

Effect of marbofloxacin on cardiovascular variables in healthy isoflurane-anesthetized dogs

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Objective—To study the hemodynamic effects of marbofloxacin (MBF) in isoflurane-anesthetized dogs.

Animals—6 healthy 8-month-old Beagles.

Procedure—Anesthesia was induced with sodium thiopental and maintained with isoflurane. Cardiovascular variables were monitored throughout anesthesia. Marbofloxacin was administered by an IV bolus at 2 mg/kg, followed 10 minutes later by an infusion at a rate of 40 mg/kg/h for 30 minutes (total dose, 20 mg/kg). Plasma MBF concentrations were measured by high-performance liquid chromatography.

Results—The mean peak concentration during MBF infusion was 34.2 ± 6.4 $\mu\text{g/mL}$. The IV administration of the MBF bolus did not alter any cardiovascular variable in isoflurane-anesthetized dogs. Significant changes were found during infusion when a cumulative dose of 12 mg/kg had been given. The maximal decreases observed at the end of the infusion were 16% in heart rate, 26% in systolic left ventricular pressure, 33% in systolic aortic pressure, 38% in diastolic aortic pressure, 29% in cardiac output, and 12% in QT interval. All dogs recovered rapidly from anesthesia at the end of the experiment.

Conclusions and Clinical Relevance—MBF may safely be used at 2 mg/kg IV in isoflurane-anesthetized dogs, and significant adverse cardiovascular effects are found only when 6 to 8 times the recommended dose is given. (*Am J Vet Res* 2005;66:2090–2094)

Most surgeons at the present time accept the use of antibiotic prophylaxis, and the efficacy of such a procedure has been clearly demonstrated.¹ Cephalosporins are most commonly used for such prophylaxis.² In humans, quinolones can also be used in debilitated patients or patients with potentially resistant multibacterial infections, even though their main use is to treat infections of the urinary, gastrointestinal, and respiratory tracts and of the bones and joints.³ The major adverse effects of quinolones that are relevant in terms of anesthesia include effects on the CNS (seizures, potentiated by concurrent use of non-

steroidal anti-inflammatory drugs), cardiovascular system (hypotension, bradycardia, and negative inotropic effects), and kidneys (nephropathy).⁴ Nevertheless, fluoroquinolones are considered among the safest antibiotic agents.

Marbofloxacin (MBF) is a broad-spectrum, bactericidal, third-generation fluoroquinolone developed exclusively for veterinary use. Marbofloxacin is rapidly bactericidal primarily against gram-negative bacteria (especially *Escherichia coli*, *Pasteurella* spp, and *Pseudomonas* spp), mycoplasma, and some gram-positive bacteria (especially *Staphylococcus aureus* and *Staphylococcus intermedius*). Marbofloxacin has been shown to be efficient in refractory urinary tract,⁵ respiratory tract,⁶ and skin^{7,8} infections.⁹ It may be used to treat potentially life-threatening infectious conditions, especially in emergency care. Marbofloxacin is primarily administered orally, although parenteral formulations are available in Europe. One of its major advantages, compared with other fluoroquinolones, is likely its long half-life (approx 12 hours).¹⁰ The efficacy of MBF in prevention of experimental surgical wound infection with *S intermedius* has been previously demonstrated.¹¹ Some safety aspects, potentially relevant to the surgical patient, have also been documented. Coadministration of MBF and tolfenamic acid (a nonsteroidal anti-inflammatory drug used in Europe) did not induce any neurologic signs or epileptiform activity on electrocorticograms even after IV administration of 10 times the recommended dose of MBF.⁴ Similarly, anesthesia-induced alterations of renal function cannot be considered as increasing the risk of overexposure to MBF, as it was shown that its pharmacokinetics were unchanged in dogs with moderate renal failure.¹²

Therefore, the only potential major adverse effects of MBF for anesthetized canine patients that are not currently documented are on the cardiovascular system. This issue is relevant in view of previous data published about other fluoroquinolones and antibiotics.^{4,13,14} The objective of the study presented here was therefore to document the hemodynamic effects of MBF after IV administration of a single bolus (2 mg/kg) and prolonged infusion (40 mg/kg/h for 30 minutes) in isoflurane-anesthetized dogs.

