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# Cardiovascular and respiratory effects of incremental doses of dopamine and phenylephrine in the management of isoflurane-induced hypotension in cats with hypertrophic cardiomyopathy

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**Objective**—To determine cardiopulmonary effects of incremental doses of dopamine and phenylephrine during isoflurane-induced hypotension in cats with hypertrophic cardiomyopathy (HCM).

**Animals**—6 adult cats with severe naturally occurring HCM.

**Procedures**—Each cat was anesthetized twice (once for dopamine treatment and once for phenylephrine treatment; treatment order was randomized). Hypotension was induced by increasing isoflurane concentration. Cardiopulmonary data, including measurement of plasma concentration of cardiac troponin I (cTnI), were obtained before anesthesia, 20 minutes after onset of hypotension, and 20 minutes after each incremental infusion of dopamine (2.5, 5, and 10 μg/kg/min) or phenylephrine (0.25, 0.5, and 1 μg/kg/min).

**Results**—Mean ± SD end-tidal isoflurane concentration for dopamine and phenylephrine was 2.44 ± 0.05% and 2.48 ± 0.04%, respectively. Cardiac index and tissue oxygen delivery were significantly increased after administration of dopamine, compared with results after administration of phenylephrine. Systemic vascular resistance index was significantly increased after administration of phenylephrine, compared with results after administration of dopamine. Oxygen consumption remained unchanged for both treatments. Systemic and pulmonary arterial blood pressures were increased after administration of both dopamine and phenylephrine. Acid-base status and blood lactate concentration did not change and were not different between treatments. The cTnI concentration increased during anesthesia and infusion of dopamine and phenylephrine but did not differ significantly between treatments.

**Conclusions and Clinical Relevance**—Dopamine and phenylephrine induced dose-dependent increases in systemic and pulmonary blood pressure, but only dopamine resulted in increased cardiac output. Hypotension and infusions of dopamine and phenylephrine caused significant increases in cTnI concentrations. (*Am J Vet Res* 2012;73:908–916)

Hypertrophic cardiomyopathy is the most common form of heart disease that affects cats.[1–5] The disease is characterized by diffuse or segmental hypertrophy of the left ventricular myocardium that involves the interventricular septum, left ventricular free wall, and papillary muscles.[4] Dynamic left ventricular out-

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**Abbreviations**

| | |
|---|---|
| CO | Cardiac output |
| cTnI | Cardiac troponin I |
| CVP | Central venous pressure |
| $Do_2$ | Oxygen delivery |
| $_{ET}$ISO | End-tidal concentration of isoflurane |
| HCM | Hypertrophic cardiomyopathy |
| HR | Heart rate |
| LVSWI | Left ventricular stroke work index |
| $M\dot{V}o_2$ | Myocardial oxygen consumption |
| OER | Oxygen extraction ratio |
| PAOP | Pulmonary artery occlusion pressure |
| PAP | Pulmonary artery pressure |
| RPP | Rate pressure product |
| RVSWI | Right ventricular stroke work index |
| SAM | Systolic anterior motion |
| SVR | Systemic vascular resistance |
| SVRI | Systemic vascular resistance index |
| $\dot{V}o_2$ | Oxygen consumption |
| VPC | Ventricular premature contraction |

flow tract obstruction attributable to SAM of the mitral valve occurs when enlarged papillary muscles pull the mitral valve into the outflow tract, which results in turbulence and, possibly, a decrease in CO.[3,6] The incidence of SAM in cats with HCM is variable, but it is a labile condition that increases and decreases in severity as contractility changes.

The plasma concentration of cTnI is a sensitive and specific biochemical marker for myocardial damage. The plasma concentration of cTnI is increased in cats with HCM[7–9]; however, to our knowledge, plasma concentrations of cTnI have not been measured during the perianesthetic period.

Complications in anesthetized humans with HCM include congestive heart failure, supraventricular and ventricular tachyarrhythmias, and systemic hypotension.[10–15] Hypotension develops in healthy cats and cats with HCM anesthetized with inhalation anesthetic agents because of the negative inotropic and systemic vasodilatory effects.[16,17] Persistent hypotension in healthy anesthetized cats is treated by the administration of positive inotropes, such as dopamine and dobutamine. These drugs are expected to increase blood pressure by increasing CO.[18] Blood pressure can also be increased by administration of $\alpha_1$-adrenergic receptor agonists, such as phenylephrine; however, this technique may be less desirable because CO and tissue perfusion may actually decrease.[18]

In contrast, for cats with HCM, it is hypothesized that administration of positive inotropes may induce or increase dynamic outflow tract obstruction, which would potentially reduce or limit CO. Additionally, by increasing myocardial work and $\dot{V}O_2$, positive inotropes may compromise the balance between $M\dot{V}O_2$ and myocardial $DO_2$ in patients with HCM. Alternatively, the administration of a vasoconstrictor may decrease the pressure gradient across the aortic valve, which would limit dynamic obstruction and potentially improve CO.[6,12] Consistent with this, conscious cats with HCM and SAM that received medetomidine, a drug expected to increase SVR, had complete resolution of dynamic outflow tract obstruction as assessed by echocardiographic examination.[19]

These hypotheses have not been investigated in anesthetized cats with HCM. The purpose of the study reported here was to determine plasma concentrations of cTnI and cardiorespiratory effects attributable to incremental doses of dopamine and phenylephrine in hypotensive, isoflurane-anesthetized cats with severe, naturally occurring HCM. We hypothesized that dopamine would increase CO and the plasma concentration of cTnI more than would phenylephrine and that both dopamine and phenylephrine would effectively increase blood pressure.

