on survival.

Predictors that were significant at $p < 0.2$ were tested in a multivariable model. The best model for explaining anesthetic risk included 5 variables. The risk of anesthetic mortality was multiplied by 1.5 when the weight of the horse increased by 100 kg; 2.1 when the ASA score increased by one point; by 5.5 when the surgeon who operated was a senior and by 9.8 during orthopedic surgery. The risk was decreased by 0.4 when the anesthesiologist used dobutamine during the second half of the surgery. Odd-ratio of the explanatory variables for the risk of anesthetic mortality are presented in **Table 3**.

Non-fatal Complication Rates

The complication rate was 17.5% ($n = 204$; 95% CI [15.2–20.0]) of which 46.9% [39.4–54.5] were neuromuscular, 22.6% [16.7–29.5] were respiratory, 15.8% [10.8–22.0] were systemic, 13.6% [8.9–19.5] were cardiovascular, 1.1% [0.1–4.0] were other complications. The details of the nature of the complications and their frequencies are presented in **Figure 1**. Almost all the complications (92 [87–96] %) occurred during recovery.

Risk factors were associated with different types of complication (univariable logistic regression).

Neuromuscular complications were significantly associated to increased age ($p < 0.01$), increased weight ($p < 0.01$), increased ASA physical status ($p = 0.01$), colic surgery ($p = 0.02$), orthopedic surgery ($p < 0.01$), surgeon experience ($p < 0.001$); emergency vs. elective procedure ($p = 0.03$), when horses were not fasted ($p = 0.04$), lateral recumbency ($p = 0.04$), longer duration of anesthesia ($p < 0.001$), lower plasma calcium concentration ($p < 0.001$), higher hypotension index ($p < 0.01$), worst quality of recovery ($p < 0.00001$), longer duration of recovery ($p < 0.00001$).

Respiratory complications were significantly associated to the year ($p < 0.01$), increased age ($p < 0.001$), higher weight ($p < 0.001$), higher ASA score ($p < 0.001$), colic surgery ($p < 0.00001$), surgeries other than castration ($p = 0.03$), surgeries other than skin tumor resection ($p = 0.04$), surgeon experience ($p < 0.01$), emergency procedure ($p < 0.01$), end of the day and night ($p < 0.00001$), longer duration of anesthesia ($p < 0.0001$), lower $Pa0_2/FiO_2$ ratio ($p < 0.001$), worst quality of recovery ($p < 0.01$), and longer duration of recovery ($p < 0.01$).

Systemic complications were significantly associated to increased ASA score ($p < 0.0001$), colic surgery ($p < 0.001$), emergencies ($p < 0.01$), longer duration of anesthesia ($p = 0.01$), worst quality and longer duration of recovery ($p < 0.00001$).

Category of complications Frequency (%)	Nature of the complications	Frequency (%)
Neuromuscular 47 [39 - 54]	Neuropathy	19 [13 - 26]
	Myopathy	11 [6-16]
	Wounds	7 [4-12]
	Ataxia	3 [1-7]
	Fracture	3 [1-6]
	Vestibular syndrome	1.1 [0.1-4.0]
	Seizure	1.1 [0.1-4.0]
	Myelomalacia	0.6 [0.0-3.1]
	Claude Bernard Horner syndrome	0.6 [0.0-3.1]
Respiratory 22 [17-29]	Pulmonary edema	18 [13-25]
	Dyspnea	2.8 [0.9-6.4]
	Respiratory arrest	1.7 [0.3-4.9]
Systemic 16 [11-22]	Weakness syndrome	16 [11-22]
Cardiovascular 14 [9-19]	Blood loss	7 [4-12]
	Cardiac arrest	3.4 [1.2-7.2]
	Arrhythmia	1.7 [0.3-4.9]
	Cardiac murmur	1.1 [0.1-4.0]
Other 1.1 [0.1-4.0]	Paraphimosis	0.6 [0.0-3.1]
	Rectal prolapse	0.6 [0.0-3.1]

FIGURE 1 | Details and frequencies of the anesthetic complications suffered by horses anesthetized between January 2012 and December 2016 at the Equine Teaching Hospital of Lyon.

Cardiovascular complications were significantly associated to increased age ($p < 0.001$), lateral recumbency ($p = 0.03$), lower PaO_2/FiO_2 ratio ($p = 0.02$).

Variables Explaining the Risk of Non-fatal Complications in Multivariate Models

The risk of neuromuscular complications was multiplied by 1.3 when the weight of the horse increased by 100 kg, by 1.3 when the duration of anesthesia increased by 1 h, by 2.1 when the surgeon who operated was a senior and by 1.2 when the blood pressure decreased by 10 mmHg. It decreased by 0.6 when the surgery was an arthroscopy.

The risk of respiratory complications was multiplied by 1.7 when the age increased by 10 years, by 1.6 when the weight of the horse increased by 100 kg, 1.5 for each hour of additional anesthesia and 2.6 when the surgeon was a senior. It decreased by 0.7 when the PaO_2/FiO_2 ratio increased by one unit.

The risk of systemic complications was multiplied by 1.93 when the ASA score increases by 1 point.

The risk of cardiovascular complications was multiplied by 1.1 each additional year of age of the horse, and by 4.9 when the horse was placed in lateral recumbency; It decreased by 0.5 when the PaO2 / FiO2 ratio increased by one unit.

Odds-ratio of the explanatory variables for the complications are presented in **Table 3**.

The links between explanatory variables are presented in Appendix 1 (**Supplementary Material**).

DISCUSSION

Mortality Rate

The overall anesthetic mortality rate at the equine veterinary teaching hospital of Lyon was 1.4% overall and 0.96% for non-colic cases. These results are slightly higher than those that were reported by Dugdale et al. (1.1% for all cases and 0.9% for elective

cases for the same postoperative period of observation) (3). In 1993, 26 years earlier, Young and Taylor (10) had found an even lower rate for elective cases (0.68%).

Nevertheless, when the observation period was extended to 7 days postoperatively, the published figures of mortality were 1.9% overall anesthesia and 0.9% when colic surgeries were excluded (2). As mentioned in the introduction, it is very difficult to compare the results of studies that differ by many parameters. The need for a multicenter prospective study is still relevant as suggested by Gent and Bettschart-Wolfensberger (12). Horses presented for colic surgery had a very high mortality rate (one third) either because the lesions were inoperable (30%) or due to anesthetic complications (3%). These results lie between those given by Dugdale et al. (1.6%) and those of Mee et al. (4.3%) (3, 13). A possible explanation for this high mortality rate is that colic surgeries are performed on more and more complicated cases. Leisure horses' owners are increasingly willing to operate their horses even if the prognosis is poor.

Many studies showed a significant increase in anesthetic risk for colic surgery (2, 3, 13, 14). In this study, the factors considered as the consequences of the colic syndrome (such as decreased blood pressure, increased ASA score, hypoxemia, hypotension, duration of anesthesia, senior surgeon, emergency, horses not fasted, etc…) also appeared as explanatory factors for mortality, neuromuscular, respiratory or cardiovascular complications. This may explain why colic surgery itself did not appear in the final explanatory models of mortality and morbidity.

Explanatory Factors for Mortality

Our study showed that increased age was associated to increased anesthetic mortality rate. This is consistent with several studies that showed an increase in risk for horses aged 15, 14, and 12 years, respectively (2, 3, 15). However, the absence of foal in our sample did not allow us to show a higher anesthetic risk in horses <1 month, unlike Johnston et al. (2, 15). Muscle diseases, sarcopenia and osteoarthritic degenerative changes are among the most commonly reported clinical problems in aged horses which appear to be prone to fractures and to difficult recoveries (16). In our study, the age is indeed associated to an increased risk of neuromuscular complications. Age increased with weight, ASA score, and duration of surgery. That is certainly why it did not appear to be a risk factor itself in the final model of anesthetic mortality (which included weight and ASA score) and neuromuscular complications (which included weight and duration of surgery).

