Sudden cardiac death associated with occult hypertrophic cardiomyopathy in a dog under anesthesia

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Abstract — A 6-year-old, 3.0 kg, neutered female, Yorkshire terrier was referred for orthopedic surgery. Cardiac arrest followed unsuccessful treatment of bradycardia and systemic arterial hypotension under general anesthesia. Postmortem examination revealed hypertrophic cardiomyopathy. A possible relationship between treatment of bradycardia, systemic arterial hypotension, and sudden cardiac death is described.

Résumé — Arrêt cardiaque soudain associé à une cardiomyopathie hypertrophique non diagnostiquée chez un chien sous anesthésie. Une femelle Terrier du Yorkshire, castrée, âgée de 6 ans et pesant 3 kg, est référée pour une chirurgie orthopédique. Un arrêt cardiaque sous anesthésie générale fait suite à une bradycardie et une hypotension artérielle systémique sévère ne répondant pas au traitement anticholinergique classique. La nécropsie révèle une cardiomyopathie hypertrophique non diagnostiquée cliniquement. Une relation possible entre le traitement de la bradycardie et l'apparition de l'hypotension artérielle systémique entraînant un arrêt cardiaque soudain est suspectée dans ce cas précis.

(Traduit par les auteurs)

Mortality rates in the perioperative period in small animals has been reported as ranging from 0.1% to 0.43% (1,2). Such a wide range in frequency may be attributable to a host of factors, including choice of anesthetic agent, experience of anesthetist/surgeon, presenting disease, concurrent disease, age, and sex (3). The role of concurrent disease in anesthetic mortality in humans has been reported as being a strong contributory factor, accounting for 44.3% of mortality (3). Therefore, adequate preoperative diagnosis and patient preparation could be expected to decrease this contribution significantly.

Hypertrophic cardiomyopathy (HCM) in dogs is infrequently encountered and may present without clinical signs or abnormal findings on examination (4–6). As such, it is one disease that, in association with the cardiovascular effects of general anesthesia, may contribute to perioperative morbidity and mortality.

Case description

A 6-year-old, 3.0 kg, neutered female, Yorkshire terrier was referred to the Université de Montréal's Teaching Hospital for examination of a lameness suspected of being caused by medially luxated patellas. The animal had a 4-year history of difficulty in climbing stairs and of regularly "bunny hopping" with the hind legs. Intermittent treatment with carprofen (Rimadyl; Pfizer, Kirkland, Quebec), 2.2 mg/kg bodyweight (BW), PO, was carried out as required. There was no history of exercise intolerance.

No abnormalities were detected during a general physical examination; no murmur or arrhythmia was detected on cardiac auscultation. A lameness examination revealed bilateral, Grade III, medially luxated patellas. Clinically, the lameness was worse on the left hind limb. A decision was reached, with the owner's permission, for surgical correction of the patellar luxation on the left limb.

Results of a complete blood (cell) count (CBC) and serum biochemical analysis were unremarkable, and surgery was planned to take place in 4 d. Food was withheld for the 12 h preceding anesthesia. Water was available until the time of premedication.

Prior to premedication, the animal was classified according to the American Society of Anesthesiologists' (ASA) physical classification status as a category II (7,8) and its nervous temperament was taken into account in planning the anesthetic protocol. The premedication consisted of hydromorphone (Hydromorphone HP 10 Injection USP; Sabex, Boucherville, Quebec), 0.1 mg/kg BW, and acepromazine (Acépromazine, 1 mg/mL; D Giroux — Pharmacien, St-Hyacinthe, Quebec) 0.03 mg/kg, combined in the same syringe and injected, IM, 15 min before IV catheter placement. The degree of sedation was classified as "light" (from a range of

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"light, moderate, profound", or "no" sedation). The animal was restrained without difficulty for the IV catheter placement in the left cephalic vein.

Prior to induction, pulse rate and rhythm were assessed; no abnormalities were detected. Induction was achieved with thiopental (Pentothal; Abbott Laboratories, Oakville, Ontario), 5.2 mg/kg BW, IV, and a 5.5 mm internal diameter (ID) cuffed endotracheal tube was placed without difficulty. The animal was connected to a Bain circuit and the flow rate of oxygen set at 200 mL/kg BW/min. Endotracheal tube placement was confirmed with bilateral chest auscultation, and the airway was checked for any leaks around the endotracheal tube cuff. The isoflurane concentration on the vaporizer was 1.5%.