## Materials and Methods

**Animals**—Six Maine Coon or Maine Coon–domestic shorthair crossbred cats (4 males and 2 females) that ranged from 8 to 15 years of age and weighed between 3.1 and 5 kg were used in the study. The cats were part of a research colony maintained at the University of California-Davis that consisted of cats with naturally occurring HCM. The study was conducted with the approval of the University of California-Davis Institutional Animal Care and Use Committee.

Health status of the cats was assessed on the basis of results of physical examination, serum biochemical analysis, and a CBC performed prior to initiation of the study. Cats were judged to have severe HCM without evidence of heart failure on the basis of echocardiography performed by a veterinary cardiologist (MDK). Classification of severe HCM was made on the basis of evidence of global or regional severe thickening of the left ventricular wall (≥ 7 mm thick). The left atrium of all cats was judged to be of normal size or moderately enlarged, and none of the cats had SAM. Cats were housed separately or in groups and allowed ad libitum access to food and water, except for the 12 hours prior to anesthesia when food (but not water) was withheld.

**Anesthesia and instrumentation**—Oxymorphone[a] (0.05 mg/kg, SC) was administered to each cat. Thirty minutes later, a 22-gauge, 2.5-cm catheter[b] was placed in the right cephalic vein for administration of drugs and fluids. Anesthesia was induced by the administration of midazolam[c] (0.2 mg/kg, IV) and etomidate[d] (up to 2 mg/kg, IV), which provided sufficient anesthesia to enable researchers to intubate the trachea. Anesthesia was maintained with isoflurane[e] administered in 200 mL of oxygen/kg/min via a coaxial Mapleson F anesthetic circuit. Cats were maintained at a light surgical plane of anesthesia for the duration of instrumentation. Lactated Ringer's solution[f] was administered at a rate of 3 mL/kg/h until drug infusion began, at which time the infusion rate of the lactated Ringer's solution was decreased in accordance with the volume of the drug infusion such that the total volume of fluids administered remained at 3 mL/kg/h. Cats were allowed to breathe spontaneously throughout the study. Core body temperature was maintained between 38° and 39°C with a warm water circulating pad[g] and forced warm air.[h]

A 5F, 7.5-cm catheter introducer[i] was placed in the right jugular vein. Fluoroscopic guidance was used to insert a 4F, 75-cm thermodilution catheter[j] via the introducer so that the distal port and thermistor were positioned in the pulmonary artery. The proximal port was 9.8 cm from the distal port. This catheter was used to measure CO, PAP, PAOP, CVP, and core body temperature and for collection of mixed-venous blood samples. A 24-gauge, 9-cm catheter[k] was inserted in a femoral artery at the level of the femoral triangle via surgical cutdown. This catheter was used to measure systemic arterial blood pressure and for collection of arterial blood samples. Instrumentation required approximately 90 minutes to complete. After completion of instrumentation, cats were positioned in left lateral recumbency for the duration of the anesthetic period.

**Study design**—A prospective randomized crossover study was performed. Each cat received 2 treatments (order of treatments was randomized with a computer-generated random list); there was a 3-week interval between treatments.

On completion of instrumentation, hypotension was induced in the first cat by titration of isoflurane to achieve a mean arterial pressure of 60 mm Hg. This was accomplished by administration of isoflurane to an

ETISO of 2.4% to 2.5%. The ETISO was maintained at this concentration for the duration of the experiment. The same ETISO was used in subsequent cats. An infrared spectrometer[l] was used to measure ETISO in samples collected manually via a catheter placed in the endotracheal tube; the tip of the catheter was located 1 cm from the end of the endotracheal tube. The spectrometer was calibrated daily with 4 isoflurane standards of known concentration.

Data were collected 20 minutes after reaching the target ETISO (baseline hypotension). After data collection was completed, treatments were administered. Three incremental doses of dopamine[m] (2.5, 5, and 10 µg/kg/min) or phenylephrine[n] (0.25, 0.5, and 1 µg/kg/min) were administered as a constant rate infusion. The low dose of dopamine or phenylephrine was administered first. A 400 µg/mL solution of dopamine or 20 µg/mL solution of phenylephrine was administered by a syringe infusion pump[o] via the catheter in the cephalic vein. Data were collected 20 minutes after onset of the infusion. The infusion then was increased to the next incremental dose; the infusion protocol and data collection were repeated for the middle and high doses of each drug.

**Data collection**—Hemodynamic data were monitored and recorded with a physiologic recorder[p] and data acquisition system.[q] Data recorded included systolic, diastolic, and mean arterial blood pressures; CVP; PAP; PAOP; HR; and heart rhythm. Pressure transducers were calibrated against a mercury manometer prior to each experiment. A lead II ECG was used for analysis of HR and heart rhythm. Cardiac output was measured[r] via the thermodilution technique. Three milliliters of cold (0° to 1°C) 5% dextrose solution was injected into the proximal port of the thermodilution catheter for each determination. Three measurements of CO that were within 10% of each other were used to calculate a mean value that was recorded for each data collection period.

Arterial and mixed-venous blood samples were collected simultaneously for blood gas analysis and assessment of concentrations of electrolytes, blood glucose, lactate, and hemoglobin. Analyses were performed with a blood gas analyzer.[s] Samples were stored on ice until analysis; all samples were analyzed within 10 minutes after collection. Quality control standards for the blood gas machine were assayed on each study day prior to anesthesia of the cats.