The results of this study are in agreement with those of many publications that show a high risk of anesthetic mortality when the ASA score is high in human as well as in animals (3, 9). This could be explained by the fact that the ASA score was linked to many confounding factors such as age, types of surgery, urgency, duration of anesthesia, period of intervention.

Unlike studies by Mee et al. (13) and Dugdale et al. (4), we found that weight is a significant risk factor for anesthetic mortality. Among the confounding factors we found age, colic surgery, PaO_2/FiO_2 ratio, blood pressure and duration of anesthesia. Indeed it has been shown that the weight of the horse influences the duration of recovery and increases post-operative complications (17, 18).

The risk of anesthetic mortality was multiplied by 10 during orthopedic surgery. This result is in accordance with Johnston et al. (2). This can be explained by the length of these surgeries that are often long, the urgency, that recoveries are complicated (with a significant risk of fracture), that the ASA score is increased. In addition, the surgeon's seniority was identified as a risk factor in our study, yet a senior surgeon is often involved in orthopedic surgery.

Colic and fracture surgeries are performed urgently in horses having a high ASA score. It is therefore natural to find a higher mortality rate for emergency surgeries as Mee et al. also showed in 1998 (13).

The duration of anesthesia increased the risk of anesthetic mortality and systemic complications. Our data demonstrated that anesthesia lasted longer when the ASA score increased, the latter being a variable in the final model of anesthetic mortality and systemic complications. Anesthesia was also longer when the horse was heavier, during surgery performed by a senior, during orthopedic surgery; all these variables were present in the final model of anesthetic mortality. The literature is divided on this point. Some studies including only emergency surgeries showed an increase in anesthetic risk during long surgery (2, 13). In contrast, Mee's study of non-urgent surgeries showed no significant difference (19).

Complication Rate

The non-fatal complications rate was of 17%, which is similar to those found in the literature: 16.4% for Kim (14) and 13.7% for Senior et al. (20).

Nature of Complication

The nature of these complications was predominantly neuromuscular or respiratory.

The majority (92%) of the complications observed before the horse returns to its box occurred during the recovery phase.

We did not observe colic during recovery. Nevertheless, continuing the observation of the records up to 48 h postoperatively, we observed slowing of intestinal transit in 19 horses and other types of colic in 19 other horses, all operated for surgeries other than emergency abdominal surgeries. All resolved medically. Among the horses who underwent colic surgery ($n = 229$), 11 were euthanized as their condition worsened.

Among the other complications described up to 48 h after recovery, we recorded 21 corneal ulcers, 13 peaks of hyperthermia, 7 thrombophlebitis, 3 diarrheas, a case of bronchopneumonia, a case of peritonitis and a case of bilateral nasal discharge and cough. Some horses were euthanized because of the aggravation of their condition: three horses who had undergone fracture surgery for which the reduction was not effective, a case of septic arthritis and a case of dysphagia after guttural pouch surgery. The difference between the nature of complications observed during the period of anesthesia and those observed at the return to the hospitalization box indicates the need to separate these observation periods in future studies.

Explanatory Factors for Neuromuscular Complications

Our study showed an increase in neuromuscular complications when weight increased. This seems logical since the weight of the body affects the weight worn on the muscles and nerves of the dependent legs during recumbency. The etiology of neuropathy and myopathy syndromes is temporary ischemia due to prolonged pressure on muscle groups (21). Nevertheless, this is disputed by the study of Kim who found that, but did not discuss why, the risk is increased in horses under 500 kg (14).

Maybe for the same reasons, our results showed that lateral recumbency increased the risk of neuromuscular complications in agreement with Johnston et al. (22). Indeed, we observed a series of facial paralysis in horses placed in lateral decubitus (despite the removal of the halter). We also recorded few radial or femoral paresis. Movements of the limb (to massage the shoulder) are now systematically implemented in horses placed in lateral recumbency. The insufflation of the air mattress is also controlled according to the weight of the horse so that it is not too hard.

Furthermore, the risk of neuromuscular complications was multiplied by 1.2 when the blood pressure decreases by 10 mmHg. This reinforces the observations of several authors on the important role of hypotension, in addition to ischemia, in the development of myopathy (21, 23, 24). This was confirmed by the implication of a high hypotension index as a factor favoring neuromuscular complications, as emphasized by the study of Young and Taylor (10). It allowed the evaluation of the intensity and duration of hypotension during anesthesia.

A high ASA score is associated with longer anesthesia and with surgery performed more often by a senior. These two variables are in the final explanatory model of neuromuscular and respiratory complications. This probably explains why the ASA score no longer appeared directly in the explanatory models of these complications. Another possible reason is that ASA 2 and 3 scores were the most represented during orthopedic surgery, the latter being a factor increasing the risk of neuromuscular complications.

The duration of anesthesia multiplied by 1.4 the risk of neuromuscular complications every hour of additional surgery. This can be logically explained, among other things, by the fact that the duration of ischemia is correlated with the risk of myopathy (21).

Hypocalcemia was associated with an increased risk of neuromuscular complications. We could not study this parameter in our final model since the systematic measurement of this variable only concerned colic surgery. However, it would be interesting to know if this parameter would prove to be particularly important. For that, it would also be necessary to extend our duration of observation to be able to observe its effect on the digestive complications. Indeed, it was demonstrated that decreased serum calcium promoted the appearance of ileus (25).

Explanatory Factors for Respiratory Complications

Our model showed that the risk of respiratory complication increased when the PaO_2/FiO_2 ratio decreased and the age increased. In addition, the link between these variables showed that the older the horse, the worse its oxygenation is. Hypoxemia is one of the causes of pulmonary edema (26), which represents 80% of the respiratory complications observed in our study which represented 22 % of total complications, therefore the incidence of pulmonary oedema was 18% of all the complications observed. Despite the aging of the population of anesthetized horses, the management of hypoxemia has improved over the years at our hospital, mainly thanks to the more and more systematic use of salbutamol, the administration of which has been facilitated by the acquisition of a spray system placed in the Y-piece of the circuit. This has certainly led to an overall decrease in respiratory complications by reducing the risk of pulmonary edema.

Our study also showed an increase in respiratory complications associated with heavy weight. Body weight as well as body shape influence arterial oxygenation and alveolar arterial oxygen gradient, increasing the risk of hypoxemia (27).

The duration of anesthesia multiplied by 1.5 the risk of respiratory complications every hour of additional surgery. It is also possible that the duration of anesthesia influenced the severity of atelectasis and therefore hypoxemia and its consequences.

Respiratory complications were strongly associated to colic surgeries. Horses operated for colic often have low plasma protein concentration (28) which promotes the development of pulmonary edema (26). Out of hours surgeries also increased the risk of respiratory complication. This could be explained by the link that exists with colic and emergency surgeries.

Upper respiratory tract obstruction (e.g., laryngeal edema due to low head position during long surgery or nasal edema) is also a potential cause of pulmonary edema.

Nevertheless, in our clinic, the horses are systematically recovered with a naso-pharyngeal or oro-tracheal tube (after colic surgeries) and a vasoconstrictor is administered in the nostrils at the end of the surgery. The endotracheal tubes are removed only when the horse is standing. Upper airway obstruction is therefore an unlikely cause of pulmonary edema in this study.

Explanatory Factors for Cardiovascular Complications

Lateral recumbency multiplied the risk of cardiovascular complications by 5. The latter was more commonly used in older horses undergoing arthroscopies, orthopedic surgeries or surgeries of the head. Lateral recumbency was also associated to ASA score higher than 3.

We found that age was also part of the explanatory model of cardiovascular complications. Indeed, most of these confounding factors with age are associated with increased anesthetic risk.

