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Case Report

Suspected venous air embolism in three horses

A. Pellegrini-Masini*, I. Rodriguez Hurtado†, A. J. Stewart‡ and T. J. Divers§

Department of Large Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens, Georgia, USA; †Department of Large Animal Medicine, College of Veterinary Medicine, University Alfonso X El Sabio, Madrid, Spain; ‡Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, Auburn, Alabama, USA; and §Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA.

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Summary

Venous air embolism was suspected in 3 hospitalised horses on the basis of an inadvertently open jugular venous line. Subsequently the 3 horses developed clinical signs including cardiovascular collapse, cardiac dysrhythmia, pulmonary oedema, behavioural abnormalities and neurological signs consistent with central nervous system injury. Treatment included intranasal oxygen therapy, i.v. fluid administration and anti-inflammatory therapy. Specific therapy aimed at treating air embolism in man is reviewed, with pertinent therapy potentially applicable to horses emphasised.

Introduction

The occurrence of vascular air embolism, defined as entry of gas into vascular structures, is well documented in the human medical literature after decompression injury in scuba diving, thoracic trauma or wounds exposing noncollapsed blood vessels to atmospheric air in the presence of a negative pressure gradient (Muth and Shank 2000). In addition, iatrogenic air embolism has been reported after intravascular catheter disconnection, haemodialysis, surgery (neurosurgery, cardiac, obstetric, arthroscopic or laparoscopic sugery), medical procedures associated with air insufflation (such as urogenital tract endoscopy), epidural injections and pulmonary barotrauma (secondary to hyperbaric medicine or positive-pressure ventilation) (Jaffe *et al.* 1995; Muth and Shank 2000).

While entry of a small volume of air is likely to be asymptomatic, rapid entry of a large volume of air may lead to neurological deficits, blindness, cardiovascular collapse and death (Jaffe *et al.* 1995; Muth and Shank 2000). Because of their negative pressure compared to atmosphere, veins are the most common site of air entrance (Jaffe *et al.* 1995; Muth and Shank 2000). The total volume of air and the rate of entrance are determinants for manifestation and severity of clinical signs; in dogs an acute air bolus of 7.5–15 ml/kg bwt can produce death (Munson and Merrick 1966; Alvaran *et al.* 1978). The air entrance rate is affected by the presence of a pressure gradient between the entry vessel and the right atrium: in human medicine, surgery in a sitting position (and particularly posterior fossa craniotomy, which exposes noncollapsible venous sinuses) has a high inherent risk of venous air embolism (VAE) (Gale and Leslie 2004; Domaingue 2005; Wong and Irwin 2005). The use of a large bore catheter in horses, and the length of their necks, which creates a pressure gradient from the jugular vein to the right atrium when the head is elevated, contribute to expose horses to the risk of air aspiration. Considering that a pressure decrease of 5 cmH_2O across a 14 gauge needle can generate suction of approximately 100 ml/s of air (Flanagan *et al.* 1969), large volume VAE can develop in a relatively short time in a horse.

Air embolism in horses is infrequently reported (Bradbury *et al.* 2005; Hollbrook *et al.* 2007; Sams and Hofmeister 2008). This case series describes 3 horses in which inadvertent disconnection of an i.v. line was accompanied by clinical signs consistent with air embolism.

Case details

Case 1

History

A 20-year-old Thoroughbred gelding was evaluated for a fractured mandible of a few hours' duration. Initial physical examination revealed tachycardia (60 beats/min) and

*Author to whom correspondence should be addressed.

tachypnoea (28 breaths/min), attributed to excitement. A grade 2/6 holodiastolic decrescendo musical heart murmur was heard over the aortic valve area. Fracture of the mandibular symphysis and of left incisors 2 and 3 was diagnosed. A 14 gauge i.v. catheter was placed in the left jugular vein; the horse was administered detomidine (0.01 mg/kg bwt i.v.), butorphanol (0.1 mg/kg bwt i.v.), ampicillin (15 mg/kg bwt i.v.), phenylbutazone (4.4 mg/kg bwt i.v.) and tetanous toxoid. The fracture was repaired standing, using a Jacob's wire applied in a figure-8 fashion.