Materials and Methods

Animals—The study was conducted according to the guidelines of the National Institutes of Health Guide for Care and Use of Laboratory Animals.¹⁵ Six 8-month-old healthy female Beagles,^b weighing 9 to 10 kg at the beginning of the study, were used. They were acclimated for 2

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months before the study was begun and observed daily for general health. No medication (except the drugs mentioned in the study) was given. Dogs were fed with commercial canned food, and tap water was provided ad libitum.

Anesthetic procedure—Food was withheld from dogs for 24 hours. Anesthesia was induced by thiopental sodium^c administration (30 mg/kg, IV) without premedication. Anesthesia was maintained with isoflurane^d after endotracheal intubation, with an oxygen flow rate of approximately 1 L/min. End-tidal isoflurane concentration was maintained at about 1.7% and continuously monitored by use of an anesthetic analyzer.^e After the last measurement of cardiovascular variables, catheters were removed and anesthesia was stopped. Dogs were then allowed to recover under supervision.

MBF administration—Marbofloxacin (1% aqueous solution,^f 200 mg in 20 mL of sterile water) was administered IV via an indwelling catheter placed in the right cephalic vein according to the following modalities: 1) an IV bolus at 2 mg/kg, 30 minutes after the beginning of the recording of cardiovascular variables, and 2) an infusion at a rate of 40 mg/kg/h for 30 minutes (total dose, 20 mg/kg), 10 minutes after administration of the MBF bolus.

Measurement of cardiovascular variables—An aseptic technique was used to surgically exteriorize the right femoral vein. A thermodilution catheter^g was inserted into the femoral vein and positioned in the main pulmonary artery to measure the mean right atrial pressure (MRAP), systolic pulmonary artery pressure (SPAP), mean pulmonary artery pressure (MPAP), diastolic pulmonary artery pressure (DPAP), and cardiac output (CO) by thermodilution. The accurate placement of the catheter was ensured from the characteristic pressure wave patterns. Cardiac output was determined with 3 mL of iced 5% saline (0.9% NaCl) solution through a close injectable delivery system. Cardiac output was measured 3 times at 1-minute intervals, and the values were averaged.

The left femoral artery was surgically exteriorized and a catheter^h introduced to measure systolic aortic pressure (SAoP), mean aortic pressure (MAoP), diastolic aortic pressure (DAoP), systolic left ventricular pressure (SLVP), mean left ventricular pressure (MLVP), and diastolic left ventricular pressure (DLVP). An ECG (lead II) was continuously monitored. Heart rate (HR); RR, PR, and QT intervals; and QRS complex duration were determined. An ECG recording was printed before each determination of CO or if arrhythmia was observed.

After instrumentation, baseline data (except CO) were continuously monitored during a 30-minute control period.^c After IV administration of the bolus, all variables (pressures and ECG) were recorded continuously for 100 minutes. Cardiac output was determined at the end of the control period, at 5 minutes after the IV administration of the MBF bolus, at 15 and 30 minutes after the beginning of MBF infusion, and at 60 minutes after the end of the infusion.

Cardiovascular parameters—Stroke volume (SV), systemic vascular resistance (SVR), cardiac index (CI), stroke index (SI), cardiac power output (CPO), and cardiac power index (CPI) were determined from recorded cardiovascular variables by use of the following formulae¹⁶:

$$SV \text{ (mL)} = CO \text{ (mL/min)}/HR \text{ (beats/min)}$$

$$SVR \text{ (dyne}\cdot\text{s/cm}^5\text{)} = ([MAoP \text{ (mm Hg)} - MRAP \text{ (mm Hg)}) \times 80/CO$$

$$CI \text{ (mL/kg/min)} = [CO \text{ (L/min)}/\text{body weight (kg)}] \times 1,000$$

$$SI \text{ (mL/kg/beat)} = CI \text{ (mL/kg/min)}/HR \text{ (beats/min)}$$

$$CPO \text{ (W)} = ([MAoP \text{ (mm Hg)} - MRAP \text{ (mm Hg)}) \times CO \text{ (L/min)} \times 2.2167 \times 10^{-3}$$

$$CPI \text{ (W}\cdot\text{10}^{-3}\text{/kg)} = [CPO \text{ (W)}/\text{body weight (kg)}] \times 1,000$$

Blood sample collection—Samples for measurement of plasma concentration of MBF were obtained just before and 1 and 10 minutes after IV administration of the bolus, then 5, 10, 15, 20, and 30 minutes after the beginning of MBF infusion and 1 hour after the end of the infusion. Three milliliters of blood was directly obtained from the jugular vein, placed in a heparinized tube, and centrifuged (1,000 \times g, 10 minutes, 4°C). Three aliquots of plasma (0.5 mL) were stored at -20°C until analyzed.