Explanatory Factors for Systemic Complications

The ASA score was the only variable retained in the final model of systemic complications. It was therefore the only explanatory variable of the weakness syndrome (i.e., systemic complications) that we had defined by a prolonged recovery time, the treatment of the horse by more than one injection in the recovery box and prolonged sternal position. Mee et al. also showed an increased risk of systemic complication in horses with high ASA scores

(19). Indeed, the American Society of Anesthesiologists (ASA) Physical Status (PS) classification proved to be a very good tools for identifying the animals at a greater risk of anesthesia-related death and complications (9).

Recovery

Although recovery quality has been associated to factors that also affect mortality (4), Mee et al. found no significant relationship between them (19). To our knowledge our study is the first to show that poor and prolonged recoveries are significantly associated with increased risks of anesthetic mortality and neuromuscular, respiratory and systemic complications. This confirms the reliability of the recovery score used, based on objective descriptors (11). Most complications occurred during recovery unlike Johnston's et al. study that suggested increased fatalities (cardiac arrest) in the early time period of anesthesia (2). This suggests that advances in monitoring and in the safety of anesthesia molecules have shifted the risk period to the recovery box where conditions are more difficult to control.

Common Explanatory Factors

Among the most common explanatory factors for complications and mortality that we observed in the final models, the surgeon's experience and horse weight appeared 3 times, the ASA score, the duration of anesthesia and age of the horse appeared 2 times. A high PaO_2/FiO_2 ratio appeared to decrease the risk of respiratory and cardiovascular complications. Weight, surgeon experience and PaO_2/FiO_2 ratio were the least cited factors in the literature (14). It is interesting to note that the most experienced surgeons tended to be responsible for cases with the highest risk and therefore associated to increased mortality and morbidity. Unfortunately, we were not able to prove the same for the anesthetists as the names noted on the anesthesia sheet were often only those of the residents even if a senior had supervised them.

Bias

One of the biases of our study is the categorization of surgeries. All surgeries in the same category are not necessarily perceived as having the same risk.

The important limitation of this study is obviously the small sample size. To identify risk factors that we could modify to improve outcomes, epidemiological studies have to be prospective and have to include many cases from several centers. Nevertheless, as Senior (1) recommended, the study of cases of a single clinic can also contribute to improving the safety of our equine patients comparing our results to those published by other clinics. It also helps to identify confounding factors. It could at least be as effective as the publication of guidelines (1).

The prospective aspect is very important in order to limit recruitment errors. In this study we could not extend a reliable observation after the horse returned to his box and we could not observe the effect of the recovery method on the risk of complication. The prospective aspect is even more essential to homogenize multicenter studies.

The study of intrinsic and extrinsic factors that determine anesthetic mortality and morbidity is dependent on several definitions, those of mortality and morbidity themselves but also that of their correlation with the anesthetic procedure. The definition of mortality (fatal outcome) is easy, however the definition of morbidity is complex and can give rise to various interpretations.

CONCLUSION

This study allowed us to identify the weight, the age of the horse, the surgeon's experience, the ASA score and the duration of anesthesia as risk factors for mortality and anesthetic complication. Unfortunately, among these factors only duration of anesthesia could be improved. These results reinforce those of previous studies and underline the interest of regularly reporting these data. In particular, to recruit them, on a larger scale, in a multicenter prospective study.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the animal study because this is a statistical analysis of retrospective data retrieved from the archival database of the clinic where the study was carried out. Written informed consent for participation was not obtained from the owners because this is a statistical analysis of retrospective data retrieved from the archival database of the clinic where the study was carried out.

AUTHOR CONTRIBUTIONS

CL, LA, and KP participated in conception of the work, data acquisition and interpretation, and wrote or contributed to the writing of the manuscript and revised the manuscript. LA and KP performed data analysis.

ACKNOWLEDGMENTS

The authors would like to thank all the staff of the Equine Teaching Hospital of Lyon who daily recorded the medical records. The authors also thank Dr. Emmanuelle Gilot-Fromont for her precious contribution.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00514/full#supplementary-material

REFERENCES

1. Senior JM. Barking up the wrong tree: would international guidelines improve safety in equine anesthesia? *Equine Vet J*. (2015) 47:14–5. doi: 10.1111/evj.12348
2. Johnston GM, Eastment J, Wood J, Taylor P. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of Phases 1 and 2. *Vet Anaesth Analg*. (2002) 29:159–70. doi: 10.1046/j.1467-2995.2002.00106.x
3. Dugdale AH, Obhrai J, Cripps PJ. Twenty years later: a single-centre, repeat retrospective analysis of equine perioperative mortality and investigation of recovery quality. *Vet Anaesth Analg*. (2016) 43:171–8. doi: 10.1111/vaa.12285
4. Dugdale AH, Taylor PM. Equine anesthesia-associated mortality: where are we now? *Vet Anaesth Analg*. (2016) 43:242–55. doi: 10.1111/vaa.12372
5. Brodbelt DC, Blissitt KJ, Hammond RA, Neath PJ, Young LE, Pfeiffer DU, et al. The risk of death: the confidential enquiry into perioperative small animal fatalities. *Vet Anaesth Analg*. (2008) 35:365–73. doi: 10.1111/j.1467-2995.2008.00397.x
6. Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, et al. Survey of anesthesia-related mortality in France. *Anesthesiology*. (2006) 105:1087–97. doi: 10.1097/00000542-200612000-00008
7. American College of Veterinary Anesthesia and Analgesia. *Guidelines for Anesthesia in Horses*. (2019). Available online at: http://www.acvaa.org/docs/Equine (accessed October, 2019).
8. Association of Veterinary Anaesthetists. *Recommended Requirements When Performing General Anesthesia of Dogs, Cats and Horses*. (2019). Available online at: http://www.ava.eu.com/recommendations/AVAeng.pdf (accessed October, 2019).
9. Portier K, Ida KK. The ASA physical status classification: what is the evidence for recommending its use in veterinary anesthesia? -A systematic review. *Front Vet Sci*. (2018) 5:204. doi: 10.3389/fvets.2018.00204
10. Young SS, Taylor PM. Factors influencing the outcome of equine anesthesia: a review of 1,314 cases. *Equine Vet J*. (1993) 25:147–51. doi: 10.1111/j.2042-3306.1993.tb02926.x
11. Portier KG, Séna A, Senior M, Clutton RE. A study of the correlation between objective and subjective indices of recovery quality after inhalation anesthesia in equids. *Vet Anaesth Analg*. (2010) 37:329–36. doi: 10.1111/j.1467-2995.2010.00542.x
12. Gent TC, Bettschart-Wolfensberger R. Peri-anesthetic mortality in horses - the need for CEPEF-4. *Vet Anaesth Analg*. (2013) 40:e1–2. doi: 10.1111/vaa.12070
13. Mee AM, Cripps PJ, Jones RS. A retrospective study of mortality associated with general anesthesia in horses: emergency procedures. *Vet Rec*. (1998) 142:307–9. doi: 10.1136/vr.142.12.307
14. Kim A. Retrospective analysis of equine general anesthesia performed at korea racing authority. *J Vet Clin*. (2014) 31:102. doi: 10.17555/ksvc.2014.04.31.2.102
15. Johnston GM, Taylor PM, Holmes MA, Wood JL. Confidential enquiry of perioperative equine fatalities (CEPEF-1): preliminary results. *Equine Vet J*. (1995) 27:193–200. doi: 10.1111/j.2042-3306.1995.tb03062.x
16. Seddighi R, Doherty TJ. Anesthesia of the geriatric equine. *Vet Med Res Rep*. (2012) 3:53–64. doi: 10.2147/VMRR.S34162
17. Rothenbuhler R, Hawkins JF, Adams SB, Lescun TB, Weil AB, Glickman LT, et al. Evaluation of surgical treatment for signs of acute abdominal pain in draft horses: 72 cases (1983-2002). *J Am Vet Med Assoc*. (2006) 228:1546–50. doi: 10.2460/javma.228.10.1546
18. Wawra E, Senior J, Clutton RE. Factors influencing the duration and quality of recovery from general anesthesia in horses: a retrospective study of 590 cases. In: *Presented at the Proceedings of the 10th World Congress of Veterinary Anesthesia*. Glasgow (2009). p. 48.
19. Mee AM, Cripps PJ, Jones RS. A retrospective study of mortality associated with general anesthesia in horses: elective procedures. *Vet Rec*. (1998) 142:275–6. doi: 10.1136/vr.142.11.275
20. Senior JM, Pinchbeck GL, Allister R, Dugdale AH, Clark L, Clutton RE, et al. Reported morbidities following 861 anesthetics given at four equine hospitals. *Vet Rec*. (2007) 160:407–8. doi: 10.1136/vr.160.12.407
21. Young SS. Post anesthetic myopathy. *Equine Vet Educ*. (2010) 15:60–3. doi: 10.1111/j.2042-3292.2005.tb01829.x
22. Johnston GM, Eastment JK, Taylor PM, Wood JL. Is isoflurane safer than halothane in equine anesthesia? Results from a prospective multicenter randomized controlled trial *Equine Vet J*. (2004) 36:64–71. doi: 10.2746/0425164044864723
23. Bidwell LA, Bramlage LR, Rood WA. Equine perioperative fatalities associated with general anesthesia at a private practice–a retrospective case series. *Vet Anaesth Analg*. (2007) 34:23–30. doi: 10.1111/j.1467-2995.2005.00283.x
24. Grandy JL, Steffey EP, Hodgson DS, Woliner MJ. Arterial hypotension and the development of postanesthetic myopathy in halothane-anesthetized horses. *Am J Vet Res*. (1987) 48:192–7.
25. Koenig J, Cote N. Equine gastrointestinal motility–ileus and pharmacological modification. *Can Vet J*. (2006) 47:551–9.
26. Senior M. Post-anesthetic pulmonary edema in horses: a review. *Vet Anaesth Analg*. (2005) 32:193–200. doi: 10.1111/j.1467-2995.2005.00186.x
27. Dupont J, Serteyn D, Sandersen C. Prolonged recovery from general anesthesia possibly related to persistent hypoxemia in a draft horse. *Front Vet Sci*. (2018) 5:235. doi: 10.3389/fvets.2018.00235
28. Lane JK, Cohen JM, Zedler ST, Hollis AR, Southwood LL. Right dorsal colon resection and bypass for treatment of right dorsal colitis in a horse. *Vet Surg*. (2010) 39:879–83. doi: 10.1111/j.1532-950X.2010.00723.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