Clinical findings and treatment

Two hours later the horse was lying down, frequently snorting and had diffuse muscle fasciculation. The extension tubing was found disconnected from the catheter hub and it was replaced. The horse had dark pink mucous membranes, was tachypnoeic and tachycardic (80 beats/min). A mill-wheel murmur (a continuous, loud, churning, drum-like cardiac murmur caused by a right atrial and right ventricular outflow obstruction, also known as a cog wheel or water wheel murmur [Andrews 2002]) was heard on cardiac auscultation. Venous blood gas analysis did not reveal any abnormalities. Intranasal oxygen was provided at 8 l/min. The horse remained in sternal recumbency for about 20 min, then stood up and showed interest in hay. Heart rate decreased to the normal range. One hour later, he had an episode of *grand mal* seizure consisting of diffuse muscle fasciculations, profound ataxia, recumbency, thrashing, horizontal and vertical nystagmus. Diazepam (0.05 mg/kg bwt i.v.), phenobarbital (6 mg/kg bwt i.v.) and prednisolone sodium succinate (2 mg/kg bwt i.v.) were administered i.v., followed by mannitol (1 g/kg bwt i.v.) and heparin (60 iu/kg bwt i.v.). Lactated Ringer's solution with 20 mEq/l of potassium chloride was initiated at 5 ml/kg bwt/h. After recovery from the seizure episode, the horse displayed residual neurological signs consisting of a dull mentation (attributed to post ictal depression), *grade 2/4* ataxia, muscle fasciculations over the left side of the body and bilateral blindness, characterised by lack of menace response with the presence of direct and consensual pupillary light response.

The following day the mill-wheel murmur had resolved and echocardiography showed mild aortic and mitral insufficiency, deemed clinically insignificant. Treatment was continued with dimethyl sulphoxide (1 g/kg bwt q. 24 h as a 10% solution in lactated Ringer's), magnesium sulphate (6 mg/kg bwt q. 24 h in i.v. fluids), mannitol (1 g/kg bwt i.v. q. 24 h), thiamine (10 mg/kg bwt q. 24 h in i.v. fluids), flunixin meglumine (1.1 mg/kg bwt i.v. q. 12 h), aspirin (5 mg/kg bwt *per os* q. 48 h), vitamin E (20 iu/kg bwt *per os* q. 24 h), ampicillin (15 mg/kg i.v. q. 8 h) and omeprazole (4 mg/kg bwt *per os* q. 24 h). The horse experienced another mild seizure episode approximately 20 h after the first, which abated after i.v. administration of 3 g of phenobarbital. An oral phenobarbital course (5 mg/kg bwt *per os* q. 12 h) was initiated. Cerebral-spinal fluid collected from the lumbal-sacral space showed normal cytology with increased protein (1.37 g/l, reference range 0.40–0.90 g/l).

Outcome

The ataxia and muscle fasciculations resolved by Day 3. The left eye recovered peripheral vision by Day 3 and full vision in one week. All the medications apart from phenobarbital were discontinued and the horse was discharged 9 days after admission, with recommendations to taper the phenobarbital course under veterinary supervision. Reportedly, the horse did not experience any other neurological episodes, but did not regain vision in his right eye.

Case 2

History

A 25-year-old Morgan gelding was evaluated because of a history of grain overload. On initial evaluation no significant abnormalities were noticed on physical and rectal examination. Gastric reflux was not obtained upon the passage of a nasogastric tube. Complete blood count, fibrinogen and plasma biochemistry were within the normal reference ranges. Intravenous fluids administration was initiated at 5 ml/kg bwt/h after placement of an i.v. jugular catheter. Endotoxaemia preventative treatment included flunixin meglumine (1.1 mg/kg bwt i.v. q. 12 h) and pentoxifylline (8.4 mg/kg bwt *per os* q. 8 h). Acepromazine (0.025 mg/kg bwt i.v. q. 8 h) was also administered in an attempt to increase digital and laminar blood flow (Ingle-Fehr and Baxter 1999). One gallon of mineral oil was administered via nasogastric tube and foam pads were applied to the soles of the front feet. The horse did not develop any abnormal clinical signs and the fluid administration was discontinued on the following day.