After collection of the final set of data, all catheters were removed, the femoral arterial site was surgically closed, and cats were allowed to recover from anesthesia. Cats received meloxicam[t] (0.2 mg/kg, IV) once after extubation or oxymorphone (0.05 mg/kg, SC) or both prior to recovery. Oxymorphone (0.05 mg/kg, SC) was administered up to 3 times/d, as needed, after surgery to control pain associated with the instrumentation.

**Calculation of hemodynamic and respiratory variables**—Hemodynamic and respiratory variables were calculated via standard equations.[20–22] Variables calculated included RPP, stroke volume index, SVRI, LVSWI, RVSWI, $D_{O_2}$, $\dot{V}_{O_2}$, alveolar-arterial difference in partial pressure of oxygen, OER, pulmonary capillary blood oxygen content, and the shunt fraction.

**Measurement of plasma concentrations of cTnI**—A sample (1.75 mL) of mixed-venous blood was collected into a lithium heparinized blood collection tube at the time of echocardiography (awake cats) and at each data collection point during anesthesia. Blood samples were immediately centrifuged at 4°C. Plasma was harvested and stored frozen at –79°C until the time of analysis; all plasma samples were analyzed within 6 months after blood collection. Plasma concentrations of cTnI were measured by use of a solid-phase radial partition immunoassay.[23,u] Limit of quantitation for the assay was 0.01 ng/mL.

**Statistical analysis**—Data were tested for a normal distribution via the Shapiro-Wilk test. All data were normally distributed and were reported as mean ± SD, except for plasma concentrations of cTnI, which were not normally distributed and were reported as median and range values. Hemodynamic, respiratory, and blood gas data were analyzed by use of a multivariate ANOVA for repeated measures. The dependent variables were treatment (dopamine or phenylephrine) and dose (low, medium, and high). A Dunnett post hoc test was used to determine differences between dose and baseline (hypotension) values when a dose effect was detected with the ANOVA. Plasma concentrations of cTnI were logarithmically transformed to fit the criteria for normality and then were analyzed by use of a 2-way repeated-measures ANOVA to evaluate the effect of treatment and dose. A Dunnett post hoc test was used to compare concentrations for each dose and for the baseline (hypotension) time point with the concentration in the awake cats obtained during echocardiography. Values of $P < 0.05$ were considered significant.

## Results

Values for the hemogram and serum biochemical analysis were within reference limits for all cats, except for one. In that cat, the BUN concentration was high (42 mg/dL; reference range, 18 to 33 mg/dL); however, the creatinine concentration was within the reference range. A small, irregularly shaped right kidney was palpable during physical examination of that cat.

The ETISO did not change over time and was not significantly different between treatments (mean ± SD, 2.44 ± 0.05% for dopamine and 2.48 ± 0.04% for phenylephrine). Mean core body temperature (data pooled for the baseline period and each of the 3 doses) for the dopamine treatment (38.4 ± 0.1°C) did not differ significantly from that for the phenylephrine treatment (38.4 ± 0.3°C). We did not detect a significant effect of treatment or dose on respiratory rate, end-tidal partial pressure of carbon dioxide, or partial pressure of carbon dioxide in arterial or mixed-venous blood samples. No significant differences in cardiovascular variables were detected at baseline (hypotension) between treatments.

Cardiorespiratory data were summarized for the dopamine treatment (**Table 1**). Within the dopamine treatment, systemic blood pressure, PAP, cardiac index, HR, RPP, LVSWI, mixed-venous oxygen content, and venous hemoglobin concentration were significantly greater than baseline values for the 2 higher infusion rates (5 and 10 µg/kg/min). Cardiac index and $D_{O_2}$ were

significantly greater for the dopamine treatment than for the phenylephrine treatment. Values for RVSWI, $D\bar{o}_2$, pulmonary vascular resistance index, arterial and pulmonary capillary oxygen contents, mixed-venous hemoglobin oxygen saturation, mixed-venous partial pressure of oxygen, and arterial hemoglobin concentration were significantly higher than baseline values only when dopamine was infused at a rate of 10 µg/kg/min. The OER was significantly lower than the baseline value during dopamine infusions at the rates of 5 and 10 µg/kg/min. The SVRI and $\dot{V}o_2$ did not change significantly.

Cardiorespiratory data were summarized for the phenylephrine treatment (**Table 2**). Systolic, diastolic, and mean systemic artery pressures and mean PAP were significantly higher than baseline values when phenylephrine was infused at a rate of 1 µg/kg/min. Systolic arterial pressure, but not mean or diastolic arterial pressures, was also significantly higher than baseline values during infusions of phenylephrine at a rate of 0.5 µg/kg/min. Values for SVRI; RPP; arterial and mixed-venous hemoglobin concentrations; oxygen content in arterial, mixed-venous, and pulmonary capillary blood; and $D\bar{o}_2$ were significantly higher than baseline values when phenylephrine was infused at a rate of 1 µg/kg/min. The SVRI was significantly higher for the phenylephrine treatment than for the dopamine treatment. No significant changes in LVSWI, RVSWI, and $\dot{V}o_2$ were detected at any infusion rate of phenylephrine.