CASE REPORT
published: 24 April 2020
doi: 10.3389/fvets.2020.00210

Recurrent Hyperkalemia During General Anesthesia in a Dog

Carissa W. Tong[1]*, *Anusha Balakrishnan*[1] and *Rachel Matusow Wynne*[2]

[1] Department of Emergency and Critical Care, Cornell University Veterinary Specialists, Stamford, CT, United States,
[2] Department of Ophthalmology, Cornell University Veterinary Specialists, Stamford, CT, United States

Objective: To describe the development of recurrent hyperkalemia in a dog that underwent general anesthesia at two different hospitals within a month. The definitive underlying cause of the hyperkalemia remains unknown.

Case summary: A 11 year-old male neutered Rottweiler underwent general anesthesia on two separate occasions at two different hospitals for ophthalmic surgery within a month and developed marked hyperkalemia on each occasion. The patient received similar drug protocols in both instances, including propofol, midazolam, non-depolarizing neuromuscular blocking agents, and isoflurane inhalant anesthetic. The patient showed ECG changes consistent with hyperkalemia during the first anesthetic event, but not the second. No underlying cause of hyperkalemia was definitively identified. The patient responded to standard therapy for hyperkalemia on both occasions and serum potassium levels returned to normal. The patient was discharged from the hospital without further complications and post-operative rechecks showed persistently normal serum potassium levels.

New or unique information provided: Considering that there is a relationship between the development of severe hyperkalemia and propofol administration in human patients, it is possible that such a relationship exists in veterinary patients. However, numerous other diseases and medications can also lead to peri-operative hyperkalemia. Veterinary professionals should be aware that hyperkalemia can develop intra-operatively and remains be an important differential diagnosis in bradycardic patients under anesthesia that are not responding to traditional therapies.

Keywords: propofol, hyperkalemia, propofol infusion syndrome, anesthesia, canine

OPEN ACCESS

Edited by:
Keila Ida,
Texas A&M University, United States

Reviewed by:
Rene Doerfelt,
Ludwig-Maximilians Universität München, Germany
Nathan Peterson,
VCA West Los Angeles Animal Hospital, United States

***Correspondence:**
Carissa W. Tong
ctong@cuvs.org

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *29 October 2019*
Accepted: *30 March 2020*
Published: *24 April 2020*

Citation:
Tong CW, Balakrishnan A and Wynne RM (2020) Recurrent Hyperkalemia During General Anesthesia in a Dog. Front. Vet. Sci. 7:210. doi: 10.3389/fvets.2020.00210

INTRODUCTION

Hyperkalemia is a potentially life-threatening electrolyte abnormality defined as a serum potassium level >5.5 mmol/L in dogs (1). It is an uncommon intra-operative complication but can occur secondary to a variety of causes. Recently, there have been increased reports of the development of hyperkalemia in canine patients under anesthesia (2–4). This case report describes the development of repeated severe hyperkalemia under general anesthesia in a dog of which the cause remains unknown.

CASE PRESENTATION

An 11-year-old, 49.9 kg, male neutered Rottweiler was presented to the Ophthalmology Service of Cornell University Veterinary Specialists (CUVS) for an elective bilateral phacoemulsification of diabetes mellitus-induced cataracts. The patient had an extensive medical history of the following: historical facial trauma resulting in right-sided facial nerve paralysis and right-sided lagophthalmos, inflammatory bowel disease, diabetes mellitus with episodes of diabetic ketoacidosis, bilateral cranial cruciate ligament rupture with bilateral tibial plateau leveling osteotomies, recurrent urinary tract infections, an acute intervertebral disc extrusion necessitating a C6–C7 ventral slot surgery, and a splenectomy for a splenic mass with histopathology confirming extramedullary hematopoiesis. He had a history of mild, intermittent hyperkalemia (5.6–5.9 mmol/L) that was suspected to be pseudohyperkalemia secondary to thrombocytosis. Other causes of this mild, intermittent hyperkalemia had previously been ruled out through extensive diagnostic testing, including an abdominal ultrasound, thoracic and abdominal computerized tomography, as well as endocrine testing (resting cortisol levels, adrenocorticotropic hormone [ACTH] stimulation tests, and serum lead levels). Pre-operative blood work performed 3 weeks prior to his cataract surgery with his primary care veterinarian was submitted to an external laboratory[1] and revealed mild hypoalbuminemia, elevated alkaline phosphatase, hyperglycemia, hyponatremia, mild hyperkalemia, and hypercholesterolemia (**Table 1**). His platelet count was normal (**Table 1**). His fructosamine level was normal (333 umol/L; reference interval 136–350 umol/L) which indicated good diabetic regulation (<360 umol/L). Despite the adequate fructosamine level, a 24-h blood glucose curve performed 2 days after his pre-operative blood work showed a blood glucose range of 21–36 mmol/L. As such, his Neutral Protamine Hagedorn (NPH) insulin dose was increased to 30 units subcutaneously (SQ) every 12 h.

TABLE 1 | Pre-operative bloodwork at primary care veterinarian 3 weeks prior to anesthesia.