Clinical findings and treatment

On Day 3 the catheter was noticed to be disconnected from the extension tubing, and was replaced. Within one hour, the horse displayed generalised muscle fasciculations, sweating, headshaking and grimacing. The signs rapidly progressed to profound weakness and collapse. Vital signs at that time revealed normothermia, mild tachypnoea (30 breaths/min), tachycardia (120 beats/min) with an irregularly irregular rhythm and a 3/5 holosystolic band-shaped heart murmur ausculted over the mitral valve area. Mucous membranes were pale pink with a capillary refill time of 2 s; pulse quality was poor. Electrocardiography confirmed atrial fibrillation. Within 30 min the gelding stood; muscle tremors and weakness persisted, but he was alert. Dimethyl sulphoxide (1 g/kg bwt) was administered in a 10% dilution in i.v. fluids, followed by fluids at a rate of

5 ml/kg bwt/h. Three hours later the heart rate was 70 beats/min and mild, bilateral jugular vein distension was observed. Moderate clear bilateral nasal discharge and fine crackles were audible throughout the lung fields, suggestive of pulmonary oedema. Fluid rate was decreased to 2 ml/kg bwt/h and frusemide was administered (2 mg/kg bwt i.v.) for treatment of pulmonary oedema.

Outcome

The horse gradually improved: heart rhythm and sound were normal by 24 h, and the rate decreased to the normal range by 48 h. Physical examination at that time did not reveal any significant abnormalities. All treatments were discontinued and the horse was discharged after 6 days of hospitalisation. The horse was reportedly healthy on follow-up one year later.

Case 3

History

A 2-year-old Friesian gelding was evaluated for a ventral midline abdominal hernia. The horse developed a scrotal hernia secondary to castration 9 months prior to admission. The scrotal hernia was surgically corrected by ventral midline celiotomy; however, the horse developed an incisional infection with growth of methicillin-resistant *Staphylococcus aureus,* which resulted in a ventral midline hernia. Beside the ventral midline hernia, no other significant abnormalities were detected on physical examination. Complete blood count and plasma chemistry were within the normal reference range. The horse underwent celiotomy for hernia repair and was treated perioperatively with vancomycin (5 mg/kg bwt i.v. q. 12 h, based on the susceptibility profile of the *Staphyloccus* previously isolated), procaine penicillin G (22,000 i.u./kg bwt i.m. q. 12 h) and phenylbutazone (4.4 mg/kg bwt i.v. q. 24 h) for 5 days.

Clinical findings and treatment

Three days post operatively the horse displayed acute onset of hindlimb weakness, rapidly progressing to collapse and recumbency. Upon examination, the catheter was found uncapped. The heart rate was 96 beats/min and respiratory rate 60 breaths/min. The horse was administered 1 mg/kg bwt of prednisolone sodium succinate i.v. He stood within 30 min, but was anxious and pruritic and was observed to circle, bite and kick at his flank and rub his back aggressively against the walls of the stall. A rectal examination performed under sedation with xylazine (0.4 mg/kg bwt i.v.) did not reveal any significant abnormalities. The behavioural abnormalities continued for approximately 5 h, during which time the horse was administered 3 mg/kg bwt *per os* reserpine and 0.02 mg/kg bwt i.v. detomidine. Clinical signs resolved by the following day.

Outcome

The horse was hospitalised for 16 additional days, due to an incisional infection at the surgical site. Five months later on recheck examination the ventral midline incision had healed and no episodes of behavioural abnormalities were reported.