Selected acid-base and metabolic variables were determined for the dopamine and phenylephrine treat-

Table 1—Mean ± SD values for cardiopulmonary, acid-base, and metabolic variables of 6 cats with severe HCM that received constant rate infusions of incremental doses of dopamine during isoflurane-induced hypotension.

| | | Dopamine (µg/kg/min) | | |
|---|---|---|---|---|
| **Variable** | **Hypotension** | **2.5** | **5** | **10** |
| Cardiopulmonary | | | | |
| HR (beats/min) | 133 ± 23.4 | 147 ± 18.9 | 167 ± 25.5* | 187 ± 21.9* |
| SAP (mm Hg) | 75 ± 11 | 86 ± 9 | 115 ± 17* | 146 ± 19* |
| MAP (mm Hg) | 53 ± 7.5 | 63 ± 9.2 | 81 ± 13.9* | 94 ± 22.5* |
| DAP (mm Hg) | 44 ± 6 | 52 ± 7 | 66 ± 13* | 73 ± 17* |
| CVP (mm Hg) | 10 ± 1.7 | 11 ± 2.3 | 11 ± 1.9 | 10 ± 2.0 |
| MPAP (mm Hg) | 21 ± 3.6 | 26 ± 5.2 | 32 ± 7.7* | 38 ± 7.8* |
| PAOP (mm Hg) | 14 ± 2.1 | 16 ± 2.7 | 16 ± 3.7 | 17 ± 3.0 |
| Cardiac index (L/min/m$^2$)† | 1.48 ± 0.4 | 1.69 ± 0.4 | 2.07 ± 0.1* | 2.39 ± 0.4* |
| SVI (mL/beat/kg) | 0.727 ± 0.3 | 0.720 ± 0.2 | 0.787 ± 0.2 | 0.803 ± 0.2 |
| SVRI (dyne•s /cm$^5$/m$^2$)† | 2,439 ± 627 | 2,565 ± 565 | 2,827 ± 932 | 2,835 ± 711 |
| PVRI (dyne•s /cm$^5$/m$^2$) | 393 ± 131.7 | 465 ± 125.4 | 602 ± 153.5 | 692 ± 198.9* |
| RPP | 7,002 ± 1,373 | 9,290 ± 2,212 | 13,812 ± 4,506* | 17,966 ± 6,378* |
| LVSWI (gf•m/kg) | 0.39 ± 0.2 | 0.46 ± 0.2 | 0.67 ± 0.1* | 0.83 ± 0.3* |
| RVSWI (gf•m/kg) | 0.11 ± 0.07 | 0.16 ± 0.10 | 0.24 ± 0.10 | 0.31 ± 0.10* |
| $D\bar{o}_2$ (mL/min)† | 58.0 ± 13.9 | 71.4 ± 20.6 | 94.5 ± 22.5 | 121.3 ± 14.1* |
| $\dot{V}o_2$ (mL/min) | 19.5 ± 5.7 | 20.6 ± 2.5 | 17.5 ± 6.7 | 19.6 ± 7.8 |
| OER | 0.35 ± 0.10 | 0.32 ± 0.10 | 0.19 ± 0.06* | 0.16 ± 0.07* |
| RR (breaths/min) | 12 ± 3.6 | 13 ± 3.4 | 15 ± 2.5 | 15 ± 3.9 |
| $P_{A}o_2 - Pao_2$ (mm Hg) | 180 ± 30.2 | 188 ± 45.6 | 204 ± 59.1 | 188 ± 83.7 |
| $\dot{Q}_S/\dot{Q}_T$ | 0.10 ± 0.04 | 0.11 ± 0.02 | 0.17 ± 0.07 | 0.16 ± 0.08 |
| Blood gas (measured) | | | | |
| pHa | 7.267 ± 0.03 | 7.271 ± 0.03 | 7.272 ± 0.03 | 7.277 ± 0.05 |
| Phv | 7.224 ± 0.03 | 7.229 ± 0.02 | 7.238 ± 0.03 | 7.23 ± 0.04 |
| $Paco_2$ (mm Hg) | 46.4 ± 3.2 | 44.7 ± 3.8 | 44.3 ± 3.7 | 45.6 ± 4.9 |
| $P\bar{v}co_2$ (mm Hg) | 55.9 ± 3 | 54 ± 4.3 | 51.9 ± 4.1 | 51.4 ± 6.4 |
| $Pao_2$ (mm Hg) | 455 ± 30.0 | 448 ± 46.1 | 433 ± 59.6 | 447 ± 84.2 |
| $P\bar{v}o_2$ (mm Hg) | 54.9 ± 8.7 | 59.7 ± 10.9 | 67.3 ± 7.5 | 77.4 ± 11.2* |
| Blood gas (calculated) | | | | |
| $S\bar{v}o_2$ (%) | 71.1 ± 12.5 | 76.7 ± 13.6 | 86.3 ± 6.1 | 90.9 ± 8.2* |
| $Cao_2$ (mL/L) | 14.9 ± 1 | 15.8 ± 0.7 | 17.0 ± 2.1 | 19.2 ± 2.1* |
| $C\bar{v}o_2$ (mL/L) | 9.7 ± 1.9 | 10.9 ± 2.3 | 13.8 ± 1.7* | 16.1 ± 2.3* |
| $Cc'o_2$ (mL/L) | 15.5 ± 1.1 | 16.4 ± 0.6 | 17.6 ± 2.0 | 19.8 ± 2.0* |
| Hba (g/dL) | 10.0 ± 0.8 | 10.7 ± 0.5 | 11.6 ± 1.5 | 13.2 ± 1.5* |
| Hbv (g/dL) | 10.0 ± 0.5 | 10.2 ± 0.9 | 11.6 ± 1.4* | 12.9 ± 1.6* |
| BE (mmol/L) | –5.5 ± 1.4 | –6.0 ± 0.8 | –6.1 ± 1.1 | –6.3 ± 0.6 |
| Metabolic‡ | | | | |
| Lactate (mmol/L) | 1.8 ± 0.7 | 1.8 ± 0.7 | 1.7 ± 0.6 | 1.6 ± 0.6 |
| Glucose (mg/dL) | 148 ± 37 | 186 ± 36.3 | 215 ± 45.5* | 247 ± 46.2* |

*Within a row, value differs significantly ($P < 0.05$) from the value at baseline (hypotension). †Value differs significantly ($P < 0.05$) from the value for the phenylephrine treatment in Table 2. ‡Variable measured by use of arterial blood samples.