Albumin (g/dL) (RI 27–44 g/dL)	25
ALT (U/L) (RI 12–118 U/L)	46
ALP (U/L) (RI 5–131 U/L)	148
Glucose (mmol/L) (RI 3.8–7.7 mmol/L)	32.9
Sodium (mmol/L) (RI 139–154 mmol/L)	137
Potassium (mmol/L) (RI 3.6–5.5 mmol/L)	5.6
Cholesterol (mmol/L) (RI 2.39–8.42 mmol/L)	18.4
Amylase (U/L) (RI 290–1125 U/L)	441
Phosphorus (mmol/L) (RI 0.8–1.93 mmol/L)	1.35
Calcium (mmol/L) (RI 2.22–2.84 mmol/L)	2.27
Hematocrit (%) (RI 36–60%)	38
Platelet count (10^3/uL) (RI 170–400 10^3/uL)	292

RI, reference interval; ALP, alkaline phosphatase; ALT, alanine transaminase.

[1]Zoasis Laboratory: Antech Diagnostics, Inc., Los Angeles, CA.

On admission to the hospital, his heart rate (HR) (136 beats/min; reference interval, 80 to 140 beats/min) and body temperature (38.1°C; reference interval, 37.8° to 39.5°C) were within normal limits, but his respiratory rate was elevated as he was panting. This patient was aggressive and always had a higher resting HR documented during his previous 41 visits to the hospital (128–168 bpm) which was attributed to anxiousness. Physical examination revealed normal cardiothoracic auscultation. A complete ophthalmic examination was performed by a board-certified veterinary ophthalmologist including slit lamp biomicroscopy, rebound tonometry, fluorescein staining, electroretinography, and posterior segment ocular ultrasound. He had received NPH insulin[2] SQ (15 IU) at half of his normal dose 3 h prior to admission. He had received ketorolac[3] 1 guttae (ggt) in both eyes (OU), prednisolone acetate[4] 1 ggt OU, and Genteal[5] ¼ strip OU 12 h prior to admission. His blood glucose at presentation was 21 mmol/L (reference interval 4–9.7 mmol/L). Pre-operatively, per standard ophthalmology protocol, he received a total of four doses each of ketorolac, prednisolone acetate, tropicamide[6], and neomycin-polymyxin B-gramicidin[7] OU. He also received one dose each of phenylephrine[8] and dorzolamide-timolol[9] OU.

A peripheral intravenous catheter[10] was placed and the patient was premedicated with methadone[11] (0.3 mg/kg) and midazolam[12] (0.2 mg/kg) administered intravenously (IV). General anesthesia was induced with propofol[13] (1 mg/kg) IV to allow endotracheal intubation. The patient was connected to a rebreathing anesthetic circuit with isoflurane[14] as the inhalant anesthetic and was mechanically ventilated throughout the procedure. Cefazolin[15] was given at the beginning of surgery

[2]NPH insulin: Lilly, Indianapolis, IN.
[3]Ketorolac Tromethamine 0.5% Ophthalmic Solution: Akorn Inc., Lake Forest, IL.
[4]Prednisolone Acetate 1% Ophthalmic Suspension USP: Alcon Vision LLC, Fort Worth, TX.
[5]GenTeal Tears: Alcon Vision LLC, Fort Worth, TX.
[6]Tropicamide 1% Ophthalmic Solution USP: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ.
[7]Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution, USP: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ.
[8]Phenylephrine Hydrochloride 2.5% Ophthalmic Solution, USP: Akorn Inc., Lake Forest, IL.
[9]Dorzolamide HCl 2%/Timolol Maleate 0.5% Ophthalmic: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ.
[10]I.V. catheter: Terumo (Phillipines) Corporation, Laguna, Philippines.
[11]Methadone: Mylan Institutional LLC, Rockford, IL.
[12]Midazolam: Akorn Inc., Lake Forest, IL.
[13]Propofol: Zoetis, Kalamazoo, MI.
[14]Isoflurane: Henry Schein, Dublin OH.
[15]Cefazolin: West-Ward, Eatontown, NJ.

TABLE 2 | Point of care bloodwork (venous) at CUVS.

Date/Time	12/06/2018 12:40 During isoflurane anesthesia when bradycardia occurred	12/06/2018 13:30 1-h following anesthesia	12/06/2018 21:20 9-h following anesthesia	12/07/2018 08:30 20-h following anesthesia	12/10/2018 4 days following anesthesia
Venous pH (RI 7.32–7.44)	7.178	7.250	7.375	7.435	–
pCO_2 (mmHg) (RI 39–47 mmHg)	40.2	37	30.8	28.3	–
HCO_3^- (mmol/L) (RI 18–26 mmol/L)	14.8	15.9	17.6	18.6	–
BE (mmol/L) (RI −5 to +1 mmol/L)	−13.1	−10.5	−6.4	−4.4	–
Glucose (mmol/L) (RI 3.5–6.16 mmol/L)	16.7	18.1	15	9.8	23.4
Sodium (mmol/L) (RI 140–150 mmol/L)	134.3	138.8	143	143.3	145.1
Potassium (mmol/L) (RI 3.9–4.9 mmol/L)	8.08	6.08	4.08	4.4	4.6
Chloride (mmol/L) (RI 109–120 mmol/L)	112	114	111	113	104
iCa (mmol/L) (RI 1.2–1.5 mmol/L)	1.21	1.27	1.19	1.18	1.22
Lactate (mmol/L) (RI 0.5–2 mmol/L)	1.58	1.57	1.55	1.67	2.3

RI, reference interval; pCO_2, partial pressure of carbon dioxide; HCO_3^-, bicarbonate; BE, base excess; iCa, ionized calcium.

as a peri-operative prophylactic antimicrobial agent. Monitoring consisted of continuous electrocardiography (ECG), esophageal thermometry, capnography, pulse oximetry, and indirect blood pressure measurement[16]. Once the dog was anesthetized and positioned in dorsal recumbency for surgery, cisatracurium besylate[17] (0.2 mg/kg each time) was given IV 35- and 50-min following induction of anesthesia. Train-of-four monitoring was performed in the superficial peroneal nerve to assess depth of neuromuscular blockade. Fluid therapy was provided throughout the procedure with Plasmalyte[18] (10 mL/kg/hr). The patient's HR remained between 100 and 120 bpm initially and his systolic blood pressure (SBP) between 100 and 120 mmHg as measured by an indirect oscillometric device[16]. Phacoemulsification and intraocular lens implantation of the left eye were completed uneventfully. Patient positioning was adjusted slightly after completion of the surgical procedure on the left eye to bring the right eye into appropriate position under the surgical microscope. Ninety minutes following propofol induction and 55 min following cisatracurium administration, a marked, acute decrease in his HR (25–30 bpm) and blood pressure (SBP 65–70 mmHg) were noted during phacoemulsification of the right lens. His end-tidal carbon dioxide was 39 mmHg. Given the onset of his bradycardia and hypotension, and the nature of surgery, iatrogenic triggering of the oculo-cardiac reflex was considered a possibility; therefore, anticholinergic medications, both glycopyrrolate[19] (0.02 mg/kg) and subsequently atropine[20] (0.02 mg/kg), were given IV. However, as the patient's eye was not being actively manipulated and no improvement was noted with anticholinergic medications, oculo-cardiac reflex was considered less likely. The bradycardia and hypotension did not respond to administration of a crystalloid fluid bolus (10 mL/kg Plasmalyte), decreasing inhalant anesthetic concentration, or antagonism of his previously administered methadone and midazolam with intravenous administration of naloxone[21] (0.02 mg/kg) and flumazenil[22] (0.01 mg/kg), respectively. A venous blood gas sample[23] obtained from his cephalic vein revealed metabolic acidosis with marked hyperkalemia and relative hyponatremia (**Table 2**). His blood glucose and lactate were normal (**Table 2**). Throughout this period, his ECG demonstrated sinus bradycardia with absent P waves and tented T waves, consistent with changes secondary to hyperkalemia. The patient received 10% calcium gluconate[24] (0.15 mL/kg) IV for cardioprotection. His bradycardia rapidly resolved following administration of calcium gluconate. Regular insulin[25] (0.12

[16]LifeWindow: Digicare Biomedical, Boynton Beach, FL.
[17]Cisatrucurium: AbbVie Inc, North Chicago IL.
[18]Plasmalyte-A: Baxter Healthcare Corp, Deerfield, IL.
[19]Glycopyrrolate: West-Ward, Eatontown, NJ.
[20]Atropine: Vet One, Boise, ID.
[21]Naloxone: Akorn Inc., Lake Forest, IL.
[22]Flumazenil: West-Ward, Eatontown, NJ.
[23]RapidPoint 500: Siemens, Munich, Germany.
[24]10% Calcium gluconate: Fresenius Kabi, Lake Zurich, IL.
[25]Regular insulin: Lilly, Indianapolis, IN.