Monitoring consisted of pulse oximetry (Model 3800 Oximeter; Datex-Ohmeda, Louisville, Colorado, USA), with probe placement on the tongue, and indirect sphygmomanometry (Model 811-B Ultrasonic Doppler Flow Detector; Parks Medical Electronics, Aloha, Oregon, USA), with Doppler ultrasound probe placed on the radial artery at the right ventromedial carpus. Fluid therapy (Lactated Ringer's Injection USP; Baxter Corporation, Toronto, Ontario) was instituted at 10 mL/kg BW/h. Initial evaluation revealed a heart rate of 55 beats/min (bpm) and systolic arterial blood pressure of 72 mmHg. The animal was breathing spontaneously and a palpebral reflex was present.

Glycopyrrolate (Glycopyrrolate Injection USP; Sabex), 0.005 mg/kg BW, was injected, IV. This was followed by an increase in heart rate to 150 bpm. However, this was accompanied by a decrease in systolic arterial blood pressure to 45 mmHg, which continued to decrease to a level of 30 mmHg.

At this point, the decision was taken to stop anesthesia (10 min after induction) and fluids were given at the maximum rate possible through the fluid administration set. The animal began to show signs of recovery from general anesthesia (augmentation of palpebral reflex, weak movements of head and neck) and was placed in sternal recumbency with the endotracheal tube still in place.

Immediately following positioning in sternal recumbency, a peripheral pulse could not be palpated, and the Doppler ultrasound probe ceased to register pulsatile blood flow. The animal was placed in right lateral recumbency and cardiopulmonary resuscitation was initiated. External cardiac massage at a frequency of approximately 100 bpm (with abdominal counter compression) and intermittent positive pressure ventilation (10 breaths/min) were performed. Emergency drug therapy was initiated with naloxone (Naloxone Hydrochloride Injection USP; Sabex), 40 µg/kg BW, epinephrine (Epinephrine Injection USP; Abbott Laboratories), 0.2 mg/kg BW, and atropine (Atropine sulfate; MTC Pharmaceuticals, Cambridge, Ontario), 0.08 mg/kg BW, delivered directly into the trachea via a urinary catheter (8 Fr), followed by a flush with 2 mL of 0.9% sodium chloride solution and air. During this time, the electrocardiograph (ECG) machine was connected and asystole was apparent. Intratracheal (IT) drug administration (epinephrine and atropine) was repeated at the same dose.

There was no response to drug therapy, though external cardiac massage was effective with palpation of a peripheral pulse (femoral artery).

Ten minutes following stoppage of anesthesia, a left lateral thoracotomy was performed (5th intercostal space) and internal cardiac massage commenced. Visible examination of the heart confirmed asystole. Over the following 10 min, 3 doses of epinephrine (0.1 mg/kg BW) and atropine (0.04 mg/kg BW) were applied topically to the myocardium and 2 intracardiac injections of vasopressin (Pressyn; Ferring, Toronto, Ontario), 13 IU/kg BW, were delivered. The heart remained in asystole. Internal cardiac defibrillation was attempted with 1 countershock of 3 J and 2 of 5 J. There was no response and cardiopulmonary resuscitation (CPR) attempts were halted 25 min after anesthesia was stopped.

The animal was submitted for necropsy. Gross examination revealed slight rounding of the cardiac apex. On cross-section of the heart at the mid-level of the papillary muscles, both ventricular chambers appeared slightly narrower than normal. The left ventricular free wall and interventricular septum were of similar thickness. Total heart weight was 36.8 g; 19.8 g for the left ventricle and interventricular septum, and 7.8 g for the right ventricle. Other gross changes were compatible with cardiac failure and CPR attempts (pulmonary congestion and atelectasis, and hepatic congestion with capsular lacerations).

Microscopic examination of the heart revealed changes suggestive of myofiber hypertrophy with multifocal myofiber disarray, mainly within the left and septal ventricular myocardium. In addition, small fibrous epicardial projections were present adjacent to the sino-atrial node. There was diffuse, mild pulmonary congestion and moderate atelectasis. The liver showed moderate to marked congestion. Results from examination of other organs (spleen, kidneys, eye, thyroid, and adrenal glands) were unremarkable.

The relative cardiac weights were calculated and indicated bilateral ventricular hypertrophy, based on published data on cardiac ventricular mass in dogs (9). Considering this data, the gross and microscopic observations, and the absence of an apparent cardiac or extra-cardiac cause for the biventricular hypertrophy, a diagnosis of HCM was reached.