MBF assay—Plasma MBF concentrations were determined by a validated high-performance liquid chromatography method with UV detection at 295 nm.¹⁰ Marbofloxacin was extracted from the plasma with chloroform, and ofloxacin was used as the internal standard. The separation was performed on a C18 reversed-phase column at 30°C.

Statistical analysis—Statistical analysis was performed with the use of a software program.ⁱ Data are expressed as mean \pm SD. Data were analyzed by use of a repeated-measures ANOVA for time effect, and a Dunnett test was performed between control values and those obtained following drug administration. A value of $P < 0.05$ was considered significant.

Results

Transient adverse clinical reactions (face edema, ear edema, or both) were observed in 3 dogs at 5 to 12 minutes after the start of MBF infusion. In another dog, an increase in respiratory rate for 1 to 2 minutes was observed at 7 minutes after the start of infusion. All dogs recovered rapidly from anesthesia at the end of the experiment, and no clinical signs of adverse drug effects were observed in the dogs during the days following the experiment.

A mean \pm SD plasma MBF concentration-versus-time profile was created (Figure 1). The mean maximal concentration observed after IV administration of the bolus of MBF was $8.9 \pm 2.4 \mu\text{g/mL}$. The mean peak

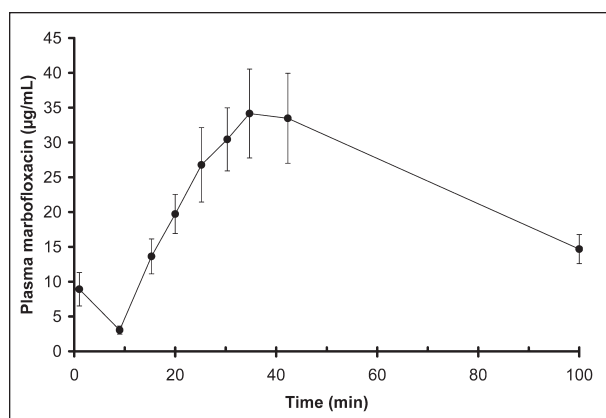


Figure 1—Arithmetic plot of mean \pm SD values of plasma marbofloxacin (MBF) concentration ($\mu\text{g/mL}$) versus time (min) determined from 6 healthy isoflurane-anesthetized dogs. Time 0 corresponds to IV administration of the bolus (at a dose of 2 mg/kg). Marbofloxacin IV infusion (20 mg/kg during a 30-minute period) was started 10 minutes after IV administration of the bolus.

Table 1—Mean \pm SD cardiovascular values in 6 healthy isoflurane-anesthetized dogs following IV administration of a bolus of marbofloxacin (time 0 minutes; 2 mg/kg) and IV infusion of marbofloxacin (started at time 10 minutes; 20 mg/kg over 30 minutes).

Time (min)	Cardiovascular variables					
	HR (beats/min)	SAoP (mm Hg)	DAoP (mm Hg)	MAoP (mm Hg)	SLVP (mm Hg)	MLVP (mm Hg)
0 (before bolus)	118 \pm 28	111 \pm 19	82 \pm 16	93 \pm 16	121 \pm 18	61 \pm 16
1	122 \pm 21	108 \pm 22	76 \pm 20	89 \pm 20	114 \pm 29	58 \pm 15
10	125 \pm 25	118 \pm 17	83 \pm 15	96 \pm 15	120 \pm 29	64 \pm 13
15	123 \pm 25	112 \pm 23	79 \pm 18	92 \pm 20	116 \pm 34	59 \pm 11
20	118 \pm 25	103 \pm 28	72 \pm 21	84 \pm 23	114 \pm 25	55 \pm 11
25	110 \pm 22	90 \pm 28†	65 \pm 17†	75 \pm 21†	101 \pm 30	48 \pm 12
30	105 \pm 20†	89 \pm 20†	63 \pm 12†	73 \pm 15†	96 \pm 29*	46 \pm 13*
35	101 \pm 18†	83 \pm 20†	59 \pm 14†	69 \pm 16†	90 \pm 28†	43 \pm 15†
40	99 \pm 18†	74 \pm 20†	51 \pm 11†	61 \pm 15†	91 \pm 16†	46 \pm 17*
100	107 \pm 25*	92 \pm 24†	61 \pm 13†	74 \pm 15†	93 \pm 40†	48 \pm 23

* , †, ‡ Values that are significantly ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively) different from control values (time 0 minutes).
HR = Heart rate. SAoP = Systolic aortic pressure. DAoP = Diastolic aortic pressure. MAoP = Mean aortic pressure. SLVP = Systolic left ventricular pressure. MLVP = Mean left ventricular pressure.