TABLE 3 | In-house chemistry panel at CUVS 1-h following anesthesia.

Albumin (g/dL) (RI 27–39 g/dL)	23
ALT (U/L) (RI 18–121 U/L)	38
ALP (U/L) (RI 5–160 U/L)	102
Glucose (mmol/L) (RI 3.5–6.3 mmol/L)	15
Cholesterol (mmol/L) (RI 3.4–8.97 mmol/L)	14.6
Amylase (U/L) (RI 337–1469 IU/L)	835
Phosphorus (mmol/L) (RI 0.8–1.9 mmol/L)	1.55
Calcium (mmol/L) (RI 2.09–2.94 mmol/L)	2.14

RI, reference interval; ALP, alkaline phosphatase; ALT, alanine transaminase.

TABLE 4 | Chemistry panel submitted by CUVS 2 weeks following anesthesia.

Albumin (g/dL) (RI 23–40 g/dL)	20
ALT (U/L) (RI 10–125 U/L)	57
ALP (U/L) (RI 23–212 U/L)	113
Glucose (mmol/L) (RI 4.07–7.86 mmol/L)	17.3
Cholesterol (mmol/L) (RI 2.86–8.55 mmol/L)	12.7
Amylase (U/L) (RI 500–1,500 IU/L)	406
Phosphorus (mmol/L) (RI 0.8–2.19 mmol/L)	2.22
Calcium (mmol/L) (RI 1.97–2.99 mmol/L)	2.07

RI, reference interval; ALP, alkaline phosphatase; ALT, alanine transaminase.

IU/kg) and terbutaline[26] (0.01 mg/kg) were also subsequently administered IV to facilitate potassium transport into the intracellular fluid compartment. As the bradycardia resolved, so did the hypotension (SBP 110–120 mmHg). Recheck venous blood gas analysis an hour later revealed mild improvement in his metabolic acidosis, hyperkalemia, and hyponatremia (**Table 2**). An in-house chemistry panel[27] was checked and revealed moderate hyperglycemia, mild hyperphosphatemia, mild hypoalbuminemia, hypercholesterolemia and a mildly low amylase (**Table 3**).

In order to further investigate the cause of his acute hyperkalemia, additional diagnostic testing performed included an abdominal ultrasound which revealed static hyperechoic hepatomegaly with heterogeneous hepatic echotexture, mild bilateral adrenomegaly, a small left renal cortical cyst, and an absent spleen. An ACTH stimulation test[28] was performed and revealed no evidence of hypoadrenocorticism or hyperadrenocorticism (pre-cortisol: 132.5 nmol/L, post-cortisol: 182.2 nmol/L). A recheck venous blood gas obtained 9 h later revealed resolution of the metabolic acidosis, hyperkalemia and hyponatremia (**Table 2**). The patient recovered well from anesthesia and his surgical procedure. He was discharged from the hospital 26 h post-operatively and remained stable at home. Recheck electrolytes measured 4 days post-operatively were within normal limits (**Table 2**).

Over the next 2 weeks, the patient was re-evaluated several times and remained normokalemic. However, his chemistry panel[28] showed that he remained mildly hypoalbuminemic and hypercholesterolemic (**Table 4**). His phosphorus and amylase levels normalized (**Table 4**). Moderate intraocular pressure elevation was detected 1 week after surgery, and dorzolamide-timolol ophthalmic solution was prescribed to be applied to both eyes twice daily. Despite this, an acute, severe pressure elevation was noted in the right eye 13 days post-operatively and in the left eye 14 days post-operatively. Over the following week, aqueocentesis was performed repeatedly (a total of three times) to relieve the intraocular hypertension, two episodes of which were facilitated using propofol for sedation (total dose each time was 0.5 mg/kg). During both instances, he did not develop any clinical signs suggestive of hyperkalemia, but his electrolytes were not rechecked immediately post-procedure.

The patient was then presented to Central Hospital For Veterinary Medicine 21-days post-operatively for bilateral endolaser cyclophotocoagulation to treat refractory glaucoma. Pre-operative point of care bloodwork[29] was within normal limits (**Table 5**). A peripheral intravenous catheter was placed. He was premedicated with hydromorphone[30] (0.1 mg/kg) and midazolam (0.2 mg/kg) IV. General anesthesia was induced with propofol (1.06 mg/kg) IV to allow endotracheal intubation. The patient was connected to a rebreathing anesthetic circuit with isoflurane as the inhalant anesthetic and he was mechanically ventilated throughout the procedure. Fluid therapy was provided with lactated Ringer's solution[31] at 10 mL/kg/hr. Atracurium[32] (0.2 mg/kg) was administered 30 min following induction and was reversed with neostigmine[33] (0.02 mg/kg) IV 150-min following induction. Two additional bolus doses of propofol (0.6 mg/kg each) were administered IV intra-operatively at 60- and 90-min following induction to maintain adequate depth of anesthesia. The patient remained hemodynamically stable throughout the surgery but upon recovery, point of care bloodwork was checked which revealed hyperkalemia with relative hyponatremia (**Table 5**). Regular insulin (0.1 IU/kg), 50% dextrose[34] (100 mg/kg) and 0.9% NaCl[35] (0.4 mL/kg)

[26]Terbutaline: West-Ward, Eatontown, NJ.
[27]IDEXX VetLab Station: IDEXX Laboratories, Westbrook, ME.
[28]IDEXX Laboratories, Westbrook, ME.
[29]Hydromorphone: West-Ward, Eatontown, NJ.
[30]VetScan i-STAT: Abaxis Inc., Union City, CA.
[31]Lactated Ringer's Solution: Dechra, Overland Park, KS.
[32]Atracurium Besylate: Schaumburg, IL.
[33]50% dextrose: Vet One, Boise, ID.
[34]0.9% NaCl: Hospira, Lake Forest, IL.
[35]Alfaxalone: Jurox Inc., North Kansas City, MO.

TABLE 5 | Point of care bloodwork (venous) at Central Hospital For Veterinary Medicine.