Discussion

Hypertrophic cardiomyopathy has been defined as "inappropriate myocardial hypertrophy of a nondilated left ventricle, occurring in the absence of an identifiable stimulus for the hypertrophy" (4). The presentation of this case without clinical or pathological signs of a predisposing cause (subaortic stenosis, systemic hypertension, hypermetabolic state) points strongly towards HCM.

Hypertrophic cardiomyopathy is commonly found in humans and cats (10), but it has been reported infrequently in dogs (4–6). A heritable basis is suspected and typical signalement involves young (< 3-year-old) male dogs, with the Rottweiler and Dalmatian breeds being overrepresented. However, the cases of HCM examined in 1 study, which looked at necropsy cases over a period of 2 y, showed a wide range of ages and breeds affected (5). The majority of dogs do not exhibit clinical signs of cardiac disease or have a history of exercise intolerance. When clinical signs are present, the most common is a systolic heart murmur or arrhythmia.

The gross pathologic presentation of HCM in most dogs is a left ventricular and interventricular septal hypertrophy of equal magnitude. There may be an impact lesion on the interventricular septum, displaying a range of appearances from a small opaque lesion to a thickened plaque, depending on the duration of the disease process. The mitral valve itself is often abnormal, betraying its tendency to migrate into the left ventricular outflow tract (LVOT). Usually, LVOT obstruction occurs in midsystole and involves the systolic cranial motion of the mitral valve. Left atrial enlargement may be present, depending on the extent of the disease.

Histologically, the majority of dogs have normally orientated myocardial fibers (though septal disorganization has been reported) and abnormal intramural coronary arteries (intimal hyperplasia, hypertrophy, and smooth muscle hyaline degeneration) (5,10). These vascular lesions are frequently associated with focal myocardial necrosis, fibrosis, and dystrophic calcification.

Compared with the majority of cases described in dogs, the presentation of this case varied in both the gross and microscopic pathological signs displayed. The presence of cardiac myocyte disarray and side branching has more in common with the morphology present in humans (10,11), where cardiac myocyte disarray is a characteristic feature. The significance of the presence of fibrous epicardial projections at the level of the sinoatrial node is unknown and, to our knowledge, has not been reported in combination with HCM in the veterinary literature. By comparison with the majority of cases described in dogs, this case did not show any histological signs of vascular lesions. In common with reported cases (5), this case had no clinical signs of heart disease or history of exercise intolerance.

To our knowledge, HCM in a Yorkshire terrier has been reported in the literature only once before (6). That case involved an older animal (14 y old) that was demonstrating clinical signs of heart disease with audible systolic murmurs and, interestingly, the histological appearance of cardiac myocytes in disarray.

The functional effects of HCM are dynamic LVOT obstruction and reduced diastolic filling. As a result, there is a limited ability to increase cardiac output in response to sympathetic stimulation. Dynamic LVOT obstruction is typified by a pressure gradient across the area of obstruction (high pressure below and low pressure beyond). Therefore, decreases in systemic vascular resistance (SVR), preload, or both, and increases in cardiac contractility worsen the consequences of the obstruction. Secondary to LVOT obstruction, systolic wall tension is increased, increasing myocardial oxygen consumption and decreasing coronary blood flow. Diastolic filling is further reduced by increases in heart rate and decreases in preload. This situation has been classified as a low, fixed cardiac output (12).

Mortality rates during the perianesthetic period for dogs have been reported at a level of 0.43% in a university teaching hospital (13), and within this study, the occurrence of cardiac arrest followed by CPR was 0.5%. The total number of cases examined was 2556 dogs. Furthermore, hypotension was described as the most common complication (7%); the percentage associated with bradycardia was not recorded. The level of success of CPR following cardiac arrest was recorded as 47% (including CPR performed on cats, though cats contributed only 3 of the 15 cases of CPR) (13). The CPR technique was not described, though this has changed little over recent years, maintaining the steps of securing an airway, supporting ventilation and circulation, and drug therapy.

In this case, the discovery of low systolic arterial blood pressure and bradycardia (heart rate < 70 to 90 bpm in dogs [13,14]) was treated with a view to improving cardiac output and arterial blood pressure. Therapy was founded on the following general formulas:

$$CO = HR \times SV$$

$ABP = CO \times SVR$, where CO is cardiac output, HR is heart rate, SV is stroke volume, ABP is arterial systemic blood pressure, and SVR is systemic vascular resistance.