Discussion

Clinical signs of air embolism are diverse. Deep-sea scuba divers experiencing mild gas embolism describe nonspecific clinical signs of myalgia, pruritus, headache and fatigue (Eckenhoff *et al.* 1986), which may be consistent with the clinical signs displayed by *Case 3* in this report and in a previously suspected equine case (Bradbury *et al.* 2005). A large bolus of air can rapidly induce outflow obstruction (air-lock) of the right ventricle with failure to decompress the tension of the ventricular wall, right-sided heart failure, hypotension and cardiovascular collapse (Mirski *et al.* 2007). Smaller volumes produce less marked cardiovascular changes. The tachycardia, tachypnoea, anxiety and recumbency displayed by the 3 horses could be explained by decreased cardiac output and hypotension, secondary to air-lock in the right ventricle. A prolonged time of entrainment accounts for the ability to withstand larger volumes because the pulmonary circulation acts as a reservoir for the dissipation of the intravascular air (Mirski *et al.* 2007). Within the pulmonary vasculature, air emboli stimulate release of endothelin-1 inducing vasoconstriction, pulmonary hypertension and ventilation/perfusion mismatch (Mirski *et al.* 2007). Pulmonary hypertension, transient increase in endothelial permeability and decreased pulmonary lymph drainage secondary to increased systemic venous pressure may induce pulmonary oedema (Okhuda *et al.* 1981; Stewart *et al.* 2006), experienced by *Case 2* in this series and previously described in another horse with presumed air embolism (Hollbrook *et al.* 2007).

Microbubbles in the pulmonary circulation diffuse through the alveolar-capillary membrane and are expelled with exhaled gas (Domaingue 2005). However, if the air volume exceeds the filter capacity of the pulmonary capillary bed, or in the presence of a right-to-left shunt, air can reach the systemic arterial circulation (paradoxical air embolism) (Muth and Shank 2000; Domaingue 2005; Mirski *et al.* 2007). Through the aorta, air can be distributed to virtually all organs: while small emboli in the skeletal muscles or viscera may be uneventful, entry of air into the coronary or cerebral circulation is life threatening (Muth and Shank 2000). The onset of dysrhythmias as a result of coronary arteries gas embolism is well described in human medicine (Muth and Shank 2000); the atrial fibrillation experienced by *Case 2* could

have been secondary to coronary air embolism, or a consequence of pulmonary oedema and hypoxia.

Case 1 in this series, as well as 2 previously reported cases of presumed air embolism in horses (Hollbrook *et al.* 2007; Sams and Hofmeister 2008) displayed clinical signs consistent with central nervous system involvement. Central nervous system involvement in VAE could be secondary to reduced cardiac output and cerebral hypoperfusion, or to cerebral air embolism (CAE) secondary to paradoxical air embolism (Mirski *et al.* 2007). In man, the most common occurrence of right-to-left shunts is a patent foramen ovale; however, the foramen ovale in horses closes between weeks 2 and 15 *post partum*, and patency at mature age is uncommon (Fregin 1982). Echocardiography did not reveal a patent foramen ovale in *Case 1*. Since air entrainment rate is a determinant factor for arterial spillage of air bubbles (demonstrated in dogs with rates exceeding 0.3 ml/kg bwt/min) (Butler and Hills 1985) it is likely that paradoxical air embolism in horses may develop because the lung filter capacity is overwhelmed due to rapid air entrainment in this species, favoured by the use of large bore catheters and the atmospheric-venous pressure gradient.

Air bubbles irritate the endothelium of cerebral vessels, stimulate polymorphonucleated cell adhesion and activation, initiate the coagulation cascade and disrupt the blood-brain barrier (van Hulst *et al.* 2003; Mirski *et al.* 2007). Even if microbubbles are rapidly reabsorbed, temporary interruption of blood supply caused by larger bubbles may be sufficient to initiate ischaemic injury and cytotoxic cerebral oedema (Muth and Shanks 2000; van Hulst *et al.* 2003). The increased cerebrospinal fluid protein observed in *Case 1* is consistent with findings in man (Gardner *et al.* 2008). Interestingly, the manifestation of neurological signs in *Case 1* occurred at 1 and 20 h after the VAE episode. Similarly, 2 additional literature cases of suspected VAE in horses reported delayed onset of neurological signs (Hollbrook *et al.* 2007; Sams and Hofmeister 2008). Delayed VAE has been previously described in human medicine, and attributed to late release of bubbles through the pulmonary vasculature related to changes in vascular tone (Kimura *et al.* 1994; Harvey *et al.* 1996; Capuzzo *et al.* 2000).