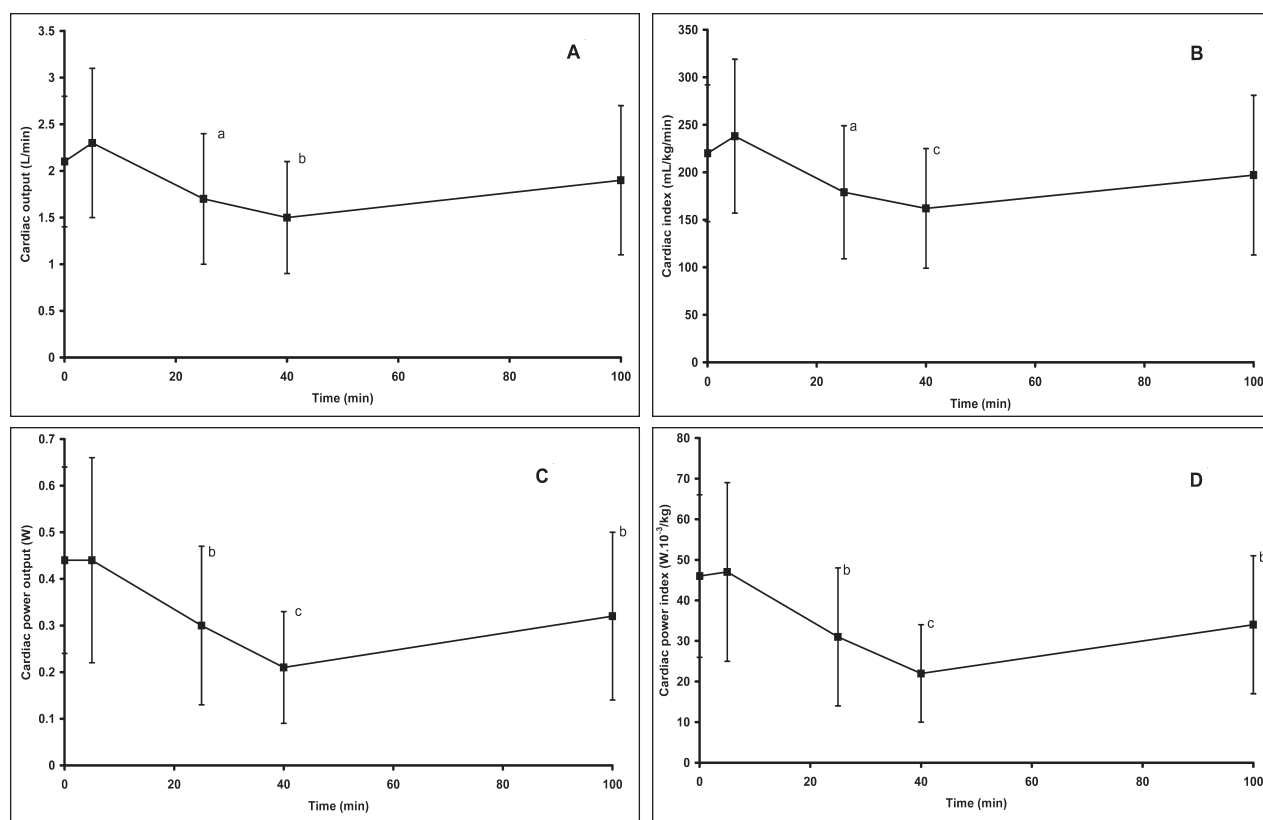


Figure 2—Effect of IV administration of MBF on cardiac output (A), cardiac index (B), cardiac power output (C), and cardiac power index (D) in 6 healthy isoflurane-anesthetized dogs. Values are expressed as mean \pm SD. Time 0 corresponds to IV administration of the bolus (at a dose of 2 mg/kg). Marbofloxacin IV infusion (20 mg/kg during a 30-minute period) was started 10 minutes after IV administration of the bolus. Letters a, b, and c indicate values that are significantly ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively) different from control values (time 0 minutes).

concentration during MBF infusion was $34.2 \pm 6.4 \mu\text{g/mL}$. One hour after the end of the infusion, the mean plasma concentration of MBF was $14.7 \pm 2.1 \mu\text{g/mL}$.