The anticholinergic drug glycopyrrolate was chosen in view of its positive chronotropic effects (15). Theoretically, this should reverse the bradycardia, improving CO and ABP. In addition to drug therapy, a fluid bolus was given to increase the circulating fluid volume and offset the vasodilatory effects of the acepromazine and isoflurane (16,17). The inspired concentration of isoflurane (1.5%) was not reduced at this stage, as the animal was judged to be in a light plane of anesthesia (presence of marked bilateral palpebral reflexes with centered, dilated pupils and irregular, shallow breathing) (18,19).

Following administration of the glycopyrrolate, the HR increased from 55 to 150 bpm. However, systemic ABP decreased further from 72 to 45 mmHg. This unexpected response to anticholinergic therapy could have resulted from further systemic vasodilation or a decrease in CO as a result of decreased SV and despite an increase in HR. Both explanations are possible, though a further decrease in SVR is perhaps less likely, as no further drugs with vasodilatory effects had been given and the inspired concentration of isoflurane remained at a low, unchanged level. Furthermore, the situation of a low CO would have favored a rapid rise in the alveolar partial pressure of isoflurane, leading to a rapid equilibration with the vaporizer setting and making progressive cardiovascular effects of isoflurane unlikely.

During CPR, both atropine and epinephrine were given by an IT route. Although IV access was available through a peripheral vein, it is common practice in our hospital to use the IT route unless a central venous catheter is in place. This technique bypasses a peripheral circulation which may be inadequate despite efficacious cardiac massage (20). The potent vasoconstriction resultant from epinephrine administration would further decrease peripheral circulation. The topical application of emergency drugs direct to the myocardium during open-chest CPR is not yet supported by evidence in the literature, and must be considered as an anecdotical route of administration.

A decrease in SV, in combination with a moderate increase in HR (presedation HR of 180 bpm), may be associated with either an insufficient diastolic filling during the cardiac cycle or ventricular outflow obstruction. This may be compounded by inadequate preload, increased afterload, and reduced contractility. Prior to

anesthesia, there were no clinical or laboratory signs of hypovolemia or hypervolemia, and acute hemorrhage did not occur. No arrhythmias were detected at any stage, though this was limited to cardiac auscultation and palpation of peripheral pulses. Cardiac contractility cannot be directly examined without an echocardiographic examination.

In light of the necropsy findings, the sudden death was most likely a result of a catastrophic decrease in CO and myocardial ischemia following the increase in HR (with a further decrease in diastolic filling and duration) accompanying glycopyrrolate administration. The ventricular compliance already compromised due to the presence of ventricular hypertrophy, dynamic LVOT obstruction, or both, precipitated a drop in CO in combination with increased myocardial oxygen consumption in response to anticholinergic therapy. The observed terminal arrhythmia in this case was asystole. Both asystole and electromechanical dissociation (EMD)/pulseless electrical activity have been described as the most common terminal arrhythmias in small animals, and this may reflect the initiating cause of cardiac arrest and the rapidity of ECG placement (21–23). It is possible that a phase of EMD or ventricular fibrillation was not observed during the time between loss of the Doppler ultrasound signal and ECG placement.

Sudden cardiac deaths in humans are a result of myocardial ischemia, arrhythmias, or myocardial disorder (of which HCM is the most common) (11). Hypertrophic cardiomyopathy in dogs is a known cause of sudden cardiac death and may be triggered by the effect of anesthetic agents or surgical stimulation. In one study, the histories of the 10 cases of HCM examined at necropsy revealed that 8 cases involved sudden death (5). Of these, 4 were under anesthesia (2 cases did not exhibit clinical signs of cardiac disease), 2 were found dead by owners (no history of cardiac disease), 1 died during a walk (no history of cardiac disease), and 1 died of unrelated causes (no history of cardiac disease).

This case represents a situation commonly encountered during general anesthesia of hypotension and bradycardia. Conventional therapy may have contributed to a negative outcome. Due to the subclinical presence of HCM, it was impossible to have detected the disease during the routine examination and it is unclear if clinical signs might have become apparent over time. Prior knowledge of the presence of subclinical HCM would have increased the risk of general anesthesia and a "cardiac-safe" protocol could have been used. The aims of such an anesthetic protocol are to minimize increases in myocardial workload and support diastolic function. Such a protocol would typically involve opioid premedication (sedation would still be indicated due to the nervous temperament of the patient), followed by a neuroleptanesthetic combination for IV induction, such as fentanyl and midazolam. If endotracheal intubation is not possible with this technique, a greatly reduced dose of thiopental could be given to effect until intubation is possible. If available, an etomidate-benzodiazepine induction would be appropriate. Anesthesia could be maintained with a fentanyl infusion combined with isoflurane. In addition, the use of epidural anesthesia to minimize cardiovascular responses to surgical stimulation

would be recommended. Fluid therapy is warranted to maintain an optimal intravascular volume, while avoiding fluid overload.
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References