BE = Base excess. $Cao_2$ = Arterial blood oxygen content. $Cc'o_2$ = Pulmonary capillary blood oxygen content. $C\bar{v}o_2$ = Mixed-venous blood oxygen content. DAP = Diastolic arterial blood pressure. Hba = Arterial blood hemoglobin concentration. Hbv = Venous blood hemoglobin concentration. MAP = Mean arterial blood pressure. MPAP = Mean PAP. $P_{A}o_2 - Pao_2$ = Alveolar-arterial difference in partial pressure of oxygen. pHa = Arterial blood pH. pHv = Venous blood pH. $P\bar{v}co_2$ = Mixed-venous partial pressure of carbon dioxide. $P\bar{v}o_2$ = Mixed-venous partial pressure of oxygen. $\dot{Q}_S/\dot{Q}_T$ = Shunt fraction. RR = Respiratory rate. SAP = Systolic arterial blood pressure. $S\bar{v}o_2$ = Mixed-venous hemoglobin oxygen saturation. SVI = Stroke volume index.

ments (Tables 1 and 2). Infusion of dopamine or phenylephrine did not change pH, arterial partial pressure of carbon dioxide, or standard base excess. The sodium concentration decreased to 146 mEq/L during dopamine infusions at rates of 5 and 10 µg/kg/min, compared with the baseline concentration (150 mEq/L). Similarly, infusion of phenylephrine at rates of 0.5 and 1 µg/kg/min decreased the sodium concentration (146 and 145 mEq/L, respectively), compared with the baseline concentration (150 mEq/L). The arterial chloride concentration decreased to 120 mEq/L when dopamine was infused at a rate of 10 µg/kg/min, compared with the baseline concentration (123 mEq/L). The blood glucose concentration increased when dopamine was infused at rates of 5 and 10 µg/kg/min (215 and 247 mg/dL, respectively), compared with the baseline concentration (148 mg/dL). Similarly, the blood glucose concentration increased when phenylephrine was infused at rates of 0.5 and 1 µg/kg/min (214 and 224 mg/dL, respectively), compared with the baseline concentration (137 mg/dL).

All cats developed VPCs during the study period during both the dopamine and phenylephrine infusions; however, the VPCs were infrequent and appeared as unifocal singlets or couplets in all cats, except for one. That cat developed frequent atrial premature complexes, frequent VPCs, and progressive ST segment elevation during infusions of dopamine at 5 µg/kg/min and phenylephrine at 0.5 µg/kg/min. That same cat developed ventricular bigeminy and a nonsustained accelerated idioventricular rhythm followed by sinus bradycardia (HR, 95 beats/min) and hypotension (mean arterial pressure, approx 40 mm Hg) that lasted for 2 minutes during infusion of dopamine at 10 µg/kg/min and had a longer period (2 to 3 minutes) of ventricular bigeminy approximately 10 minutes after discontinuation of the dopamine infusion. No treatments were instituted for the observed arrhythmias, all of which were self-limiting, and infusions of dopamine and phenylephrine were not interrupted.

Plasma concentrations of cTnI were summarized (**Table 3**). The plasma concentration of cTnI at baseline

Table 2—Mean ± SD values for cardiopulmonary, acid-base, and metabolic variables of 6 cats with severe HCM that received constant rate infusions of incremental doses of phenylephrine during isoflurane-induced hypotension.