Values of DLVP, MRAP, SPAP, DPAP, MPAP, SV, SVR, and SI did not change during the study period; however, some significant changes in other cardiovascular variables were found (Table 1 and Figure 2). A signif-

icant decrease in HR was observed from 20 minutes after the start of infusion until the last measurement. A maximal 16% decrease was observed at the end of the infusion, but 1 hour later, the values were still significantly different (-9%) from control values. Significant decreases in SAoP, MAoP, and DAoP were observed from 25 minutes (ie, 15 minutes after the start of the infusion) until 100 minutes. For SAoP, a signif-

Table 2—Mean \pm SD values of ECGs in 6 healthy isoflurane-anesthetized dogs following IV administration of a bolus of marbofloxacin (time 0 minutes; 2 mg/kg) and IV infusion of marbofloxacin (started at time 10 minutes; 20 mg/kg over 30 minutes).

Time (min)	ECG variables	
	RR interval (ms)	QT interval (ms)
0 (before bolus)	496 \pm 80	269 \pm 34
5	501 \pm 94	272 \pm 37
25	557 \pm 108*	282 \pm 35
40	652 \pm 113†	297 \pm 35*
100	577 \pm 121†	302 \pm 45†

See Table 1 for remainder of key.

19% decrease was observed 15 minutes after the beginning of the infusion (ie, when a cumulative dose of 12 mg/kg had been infused). The corresponding mean plasma concentration was about 27 μ g/mL. The maximal effect, which corresponds to a mean value of 74 mm Hg (33% decrease, compared with basal value), was observed at the end of the infusion, when the plasma concentration of MBF was 34 μ g/mL. A maximal 38% decrease in DAoP was also observed at the same time. Aortic pressure values had still not returned to control values at 1 hour after the end of MBF administration. A similar effect was observed for SLVP and MLVP, but not DLVP, with a maximum 26% decrease in SLVP during the infusion phase. The decrease in SLVP was still apparent 1 hour after the end of infusion (–23%).

Cardiac output was significantly decreased, compared with control values, at 25 and 40 minutes after IV administration of the bolus, with a maximum decrease of 29%. Values had returned to control levels at 100 minutes. Cardiac power output and CPI were significantly decreased, compared with control values, from 25 minutes until 100 minutes with a maximum 52% decrease for CPO.

Ventricular premature complexes were observed in 4 dogs. Frequency was between 1 of 9 and 1 of 46 normal beats. In 1 dog, ventricular premature complexes were also observed during the control period. Effects of MBF administration on mean values of ECG variables were determined (Table 2). The RR interval and QT interval were significantly prolonged during and until 1 hour after MBF infusion, compared with control values, with a maximum increase of 31% and 12%, respectively. No significant variation was observed for PR interval and QRS complex duration.

Discussion

The experimental design of our study only permits conclusions regarding the combined effects of isoflurane and MBF, given that the cardiovascular effects of anesthesia alone were not studied. It should nevertheless be emphasized that the main objective of our study was to see whether the combined administration of isoflurane and different amounts of MBF could affect cardiovascular variables. The anesthetic protocol selected here also did not involve any preanesthetic agents because most of these agents can have cardiovascular effects. This absence of a preanesthetic agent is also the reason why high doses of thiopental were

required. Thiopental was selected because of its short half-life. Therefore, at the time of administration of the first dose of MBF—that is, 30 minutes after induction—the effect of thiopental could be considered negligible. Isoflurane was selected because it is the inhalation anesthetic agent most frequently used in veterinary medicine. Marbofloxacin could be administered at the equilibrium isoflurane concentration by monitoring the end-tidal concentration. Basal values of the cardiovascular variables observed in our study are similar to those previously described in healthy dogs anesthetized with isoflurane at 1 and 1.5 times the minimum alveolar concentration (MAC).¹⁷

The most pronounced and earliest effect observed following MBF infusion was a decrease in DAoP and SAoP. Hypotension, the most common complication encountered in anesthetized patients, corresponds to a mean arterial pressure of < 60 to 70 mm Hg.¹⁸ At the end of the infusion of MBF (ie, when a cumulative dose of 22 mg/kg had been given), dogs had a transient episode of hypotension. The MAoP increased to a higher value (74 \pm 15 mm Hg) 1 hour after the end of the infusion.