Venous air embolism is suspected in the 3 horses reported in this series because of concomitant inadvertently open i.v. lines; however, the diagnosis was not confirmed. The possibility of head trauma was considered for *Case 1* because of the mandibular fracture; however, the concurrent occurrence of a mill-wheel murmur when the extension tubing was found disconnected is suggestive of air embolism. The ataxia and behavioural abnormalities displayed by *Case 3* could be a delayed onset of intraoperative cerebral hypoxia secondary to general anaesthesia, although previously reported cases developed cerebrocortical necrosis and did not survive (McKay *et al.* 2002).

Air embolism can be confirmed by echocardiographic or Doppler technologies; techniques such as computed tomography and magnetic resonance imaging (MRI) can show evidence of CAE, but not definitively rule it out (Caulfield *et al.* 2006; Maddukuri *et al.* 2006). The neurological signs (seizure and bilateral blindness) displayed by *Case 1* are suggestive of a diffuse lesion of the prosencephalon, involving bilaterally the occipital cortex. This localisation is consistent with MRI findings of cerebral air emboli in man, characterised by multiple areas of restricted diffusion along the cortical grey matter (ischaemia) in a gyriform pattern, involving both cerebral hemispheres (Caulfield *et al.* 2006). Additional techniques, such as monitoring end-tidal carbon dioxide and nitrogen gases, oxygen saturation and electrocardiography may be helpful in detection of pulmonary air emboli, particularly in anaesthetised horses undergoing at-risk procedures; however these tests are neither specific nor sensitive for VAE (Mirski *et al.* 2007; Sams and Hofmeister 2008).

Treatment of VAE is aimed at the prevention of further air entrainment; in the process of removing (or replacing) a damaged or disconnected i.v. line, vein compression has been shown in human medicine to be effective in limiting ongoing air aspiration (Mirski *et al.* 2007). In the event of VAE occurring during general anaesthesia using inhaled nitrous oxide, the administration of this gas should be immediately discontinued, since the high solubility of nitrous oxide in blood (34 times higher than nitrogen) increases the size of the entrained bubbles (Mirski *et al.* 2007).

Placement of a catheter into the right atrium for air aspiration prior to high-risk surgical procedures has been advocated in human medicine; however, its effectiveness is questionable and related to catheter type, patient positioning and monitoring techniques to allow early detection (Mirski *et al.* 2007). Emergency catheter insertion for air aspiration during an acute VAE episode is not recommended (Mirski *et al.* 2007).

Intravenous fluid therapy (received by *Cases 1* and 2) is indicated based on the evidence of haemoconcentration (secondary to fluid extravasation in the injured tissues) and hypotension during VAE (Muth and Shanks 2000; van Hulst *et al.* 2003). The use of colloids has been advocated over crystalloids to reduce the occurrence of cerebral oedema, while glucose-containing fluids are not recommended since hyperglycaemia may worsen the neurological outcome (van Hulst *et al.* 2003). Additional haemodynamic support was provided with dobutamine infusion in human patients and norepinephrine in a canine model (Mirski *et al.* 2007). A short period of systemic hypertension during cerebral air embolism has been favourably considered since it may promote bubble redistribution through the arterioles to the capillaries and into the veins; prolonged hypertension, however, may lead to increased intracranial pressure and cerebral oedema (van Hulst *et al.* 2003).

Intranasal oxygen administration was provided to *Case 1* since, besides improving patient oxygenation, this can favour clearance of air bubbles by creating a

diffusion gradient that promotes the egression of nitrogen gas from the bubbles (Muth and Shanks 2000). Concentrations of oxygen as high as possible should be provided via a tight-fitting mask, endotracheal tube or bilateral nasal insufflation to suspected cases of gas embolism. Hyperbaric oxygen therapy is considered the first-line treatment of VAE (Muth and Shanks 2000). The hyperoxia achieved in a hyperbaric chamber, besides providing increased oxygen availability for tissue perfusion, creates a tremendous diffusion gradient for nitrogen reabsorption, while the size of the bubbles decreases in a proportion inversely related to the ambient atmospheric pressure (Muth and Shanks 2000; van Hulst *et al.* 2003; Mirski *et al.* 2007). Retrospective studies concerning the outcome of CAE after hyperbaric oxygen therapy have revealed a lower rate of success with delayed treatment (Blanc *et al.* 2002). Based on the same principle, i.v. administration of perfluorocarbon emulsions (artificial oxygen-carrying carbon-fluorine compounds characterised by high gas dissolving capacity, low viscosity and biological inertness) have proven successful in reducing air bubble size, brain infarct size and overall mortality in animal models of experimentally-induced air embolism (Yoshitani *et al.* 2006).