| | | Phenylephrine (µg/kg/min) | | |
|---|---|---|---|---|
| **Variable** | **Hypotension** | **0.25** | **0.5** | **1** |
| Cardiopulmonary | | | | |
| HR (beats/min) | 133 ± 26.8 | 139 ± 24.0 | 144 ± 20.9 | 149 ±15.4 |
| SAP (mm Hg) | 78 ± 16 | 88 ± 12 | 109 ± 17* | 130 ± 14* |
| MAP (mm Hg) | 59 ± 15.6 | 68 ± 11.8 | 77 ± 12.8 | 94 ± 13.8* |
| DAP (mm Hg) | 48 ± 15 | 52 ± 7 | 55 ± 9 | 66 ± 10* |
| CVP (mm Hg) | 8 ± 3.0 | 10 ± 3.4 | 12 ± 2.5 | 12 ± 2.5 |
| MPAP (mm Hg) | 24 ± 5.2 | 30 ± 7.6 | 38 ± 13.0 | 43 ± 16.9* |
| PAOP (mm Hg) | 15 ± 3.0 | 17 ± 2.7 | 20 ± 6.8 | 21 ± 5.5 |
| Cardiac index (L/min/m$^2$)† | 1.39 ± 0.3 | 1.44 ± 0.3 | 1.46 ± 0.4 | 1.51 ± 0.3 |
| SVI (mL/beat/kg) | 0.689 ± 0.3 | 0.670 ± 0.2 | 0.642 ± 0.2 | 0.636 ± 0.2 |
| SVRI (dyne•s/cm$^5$/m$^2$)† | 3,026 ± 914 | 3,298 ± 840 | 3,674 ± 998 | 4,408 ± 982* |
| PVRI (dyne•s /cm$^5$/m$^2$) | 578 ± 346 | 759 ± 358 | 1,088 ± 608 | 1,248 ± 738 |
| RPP | 7,847 ± 2,677 | 9,316 ± 1,713 | 1,1141 ± 2,961 | 1,3951 ± 2,134* |
| LVSWI (gf•m/kg) | 0.42 ± 0.2 | 0.47 ± 0.3 | 0.50 ± 0.2 | 0.64 ± 0.2 |
| RVSWI (gf•m/kg) | 0.14 ± 0.1 | 0.19 ± 0.1 | 0.21 ± 0.1 | 0.25 ± 0.1 |
| $D_{O_2}$ (mL/min)† | 52 ± 12.8 | 58 ± 16.3 | 65 ± 13.6 | 74 ± 15.3* |
| $\dot{V}_{O_2}$ (mL/min) | 18 ± 3.7 | 20 ± 4.6 | 21 ± 4.3 | 19 ± 7.8 |
| OER | 0.36 ± 0.1 | 0.36 ± 0.1 | 0.34 ± 0.1 | 0.26 ± 0.1 |
| RR (breaths/min) | 15 ± 4.5 | 15 ± 5.4 | 18 ± 3.8 | 19 ± 3.7 |
| $P_{A_{O_2}} - Pa_{O_2}$ (mm Hg) | 229 ± 59 | 206 ± 47 | 215 ± 42 | 214 ± 54 |
| $Q_S/Q_T$ | 0.12 ± 0.04 | 0.11 ± 0.04 | 0.11 ± 0.04 | 0.14 ± 0.06 |
| Blood gas (measured) | | | | |
| pHa | 7.275 ± 0.09 | 7.269 ± 0.08 | 7.28 ± 0.07 | 7.27 ± 0.07 |
| pHv | 7.224 ± 0.09 | 7.219 ± 0.07 | 7.229 ± 0.07 | 7.226 ± 0.07 |
| $Pa_{CO_2}$ (mm Hg) | 42 ± 8.5 | 42 ± 8.6 | 39 ± 5.9 | 39 ± 5.2 |
| $P\bar{v}_{CO_2}$ (mm Hg) | 53 ± 8.9 | 53 ± 8.1 | 50 ± 7.0 | 49 ± 5.8 |
| $Pa_{O_2}$ (mm Hg) | 410 ± 57 | 434 ± 47 | 428 ± 39 | 429 ± 54 |
| $P\bar{v}_{O_2}$ (mm Hg) | 52 ± 9.9 | 55 ± 9.5 | 56 ± 10.0 | 61 ± 11.0 |
| Blood gas (calculated) | | | | |
| $S\bar{v}_{O_2}$ (%) | 67 ± 11 | 71 ± 13 | 74 ± 13 | 78 ± 12 |
| $Ca_{O_2}$ (mL/L) | 14 ± 1.8 | 15 ± 1.2 | 17 ± 1.9 | 18 ± 3.0* |
| $C\bar{v}_{O_2}$ (mL/L) | 9 ± 2.0 | 10 ± 2.3 | 11 ± 2.7 | 14 ± 3.1* |
| $Cc'_{O_2}$ (mL/L) | 15 ± 1.8 | 15 ± 1.2 | 17 ± 1.9 | 19 ± 3.0* |
| Hba (g/dL) | 9.4 ± 1.4 | 9.9 ± 0.9 | 11.3 ± 1.4 | 12.6 ± 2.2* |
| Hbv (g/dL) | 9.6 ± 1.6 | 9.7 ± 1.6 | 10.9 ± 2.0 | 12.7 ± 2.4* |
| BE (mmol/L) | –6.9 ± 3.0 | –6.8 ± 3.3 | –7.8 ± 2.3 | –8.2 ± 2.3 |
| Metabolic‡ | | | | |
| Lactate (mmol/L) | 1.8 ± 0.7 | 1.8 ± 0.7 | 1.7 ± 0.6 | 1.9 ± 0.6 |
| Glucose (mg/dL) | 137 ± 37 | 193 ± 45 | 214 ± 47* | 224 ± 52* |

†Value differs significantly ($P < 0.05$) from the values for the dopamine treatment in Table 1.
*See* Table 1 for remainder of key.

Table 3–Median (range) plasma concentrations of cTn1 (ng/mL) for 6 cats with severe HCM in blood samples collected from awake cats during echocardiography, during isoflurane-induced hypotension, and after administration of constant rate infusions of low, medium, and high incremental doses of dopamine (2.5, 5, and 10 µg/kg/min, respectively) and phenylephrine (0.25, 0.5, and 1 µg/kg/min, respectively) during anesthesia maintained by administration of isoflurane.

| | | | Constant rate infusion | | |
|---|---|---|---|---|---|
| **Treatment** | **Awake** | **Hypotension** | **Low** | **Medium** | **High** |
| Dopamine | 0.16 (0.07–0.47) | 1.29 (0.32–2.97)* | 1.48 (0.42–4.75)* | 1.83 (0.49–5.75)* | 2.26 (0.58–6.34)* |
| Phenylephrine | 0.16 (0.07–0.47) | 1.49 (0.21–7.60) | 1.94 (0.24–11.1)* | 2.41 (0.26–12.80)* | 2.92 (0.29–15.20)* |

Values reported represent the raw data, whereas the test of significance was conducted on logarithmically transformed data.

*Within a row, the concentration differs significantly ($P < 0.05$) from the concentration in awake cats during echocardiography.