Hypotension may be induced by isoflurane inhalation and is proportional to the elevation of anesthetic depth.¹⁹ In our study, the steady state of the alveolar isoflurane concentration was maintained at 1.7%, which is approximately 1.3 MAC (isoflurane MAC for dogs, 1.28 \pm 0.06%).²⁰ Thus, it is unlikely that any changes in arterial blood pressure would be the result of changes in the alveolar concentration of the inhalant anesthetic agent or intrinsic properties of isoflurane, as the mean value of SAoP before dose administration was 111 mm Hg. Therefore, the observed hypotension was the result of the direct action of MBF, as previously described for other IV administered fluoroquinolones (enoxacin at 10 mg/kg, levofloxacin at 6 to 20 mg/kg, norfloxacin at 1 to 10 mg/kg, and ofloxacin at 10 mg/kg).⁴ As observed in our study, the effect of these fluoroquinolones on blood pressure was observed at lower concentrations of the test article than those required to obtain adverse cardiac effects.

The hypotensive effect of quinolones was considered to be induced by the release of histamine.⁴ Unfortunately, blood histamine concentrations were not assessed in our study. This mechanism might also be responsible for MBF-induced hypotension in dogs, when we consider the other adverse effects (especially edema) observed in some dogs in our study. The SVR was not modified, however, which suggests that hypotension was not caused by peripheral vasodilatation but by cardiac depression. The decrease in aortic pressure was partly explained by the decrease in CO, which was maximal at the end of MBF infusion, but the values returned to control levels 1 hour later. Again, the anesthetic agent cannot be responsible for such a decrease, as the CO in isoflurane-anesthetized dogs is sustained up to 2 MAC.²⁰ The alteration in CO is mainly explained by a decrease in HR, as stroke volume was not modified following MBF infusion. Similar effects have already been described in dogs for enoxacin, sparfloxacin, and norfloxacin.⁴

Inconsistent effects of antimicrobials on blood pressure in anesthetized dogs have been reported.^{13,14} A 50% decrease in SAoP was observed after rapid IV administration (60 mg/s) of chloramphenicol at a dose of 50 mg/kg.¹⁴ This effect was greater than that of MBF in our study. No cardiovascular effect was reported with sodium cephalosporin (22 mg/kg, IV), sodium cefoxitin (22 mg/kg, IV), and sodium ampicillin (22 mg/kg, IV) after a single IV administration in healthy anesthetized dogs.¹³

The minimal HR values were observed at the end of MBF administration (maximum 16% decrease in HR associated with a 31% increase in RR interval), but none of the dogs were considered to have developed bradycardia at any time. Such a decrease in HR has been reported for anesthetized dogs for chloramphenicol,¹⁴ sodium cephalosporin, sodium cefoxitin, and sodium ampicillin.¹³

The ECG parameters were unchanged except for RR and QT intervals. Prolongation of the QT interval may indicate a delay in repolarization of the cardiac Purkinje fibers, as has been described with sparfloxacin in rabbits.²¹ The maximal QT interval was observed 1 hour after the end of the infusion but remained moderate (12% increase). However, other fluoroquinolones such as sparfloxacin have been demonstrated to induce a significant increase in QT interval, leading to a predisposition to the onset of torsades de pointes.²² Such alterations in QT interval have been reported to be in relation with abnormalities in magnesium metabolism.²³ Ventricular premature beats were observed in our study, but their frequency was low. They could result from isoflurane anesthesia or the position of the catheters in the cardiac lumen, but unlikely from MBF itself.

In conclusion, IV administration of a single bolus of MBF at 2 mg/kg had no deleterious effect on cardiovascular variables in isoflurane-anesthetized dogs. At higher dose amounts (ie, at least a cumulative dose of 12 mg/kg), most of these effects were totally reversible at 1 hour after the end of drug administration. The margin of safety for MBF given IV at 2 mg/kg in isoflurane-anesthetized dogs seems adequate.

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