1. Wagner AE, Wright BD, Hellyer PW. Myths and misconceptions in small animal anesthesia. J Am Vet Med Assoc 2003;223:1426–1432.
2. Dyson DH, Maxie MG. Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. J Am Anim Hosp Assoc 1998;34:325–335.
3. Fleisher LA. Risk of anesthesia. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Toronto: Elsevier, Churchill Livingston, 2004:893–926.
4. Sisson D, O'Grady MR, Calvert CA. Myocardial diseases of dogs. In: Fox PR, Sisson D, Moise NS, eds. Textbook of Canine and Feline Cardiology. 2nd ed. Philadelphia: WB Saunders, 1999:601–606.
5. Liu SK, Maron BJ, Tilley LP. Canine hypertrophic cardiomyopathy. J Am Vet Med Assoc 1979;174:708–713.
6. Washizu M, Takemura N, Machida N, et al. Hypertrophic cardiomyopathy in an aged dog. J Vet Med Sci 2003;65:753–756.
7. Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978;49:239–243.
8. Thurmon JC, Tranquilli WJ, Benson GJ. General considerations for anesthesia. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. Essentials of Small Animal Anesthesia and Analgesia. 1st ed. Philadelphia: Lippincott, Williams & Wilkins, 1999:1–27.
9. Bienvenu J-G, Drolet R. A quantitative study of cardiac ventricular mass in dogs. Can J Vet Res 1991;55:305–309.
10. Liu SK, Roberts WC, Maron BJ. Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. Am J Cardiol 1993;72:944–951.
11. Towbin JA. Molecular genetic basis of sudden cardiac death. Cardiovasc Pathol 2001;10:283–295.
12. Clutton RE. Cardiopulmonary disease. In: Seymour C, Gleed R, eds. BSAVA Manual of Small Animal Anesthesia and Analgesia. 2nd ed. Cheltenham: Brit Small Anim Vet Assoc, 1999:155–181.
13. Gaynor JA, Dunlop CI, Wagner AE, Wertz EM, Golden AE, Demme WC. Complications and mortality associated with anesthesia in dogs and cats. J Am Anim Hosp Assoc 1999;35:13–17.
14. Evans AT. Anesthetic Emergencies and Accident. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. Essentials of Small Animal Anesthesia and Analgesia. 1st ed. Philadelphia: Lippincott, Williams & Wilkins, 1999:515–535.
15. Dyson DH, James-Davies R. Dose effect and benefit of glycopyrrolate in the treatment of bradycardia in anesthetized dogs. Can Vet J 1999;40:327–331.
16. Lukasik V. Premedication and sedation. In: Seymour C, Gleed R, eds. BSAVA Manual of Small Animal Anaesthesia and Analgesia. 1st ed. Cheltenham: Brit Small Anim Vet Assoc, 1999:71–86.
17. Ludders JW. Inhalant anaesthetics. In: Seymour C, Gleed R, eds. BSAVA Manual of Small Animal Anaesthesia and Analgesia. 1st ed. Cheltenham: Brit Small Anim Vet Assoc, 1999:99–108.
18. Thurmon JC, Tranquilli WJ, Benson GJ. Considerations for general anesthesia. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. Lumb & Jones' Veterinary Anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1996:5–34.
19. Haskins SC. Perioperative monitoring. In: Paddleford RR, ed. Manual of Small Animal Anesthesia. 2nd ed. Philadelphia: WB Saunders, 1999:124–126.
20. How KL, Fleens N, Stokhof AA, Hellebrekers LJ. Current concepts in resuscitation of dogs and cats. Eur J Comp Anim Pract 2001;11:19–26.
21. Willms C, Kirby R, Rudloff E. Cardiopulmonary resuscitation update: stepping outside the box. Compend Contin Edu Pract Vet 2002;24:922–932.
22. Cole SG, Otto CM, Hughes D. Cardiopulmonary cerebral resuscitation in small animals — a clinical practice review. Part II. J Vet Emerg Crit Care 2003;13:13–23.
23. Waldrop JE, Rozanski EA, Swanke ED, O'Toole TE, Rush JE. Causes of cardiopulmonary arrest, resuscitation management, and functional outcome in dogs and cats surviving cardiopulmonary arrest. J Vet Emerg Crit Care 2004;14:22–29.