(hypotension) for the dopamine treatment and the low, medium, and high infusions of both drugs was significantly higher than the concentration for the awake cats. There was no significant increase in cTnI concentration from the baseline value (hypotension) at any point during drug infusion. However, the plasma concentration of cTnI increased from the baseline value in each cat during both high-dose infusions. The increase was > 30%, and in only 2 cats (1 during infusion of dopamine and 1 during infusion of phenylephrine) was this increase < 50%. The increase was ≥ 100% for 6 of the remaining 12 values. No differences in plasma concentrations of cTnI were detected between the dopamine and phenylephrine treatments.

## Discussion

To our knowledge, the study reported here was the first that has been conducted to evaluate the cardiorespiratory effects of dopamine and phenylephrine in cats with HCM during isoflurane-induced hypotension. Although both dopamine and phenylephrine increased arterial blood pressure, only dopamine increased cardiac index. Dopamine increased $D_{O_2}$ more than did phenylephrine. Phenylephrine increased SVR. Cardiac arrhythmias were observed during administration of both drugs.

Dopamine has been recommended as the catecholamine of choice for treatment of isoflurane-induced hypotension in healthy cats because of its efficacy in increasing both CO and blood pressure.[18] In the present study, significant dose-dependent increases in arterial blood pressure were induced by administration of moderate and high doses of dopamine (5 and 10 µg/kg/min, respectively) and the highest dose of phenylephrine (1 µg/kg/min). Dopamine increased cardiac index, whereas phenylephrine did not. Dopamine induces dose-dependent hemodynamic effects by activation of dopaminergic receptors, $\beta_1$-adrenergic receptors, and $\alpha_1$-adrenergic receptors.[24] The effect of dopamine on CO in the present study was most likely attributable to its chronotropic properties, rather than its inotropic properties, because HR increased but stroke volume did not change. Intrinsic myocardial contractility is independent of preload or afterload and is reduced in hearts affected by HCM.[25,26] We did not determine myocardial contractility, but the myocardial depressant effects of isoflurane coupled with the fact that there is systolic dysfunction in patients with HCM corroborates the hypothesis that increases in myocardial contractility could potentially be beneficial during isoflurane-induced anesthesia. In healthy subjects, phenylephrine increases arterial blood pressure exclusively by inducing vasoconstriction and increases SVR via activation of $\alpha_1$-adrenergic receptors in vascular smooth muscle cells.[27] In the present study, the increase in afterload caused by phenylephrine likely prevented an increase in CO.

The balance between myocardial $D_{O_2}$ and $M\dot{V}_{O_2}$ determines whether there is myocardial hypoxia and hence myocardial injury. Increases in myocardial contractility, HR, and afterload all increase $M\dot{V}_{O_2}$. In the present study, plasma concentration of cTnI was used as an indicator of myocardial injury. The plasma concentration of cTnI was markedly increased after the initial hypotensive phase, which suggested that the combination of anesthesia for approximately 90 minutes (when hypotension was not detected via Doppler ultrasonographic measurement) followed by moderate hypotension for 20 minutes was detrimental to the myocardium. It is impossible to determine from our data whether anesthesia, dopamine, or phenylephrine increased concentrations of cTnI. Increases in concentrations of cTnI in apparently healthy dogs after general anesthesia have been reported[28]; however, the proportion of dogs with such increases was low (14%). Plasma concentrations of cTnI did not significantly increase further with increases in anesthesia time and increases in the doses of dopamine or phenylephrine. However, the lack of significant differences was clearly attributable to the fact that the study was underpowered (only 6 cats) and that there was tremendous variability in cTnI concentrations among cats. A power analysis on the cTnI data alone (with 6 cats/group, $\alpha = 0.05$, cTnI difference of 0.8, and an SD of 2) yields a power of 0.1 or, conversely, to obtain a power of 0.8, one would need 100 cats/group with similar criteria. Two important points should be considered when interpreting this information. First, in previous studies, cats without cardiomyopathy generally have cTnI concentrations below the limits of detection for cTnI assays[8]; thus, a cTnI value above the limits of detection may be considered clinically important. The continued increase in cTnI concentration through the study time points (in all cats, with both drugs, at all time points during anesthesia) may also be of clinical concern. Considerable

variation in cTnI concentration may be expected because of differing phenotypic manifestations of HCM. Second, this study was powered primarily for detecting changes in cardiovascular data, and analysis of changes in cTnI concentration was a secondary outcome.

Heart rate increased in isoflurane-anesthetized cats with HCM during dopamine administration but not during phenylephrine administration. The increase in HR during dopamine administration was expected because of its activity as a $\beta_1$-adrenergic receptor agonist and resulted in the increase in CO.[24] It is unclear whether this effect was beneficial, particularly in view of the fact that medical management of HCM in cats often includes treatments to induce a reduction in HR. Phenylephrine can decrease HR via an increase in blood pressure; however this response is more common in autonomically intact, conscious animals when there is a large, rapid increase in blood pressure.[27] In the present study, administration of phenylephrine to the anesthetized cats caused only a modest and gradual increase in blood pressure, and HR did not change. Effective blockade of baroreceptor reflexes as a result of isoflurane administration likely was responsible for the lack of change in HR.[29]