Date/Time	12/26/2018 15:00 24-h prior to anesthesia	12/27/2018 15:19 Immediately following anesthesia	12/27/2018 20:11 5-h following anesthesia	12/28/2018 00:07 9-h following anesthesia	12/28/2018 13:25 21-h following anesthesia
HCT (%) (RI 35–50%)	32	25	30	30	31
BUN (mmol/L) (RI 3.57–9.28 mmol/L)	5.7	4.64	5.36	5.7	5.7
Creatinine (umol/L) (RI 44.2–114 umol/L)	79.5	79.5	61.8	61.8	70.7
iCa (mmol/L) (RI 1.12–1.4 mmol/L)	1.15	1.25	1.26	1.27	1.23
Glucose (mmol/L) (RI 3.3–6.3 mmol/L)	5.7	20.5	28.9	16	22
Sodium (mmol/L) (RI 142–150 mmol/L)	145	136	136	144	141
Potassium (mmol/L) (RI 3.4–4.9 mmol/L)	4.5	8	6.2	4.5	4.8
Chloride (mmol/L) (RI 106–127 mmol/L)	118	113	114	114	115

RI, reference interval; HCT, hematocrit; BUN, blood urea nitrogen; iCa, ionized calcium.

were given IV. Eight hours later, the hyperkalemia resolved (**Table 5**). An abdominal ultrasound was repeated to investigate possible causes of recurrent hyperkalemia, and the findings were unchanged from previous study 21 days prior. A resting cortisol level was sent to an external laboratory[28] at this time and was now low (8.28 nmol/L, reference interval 55.2–165.6 nmol/L); however, this result was suspected to be influenced by the fact that the patient had been treated with ophthalmic prednisone acetate drops. Hypoadrenocorticism was considered unlikely in this patient due to a previously reported normal cortisol level, normal ACTH stimulation test 3 weeks prior, and static ultrasonographic appearance of the adrenal glands reported on two separate occasions 3 weeks apart. A fasted triglyceride level was checked to rule out marked hypertriglyceridemia causing pseudohyperkalemia and was mildly elevated (1.96 mmol/L, reference interval 0.22–1.65 mmol/L). The patient recovered well and was discharged 6 days post-operatively.

Due to the development of repeated intra-operative hyperkalemia at two different facilities, propofol infusion syndrome was considered a potential cause for the acute hyperkalemia. Given this concern, when the patient underwent a third anesthetic episode for bilateral enucleation at CUVS 7 weeks later, alfaxalone[36] (1 mg/kg) IV was used as an anesthetic induction agent instead of propofol. Methadone (0.2 mg/kg) and midazolam (0.2 mg/kg) were used as premedication. General anesthesia was maintained using isoflurane inhalant anesthetic but no neuromuscular blocking agents were used. Pre- and post-operative electrolyte levels remained within normal limits throughout this hospital stay. The patient's diabetes mellitus was better controlled during this visit: blood glucose was 11.5 mmol/L pre-operatively and 19.7 mmol/L post-operatively. The patient had an uneventful recovery and was discharged the following day. No further hyperkalemic episodes were suspected or documented.

Five months after his cataract surgery, the patient was diagnosed with a rapidly progressive C7–T1 myelopathy. At that time, considering the patient's multitude of health issues and concerns for his overall poor prognosis, his owners elected humane euthanasia.

DISCUSSION

This report describes the repeated development of marked hyperkalemia during general anesthesia for ophthalmologic surgery in a dog. There are many causes of intra-operative hyperkalemia, broadly divided into the following categories: altered potassium distribution (e.g., increased potassium release from cells or other transcellular shifts, including severe metabolic acidosis, thrombocytosis, hemolysis, rhabdomyolysis) (1, 5), reduced renal/urinary excretion (e.g., uroabdomen, administration of potassium-sparing diuretics, intravascular volume depletion, hypoaldosteronism/hypoadrenocorticism), malignant hyperthermia, an increased exogenous potassium load (e.g., drug-related, iatrogenic potassium chloride injection) or parasitic infestation (whipworms). There are also reports of veterinary species-specific problems such hyperkalemic periodic paralysis in Quarter Horses (6) [also reported in a dog (7)], episodic hyperkalemia in Greyhounds (8), and unexplained hyperkalemia in non-domestic felids (9). There was a recent case series documenting repeated intra-operative hyperkalemia in two Greyhounds where the inciting cause was not identified (2). Greyhounds reportedly have significantly lower than

[36]Neostigmine: Amphastar Pharmaceuticals Inc, Rancho Cucamonga, CA.

average basal aldosterone levels, which may have contributed to the development of hyperkalemia or to their inability to rapidly and/or effectively respond to increases in serum potassium when they occurred. These dogs also received medetomidine which could contribute to hyperkalemia due to the inhibitory effects of alpha-2 adrenergic receptor agonists on the production of insulin (2). Our patient was neither a Greyhound nor did he receive an alpha-2 adrenergic agonist, therefore the above hypothesis is unlikely to be applicable in this case.

The patient in this report had a prior history of mild pseudohyperkalemia secondary to thrombocytosis. However, this typically results in a mild increase in potassium levels (0.3–0.5 mmol/L above baseline) secondary to increased potassium release from activated platelets. In the absence of hemolytic serum and elevated bilirubin levels, intravascular hemolysis appeared unlikely. The patient did not receive any drugs that would impair potassium excretion and the risk of iatrogenic injection of potassium chloride was considered negligible—all fluid bags and medications administered were rechecked, and the fact the hyperkalemia recurred at a different veterinary facility made this unlikely. Rhabdomyolysis was considered unlikely given the lack of pigmenturia observed on both occasions and a normal creatinine kinase level obtained 3 days after the initial event. Acute kidney injury was ruled out by normal urea nitrogen and creatinine levels, and adrenal function testing did not support hypoadrenocorticism. Considering the above, metabolic causes were thought to be less likely and the focus shifted to drug-induced hyperkalemia.

Timolol was considered to be a potential contributing cause of hyperkalemia due to a single case report in human patients which described the development of severe hyperkalemia after administration of timolol (10). Timolol is a beta-antagonist that can impair potassium homeostasis by reduced sodium-potassium-ATPase activity, preventing potassium influx and sodium efflux into cells and leading to development of hyperkalemia. Given the scarce reports of beta-antagonist induced hyperkalemia in human patients, the authors believe timolol was unlikely to be the cause of the hyperkalemia. Other medications that the patient received on both occasions included midazolam, isoflurane inhalant, propofol, and non-depolarizing neuromuscular blocking agents. Extensive literature review revealed no case reports or known associations between midazolam and the development of hyperkalemia. Isoflurane-induced malignant hyperthermia (MH) leading to hyperkalemia has been reported in both human medicine and in a dog (11). MH is thought to be an autosomal dominant inherited disease caused by a mutation of *RYR*1 gene. The most common features of MH in dogs are hypercarbia, hyperthermia, and cardiac arrhythmias (11). Rhabdomyolysis is thought to be the cause of hyperkalemia in MH. Given the patient's multiple previous exposures to isoflurane, low-normal body temperature, and normal end-tidal carbon dioxide throughout both surgeries, malignant hyperthermia was considered highly unlikely.

Propofol infusion syndrome (PRIS) has been reported in human medicine (12, 13) and in one veterinary case report (3). This is a syndrome occurring in critically ill patients receiving propofol infusions, typically at high doses (>5 mg/kg/h) or prolonged infusion (>48 h), and is characterized by one of the following changes that are otherwise unexplained: metabolic acidosis, rhabdomyolysis, or ECG changes, with or without AKI, hyperkalemia, hyperlipidemia, cardiac failure, elevated liver enzymes, or raised serum lactate (12, 13). There are also human case reports documenting hyperkalemia after a single bolus of propofol at an average dose (14, 15). There have been a few recent case reports published describing development of peri-operative hyperkalemia in dogs and all of these patients received propofol (2–4). However, aside from the case reported by Mallard et al. (3), none of the dogs developed signs supportive of PRIS except for hyperkalemia and did not receive a continuous rate infusion. The patient in our study had received propofol at varying doses (0.5–4 mg/kg) on eight occasions previously and had no hemodynamic changes consistent with PRIS. However, it is still possible that the signs noted during these two events was related to early PRIS, or was a precursor for the development of PRIS, since a dose-dependent relationship has been suggested in human medicine (12).