The neurological signs displayed by *Case 1* were treated by the administration of diazepam and, subsequently, phenobarbital. In addition to controlling seizure activity, barbiturates may have a brain protective effect after ischaemia by reducing cerebral oxygen consumption, intracranial pressure, free-radical production and endogenous catecholamine release (van Hulst *et al.* 2003).

Cases 1 and *3* received corticosteroids in the course of therapy; however, the use of steroidal anti-inflammatory drugs in CAE is contraindicated, since these drugs may aggravate ischaemic injury, are not effective to treat cytotoxic brain oedema and have the potential to induce hyperglycaemia (Muth and Shanks 2000; van Hulst *et al.* 2003). Heparin was administered to *Case 1*: since microbubbles in the circulation precipitate platelet aggregation, the use of heparin has been advocated in the treatment of air embolism; however due to the lack of scientific evidence of efficacy, its use is currently controversial (Muth and Shanks 2000; van Hulst *et al.* 2003; Mirski *et al.* 2007). Conversely, there is increasing evidence for a neuroprotective effect of lidocaine in brain-injured animal models, as well as human patients undergoing cardiac surgery, and the use of constant-rate infusion of lidocaine has been suggested in man for the treatment of CAE (Muth and Shanks 2000; van Hulst *et al.* 2003).

Mannitol was administered to *Case 1* for management of cytotoxic cerebral oedema (Rabinstein 2006) and its use has been anecdotally reported in human medicine to treat *type II* decompression injury in scuba divers and air embolism (Kizer 1980).

Additional therapy administered to *Case 1* included dimethyl sulphoxide, magnesium sulphate, thiamin, aspirin (as anticoagulant) and vitamin E for its antioxidant effects in brain mitochondria (Navarro and Boveris 2008). The use of dimethyl sulphoxide has been advocated for the treatment of cerebral oedema (Tsuruda *et al.* 1983) and for the hydroxyl radical scavenging properties of this compound (Santos *et al.* 2003). Administration of magnesium sulphate was aimed at elevation of seizure threshold (Hallak 1998) and neuroprotective properties of the drug in experimental models of cerebral ischaemia (Muir 1998). However, magnesium sulphate neuroprotective efficacy has not been supported by recent studies (McKee *et al.* 2005). Thiamin can act as a free radical scavenger and, playing a key role in cerebral glucose metabolism, protein processing, peroxisomal function and gene expression, may exert a neuroprotective effect in the diseased brain (Gibson and Blass 2007). Currently, the use of mannitol, dimethyl sulphoxide, magnesium sulphate, thiamin, aspirin and vitamin E is not considered standard of care in the treatment of CAE in man.

Conclusions

While small-volume VAE is a common and uncomplicated event during i.v. catheter placement in horses, intravascular entrainment of large volumes of air may occur with damage or inadvertent disconnection of the i.v. line and may lead to behavioural abnormalities, cardiovascular collapse, pulmonary oedema, cardiac arrhythmias and cerebral air embolism, even in the absence of an anatomic right-to-left shunt. VAE should be suspected when finding a catheter disconnected and clinical signs of acute distress in the horse. The presence of a mill-wheel murmur on cardiac auscultation is suggestive of VAE; however prompt echocardiography is necessary to confirm the diagnosis.

As clinical signs may continue to progress after identification of a disconnected venous line, aggressive pre-emptive therapy may be warranted. Crystalloids and/or colloids, high-rate oxygen administration via intranasal flow or endotracheal tube (during general anaesthesia), lidocaine, barbiturates (in the presence of signs of cerebral air embolism) and early hyperbaric oxygen therapy may be beneficial in the treatment of acute venous air embolism in horses.

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