The RPP, LVSWI, and RVSWI are crude indicators of $M\dot{V}O_2$.[30–32] Heart rate correlates well with $M\dot{V}O_2$; however, coronary blood flow does not always increase proportionately with increases in HR, thereby confounding the determination of $M\dot{V}O_2$. Analysis of the results of the present study suggested that $M\dot{V}O_2$ was increased with both drugs, especially when they were administered at higher doses. The clinical importance of this in cats with HCM during isoflurane-induced anesthesia is unclear, but this effect could predispose such cats to the development of myocardial hypoxia and subsequent arrhythmias. The propensity to develop myocardial infarction in cats that do not have coronary artery disease is low, although there are regions of microscopic myocardial necrosis and subsequent replacement fibrosis (scarring).[8] All cats in the present study had VPCs, which occurred during all phases of the study and are not unexpected in cats with HCM.[4,33] The mechanism for cardiac arrhythmias is unknown, but cardiac restructuring, including myocardial ischemia that leads to replacement fibrosis, expansion of the amount of interstitial collagen (interstitial fibrosis), and hypertrophy or chamber dilation as well as myocardial irritation caused by pulmonary artery catheter placement, may play a role.[11,12,34,35] One cat had particularly severe arrhythmias that were subjectively worse during administration of dopamine than during administration of phenylephrine. It is possible that this cat developed SAM precipitated by increases in HR or myocardial contractility (or both) in response to the dopamine infusion.

Infusion of dopamine resulted in a higher $D\dot{O}_2$ than did infusion of phenylephrine as a result of the increase in CO. The lack of increase in $\dot{V}O_2$ in the face of an increased oxygen supply to tissues resulted in a reduction in OER during dopamine infusions at a rate of 10 µg/kg/min. We did not quantify myocardial $D\dot{O}_2$ and $M\dot{V}O_2$ in this study, and global oxygen supply and demand does not necessarily reflect myocardial oxygen balance. However, areas of thickened myocardium in cats with HCM may be working in near-ischemic conditions, as evidenced by increases in cTnI concentrations.[7,8] It is possible that increases in HR and myocardial contractility may further decrease myocardial efficiency and potentiate cardiac myocyte necrosis; however, this was not reflected by differences in cTnI concentrations in the present study.

Mean PAP and pulmonary artery vascular resistance index increased during infusions of dopamine and phenylephrine at the higher doses; however, variability was large. The reason for the increase in pulmonary vascular pressures is unclear. In other studies,[36–40] investigators detected variable effects of inotropes and vasopressors on pulmonary vascular pressures. Changes in flow, capacitance, vessel blood volume, or vascular tone or a combination of these factors may have contributed to the increase. Postjunctional $\alpha_1$- and $\alpha_2$-adrenergic receptors are less widely distributed in pulmonary vascular smooth muscle cells than in the systemic circulation in cats; however, changes in receptor density induced by myocardial disease cannot be excluded.[41,42]

The blood glucose concentration increased significantly for both treatments. Stress response to anesthesia and hypotension and administration of dextrose-containing fluids for CO determination are possible explanations for this increase. Although there were significant decreases in sodium and chloride concentrations from baseline values, these differences did not reflect clinically important changes.

Phenotypic manifestation of HCM in cats differs considerably and likely impacts each cat's response.[6] The cats in the present study did not have dynamic left ventricular outflow tract obstruction. This fact, coupled with the myocardial depressant effects of isoflurane, may explain the improvement in CO in these cats in response to dopamine infusion. Whether similar cardiovascular effects would be induced in cats with HCM and SAM remains to be determined because none of the cats in the present study had echocardiographic evidence of outflow tract obstruction. The effect of sedatives and anesthetic induction drugs on the response to dopamine and phenylephrine in cats cannot be determined from this study.

Clinically, treatment recommendations for isoflurane-induced hypotension in cats with HCM are complex, are multifactorial, and require further study. Caution and vigilant monitoring are advised when these cats are being anesthetized because even cats without echocardiographic evidence of SAM before surgery could develop this condition during anesthesia.[12] Such cats may warrant use of a vasoconstrictor in place of a positive inotrope for blood pressure management. Analysis of the data for the present study suggested that if the goal of the treatment of inhalation anesthetic–induced hypotension in cats with nonobstructive HCM is to restore blood pressure to within the reference range through an increase in CO, dopamine is superior to phenylephrine.

a. Oxymorphone HCl, Endo Pharmaceuticals Inc, Chadds Ford, Pa.

b. 22-gauge Insyte catheter, Becton-Dickinson, Sandy, Utah.
c. Midazolam HCl, Baxter Healthcare Corp, Deerfield, Ill.
d. Etomidate, Ben Venue Labs Inc, Bedford, Ohio.
e. Isoflurane, Piramal Healthcare Ltd, Andrah Pradesh, India.
f. Lactated Ringer's injection USP, Baxter Healthcare Corp, Deerfield, Ill.
g. Gaymar Industries Inc, Orchard Park, NY.
h. Bair Hugger 505, Augustine Medical Inc, Eden Prairie, Minn.
i. Introducer kit, Arrow International, Reading, Pa.
j. Thermodilution balloon catheter, Arrow International, Reading, Pa.
k. Central venous catheterization kit, Arrow International, Reading, Pa.
l. Beckman Medical gas analyzer LB1, Beckman Instruments, Schiller Park, Ill.
m. Dopamine HCl, Hospira Inc, Lake Forest, Ill.
n. Phenylephrine HCl, Baxter Healthcare Corp, Deerfield, Ill.
o. Medfusion 2010i, Medex Inc, Duluth, Ga.
p. Physiograph, Gould Instrument Systems, Valley View, Ohio.
q. Ponemah, version 3.0, Gould Instrument Systems, Valley View, Ohio.
r. COM-1, American Edwards Laboratories, Irvine, Calif.
s. ABL 800, Radiometer, Copenhagen, Denmark.
t. Meloxicam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
u. Immulite 2000 analyzer, Siemens Healthcare Diagnostics Inc, Deerfield, Ill.

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