Another recent report described development of marked hyperkalemia intra-operatively in a dog with poorly controlled diabetes mellitus undergoing anesthesia for phacoemulsification (4). This patient underwent the same procedure (elective phacoemulsification), received propofol as an induction agent, was maintained on inhalant isoflurane anesthesia, and received a non-depolarizing neuromuscular blocking agent (atracurium). An additional similarity between this dog and the patient in our study was that both animals were diabetic patients that did not have optimal glycemic control. However, the diabetic patient described in the previous report also received medetomidine, which may have contributed to the hyperkalemia noted. In that report, the patient's hyperkalemia was presumed to be caused by poorly controlled diabetes mellitus leading to a combination of insulin deficiency and hyperosmolality, resulting in hyperkalemia through fluid shifts from the intracellular to extracellular compartment (4). A normal fructosamine level was documented pre-operatively in our patient; however, moderate hyperglycemia was documented in the post-operative period following development of hyperkalemia. The patient had previously been exposed to propofol on multiple occasions (prior splenectomy, spinal surgery, endoscopy, and abdominal explore); however, these instances occurred before his diagnosis of diabetes mellitus (he had been diagnosed 7 months prior to his cataract surgery). There is evidence in animal models to suggest that propofol induces whole body insulin resistance and causes glycogen synthase kinase 3β-related mitochondrial dysfunction and apoptosis, and the link between insulin resistance and mitochondrial dysfunction has been well-described (16, 17). These studies have suggested that propofol-induced insulin resistance may contribute to the development of PRIS. The authors hypothesize that once this patient became a diabetic with altered carbohydrate metabolism, he may have been more susceptible to the development of mitochondrial dysfunction which could have mediated the development of early PRIS in this case on both occasions. This may explain

why hyperkalemia or other signs suggestive of PRIS were not documented during previous exposures to propofol in this patient.

Neuromuscular blocking agents were also considered potential causes for our patient's hyperkalemia. There are well-documented reports of succinylcholine-induced hyperkalemia in human patients (18, 19) and one case report in an experimental study in dogs (20). Succinylcholine is a depolarizing neuromuscular blocking agent that differs from non-depolarizing agents in that it results in prolonged, irreversible binding at the postsynaptic acetylcholine (ACh) receptors. Succinylcholine has been reported to cause a transient, mild increase in potassium concentration up to 0.5 mmol/L above baseline (18). However, this effect can be exacerbated when the Ach receptors on skeletal muscle are upregulated or if denervation occurred such that the constituent subunits of the Ach receptor were altered (19). Both the patient in the aforementioned case report (4) and this patient received non-depolarizing neuromuscular agents, either cisatracurium or atracurium. There are no current human or veterinary reports of hyperkalemia developing after administration of either of these medications. However, the potential for non-depolarizing neuromuscular blocking agents to have contributed to intra-operative hyperkalemia cannot be entirely ruled out.

Given these considerations, the authors hypothesize that this patient's repeated, marked intra-operative hyperkalemia was most likely associated with propofol, although other contributing causes such as suboptimal glycemic control of diabetes mellitus and contributions from other medications cannot be ruled out completely. Hyperkalemia can be a life-threatening emergency and is an important differential in bradycardic patients under anesthesia that are not responsive to traditional therapies. Administration of calcium gluconate to increase the cardiac threshold potential and administration of insulin with dextrose, beta-2 agonists or sodium bicarbonate to encourage the intracellular shift of potassium are interventions that should be considered to reduce the risk of fatal arrhythmias and to decrease circulating potassium concentrations. Although a definitive underlying cause could not be identified in this patient, this case report adds to current veterinary literature by raising awareness of the potential for development of severe intra-operative hyperkalemia that could be related to various anesthetic medications. Close monitoring and prompt identification of intra-operative hyperkalemia is vital for rapid intervention to treat this life-threatening anesthetic complication.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The case report is a retrospective evaluation with no active interventional or research component, therefore ethical approval was not indicated. Client consent was not obtained as the data provided in the following case report does not contain any identifiable information.

AUTHOR CONTRIBUTIONS

CT and AB participated in the manuscript preparation. RW participated in critical revisions of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Dorbandt and the Ophthalmology Department at Central Hospital For Veterinary Medicine for sharing case information and their collaboration.

REFERENCES

1. Riordan LL, Schaer M. Potassium disorders. In: Silverstein D, Hopper K, editors. *Small Animal Critical Care Medicine*. 2nd Edn. St. Louis, MO: Elsevier Inc. (2014). p. 269–73. doi: 10.1016/B978-1-4557-0306-7.00051-9
2. Jones SJ, Mama KR, Brock NK, Guillermo Couto C. Hyperkalemia during general anesthesia in two Greyhounds. *J Am Vet Med Assoc*. (2019) 254:1329–34. doi: 10.2460/javma.254.11.1329
3. Mallard J, Rieser T, Peterson N. Propofol infusion-like syndrome in a dog. *Can Vet J*. (2018) 59:1216–22.
4. Monticelli P, Dawson C, Adami C. Life-threatening hyperkalaemia in a diabetic dog undergoing anaesthesia for elective phacoemulsification. *Vet Anaesth Analg*. (2018) 45:881–2. doi: 10.1016/j.vaa.2018.06.007
5. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. *Am J Nephrol*. (2013) 38:50–7. doi: 10.1159/000351804
6. Naylor JM. Equine hyperkalemic periodic paralysis: review and implications. *Can Vet J*. (1994) 35:279–85.
7. Jezyk P. Hyperkalemic periodic paralysis in a dog. *J Am Anim Hosp Assoc*. (1982) 18:977–80.
8. Schaer M, Halling KB, Collins KE, Grant DC. Combined hyponatremia and hyperkalemia mimicking acute hypoadrenocorticism in three pregnant dogs. *J Am Vet Med Assoc*. (2001) 218:897–9. doi: 10.2460/javma.2001.218.897
9. Reilly S, Seddighi MR, Steeil JC, Sura P, Whittemore JC, Gompf RE, et al. Selected Clinical, Biochemical, and Electrolyte Alterations in Anesthetized Captive Tigers (Panthera Tigris) and Lions (Panthera Leo). *J Zoo Wildl Med*. (2014) 45:328–34. doi: 10.1638/2013-0202r.1
10. Swenson ER. Severe hyperkalemia as a complication of timolol, a topically applied ß-ADRENERGIC ANTAGONIST. *Arch Int Med*. (1986) 146:1220–1.
11. Adami C, Axiak S, Raith K, Spadavecchia C. Unusual perianesthetic malignant hyperthermia in a dog. *J Am Vet Med Assoc*. (2012) 240:450–3. doi: 10.2460/javma.240.4.450
12. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth*. (2019) 122:448–59. doi: 10.1016/j.bja.2018.12.025
13. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med*. (2003) 29:1417–25. doi: 10.1007/s00134-003-1905-x

14. Lee JH, Ko YS, Shin HJ, Yi JH, Han SW, Kim HJ. Is there a relationship between hyperkalemia and propofol? *Electrolyte Blood Press*. (2011) 9:27–31. doi: 10.5049/EBP.2011.9.1.27
15. Mali AR, Patil VP, Pramesh CS, Mistry RC. Hyperkalemia during surgery: Is it an early warning of propofol infusion syndrome? *J Anesth*. (2009) 23:421–3. doi: 10.1007/s00540-009-0745-4
16. Yasuda Y, Fukushima Y, Kaneki M, Martyn JAJ. Anesthesia with propofol induces insulin resistance systemically in skeletal and cardiac muscles and liver of rats. *Biochem Biophys Res Commun*. (2013) 431:81–5. doi: 10.1016/j.bbrc.2012.12.084
17. Kim J, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res*. (2008) 102:401–14. doi: 10.1161/CIRCRESAHA.107.165472.Role
18. Martyn JAJ, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states. *Anesthesiology*. (2006) 104:158–69. doi: 10.1097/00000542-200601000-00022
19. Levine M, Brown DFM. Succinylcholine-induced hyperkalemia in a patient with multiple sclerosis. *J Emerg Med*. (2012) 43:279–82. doi: 10.1016/j.jemermed.2011.06.062
20. Stone W, Beach T, Hamelberg W. Succinylcholine-induced hyperkalemia in dogs with transected sciatic nerves or spinal cords. *Anesthesiology*. (1970)32:515–20.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership