Hemodynamic Effects of Verapamil in Children and Adolescents with Hypertrophic Cardiomyopathy

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SUMMARY The acute hemodynamic effects of verapamil were evaluated in nine children with hypertrophic cardiomyopathy. Verapamil, 0.1 mg/kg, was administered as an i.v. bolus over 2 minutes, followed by a 20-minute continuous infusion of 0.007 mg/kg/min. Hemodynamic measurements were obtained at rest in nine patients and at maximal supine bicycle exercise in seven before and 15 minutes after verapamil. At rest, verapamil increased the mean cardiac output from 3.3 ± 0.9 to 3.7 ± 0.9 l/min/m² (± so) (p < 0.02) and decreased left ventricular end-diastolic pressure from 19.3 ± 8.1 to 14.5 ± 6.9 mm Hg (p < 0.006). In six patients with resting left ventricular outflow tract obstruction, the systolic pressure gradient decreased from 17.5 ± 7.2 to 5.2 ± 4.5 mm Hg (p < 0.04). Repeat supine bicycle exercise testing after verapamil showed increases in total work performed (1743 ± 1284 to 3168 ± 1643 kg.m, p < 0.006) and maximal cardiac index during exercise (6.5 ± 1.3 to 7.8 ± 1.81/min/m², p < 0.05), and decreases in maximal exercise left ventricular end-diastolic pressure (29.1 ± 10.1 to 19.3 ± 10.4 mm Hg, p < 0.002) and left ventricular systolic outflow tract gradient (31.2 ± 10.5 to 1.75 ± 1.7 mm Hg, p < 0.04). These results suggest that verapamil may be an effective therapeutic agent for the treatment of hypertrophic cardiomyopathy in children.

VERAPAMIL has been reported to improve symptoms and cardiovascular compromise in adults with hypertrophic cardiomyopathy. Acutely, verapamil has been shown to decrease both resting and maximal provokable left ventricular outflow tract pressure gradient,1,2 while increasing cardiac output.1 Chronic administration of the drug relieved symptoms,3-4 increased exercisecapacity5,6 and, possibly, diminished left ventricular hypertrophy.2 The effectiveness of verapamil is attributed primarily to its influence on left ventricular relaxation and filling.7-9 Changes in coronary circulation10-13 may have additional beneficial effect.

Although verapamil has been administered acutely and chronically to children to control supraventricular tachycardia,14-17 its hemodynamic effects and efficacy have not been tested in children with hypertrophic cardiomyopathy. We assessed the acute hemodynamic effects of verapamil at rest and during exercise in a pediatric population with hypertrophic cardiomyopathy.

Methods

Subjects

Nine patients, two females and seven males, ages 7 months to 19 years (mean 10.3 years) with hypertrophic cardiomyopathy constituted the study group (table 1). The initial diagnosis was made with M-mode or two-dimensional echocardiography, which demonstrated disproportionate septal thickening with respect to the left ventricular free wall (septal-to-free wall ratio ≥ 1.5) in eight of the nine patients. In the other patient (no. 5), two-dimensional echocardiographic studies demonstrated massive septal and left ventricular free wall thickening and regional disproportionate hypertrophy of the posterior septum; this patient also had systolic anterior motion of the mitral valve. The patients had no other congenital heart defects.

At cardiac catheterization, six of the nine patients had a resting systolic left ventricular outflow tract pressure gradient of 10 mm Hg or greater and a peak systolic pressure gradient of 30–139 mm Hg after provocation with the Valsalva maneuver (two patients), isoproterenol infusion to a heart rate of at least 150 beats/min (six patients), catheter-induced premature ventricular contractions (two patients) or supine exercise testing (seven patients). Patient 6 also had a resting peak systolic right ventricular outflow tract gradient of 45 mm Hg. These six patients (nos. 1, 3, 6, 7, 8 and 9) had an obstructive form of the disease (i.e., rest or provocable left or right ventricular peak systolic outflow tract gradient at least 30 mm Hg). Three patients had a nonobstructive form of the disease (resting systolic outflow gradients of 5 mm Hg or less and provokable gradients of less than 30 mm Hg (patients 2, 4 and 5).

All patients were symptomatic (table 1). The youngest patient (no. 6), a 7-month-old infant, had intractable congestive heart failure, recurrent episodes of cardiopulmonary arrest, and developed chronic bronchopulmonary dysplasia due to prolonged endotracheal ventilation and oxygen therapy. The remaining patients had marked resting or postexertional dyspnea. Six of the eight patients had angina and four had one or more episodes of postural hypotension or syncope. Patients 1, 6, 7 and 8 had received propranolol therapy, but had no relief of symptoms. Patient 1 had undergone left ventricular myomectomy 5 years previously. Three patients had a family history of hypertrophic cardiomyopathy. Sudden death and autopsy-proved hypertrophic cardiomyopathy were doc-
umented in the mother of patient 7 and the brother of patient 6, and the mother of patient 2 had catheterization-proved hypertrophic cardiomyopathy.

Seven of the nine patients had undergone diagnostic cardiac catheterization 2 months to 6 years previously (mean 2 years). The indication for participation in this study and recatheterization was persistence of severe symptoms despite adequate medical therapy. The patients or their parents gave informed consent. None of the patients had contraindications to administration of verapamil, i.e., sick sinus syndrome, atroventricular node disease, elevated pulmonary artery wedge pressures and severe left ventricular outflow tract obstruction, or systemic hypertension or hypotension. Before the study, propranolol was withheld for at least 2 weeks. Diuretics were discontinued the day before catheterization. Seven of the nine patients were premedicated with morphine sulfate, 0.1 mg/kg, and benadryl, 1 mg/kg.

### Hemodynamic Studies

Simultaneous left ventricular and thoracic aortic pressures were measured in all patients. Left ventricular pressure was obtained with a Millar micromanometer catheter and ascending thoracic aortic pressure with a UMI pigtail catheter that had an end hole and side holes. A thermodilution catheter (Instrumentation Laboratories) was used to measure cardiac output and pulmonary artery pressure. All catheters were inserted in the right and left femoral arteries and right femoral vein. Pressures were recorded with an Electronics for Medicine VR-12 optical recorder. Catheter entrapment was excluded by the guidelines proposed by Wigle et al. End-diastolic pressure was measured where the down slope of a "a" wave in the left ventricle crossed the initial upstroke of left ventricular pressure. After resting right- and left-heart hemodynamic assessment, seven of the nine patients underwent supine bicycle exercise testing on an electronically braked supine bicycle ergometer (Quinton Instruments). All patients were familiarized with the use of the supine bicycle ergometer (exercising at 200 kg-m/ min for about a minute) both the night before catheterization and just before the catheterization. Patients were exercised for 3–4-minute stages at progressively increasing work loads, beginning at 200 kg-m/min. Considerable verbal encouragement was given to each patient during the exercise test. The exercise end point in all patients was exhaustion. No patient developed angina during supine exercise. No patient complained of catheter discomfort during exercise or had to stop exercising because of hematoma formation.

For each patient, the total work (kg-m) performed to an exhaustive level during the continuous exercise test was calculated as the sum of the products of work load (kg-m/min) and exercise time (min) at each level of exercise. After each 3–4-minute cycle, left ventricular, aortic, and pulmonary artery pressures, heart rate, pulmonary artery oxygen saturation and cardiac output were recorded.

After the hemodynamic variables returned to baseline levels (30 minutes after exercise), verapamil was administered. An initial bolus of 0.1 mg/kg of verapamil given over 2 minutes was followed by a 20-minute continuous infusion of 0.007 mg/kg/min. After the infusion, resting hemodynamic variables were measured, the exercise test was repeated, and plasma verapamil concentrations were measured by gas chroma-
The cardiac index increased from 2.2 to 3.7 (range 1.1 to 4.3) 15 minutes after the verapamil infusion. All recordings were made with an Irex System 2 recorder and a 5.0- or 3.5-MHz transducer at a paper speed of 100 mm/sec; an ECG was recorded simultaneously. Left ventricular dimension was recorded while the interventricular septum and left ventricular posterior wall were monitored at a level inferior to the insertion of the mitral valve leaflets. End-diastolic diameter was determined at the onset of the QRS complex on the ECG. Systolic diameter was measured at the peak of posterior left ventricular wall motion. Left ventricular shortening fraction was determined by subtracting end-systolic diameter from end-diastolic diameter and dividing the remainder by the end-diastolic diameter. Aortic valve closure and mitral valve opening were not simultaneously identified, but mitral opening and aortic closure were measured at identical heart rates. The left ventricular isovolumic relaxation time was calculated by subtracting the time from onset of the Q wave to aortic valve closure from the onset of the Q wave to mitral valve opening.

Statistics
The data are presented as mean ± SD. Comparisons were made by the paired t test; the experimental alpha error rate was 5% (Bonferroni method).

Results
Resting Hemodynamics
After verapamil, the mean arterial blood pressure decreased from 82 ± 9 to 73 ± 7.5 mm Hg (p < 0.05) (fig. 1). Although heart rate increased slightly after verapamil in six of nine patients, the change in mean heart rate (91 ± 21 to 96 ± 12 beats/min) was not statistically significant (fig. 1). The mean cardiac index at rest in the nine patients was 3.3 ± 0.9 l/min/m² (range 2.2–4.1 l/min/m²) and after verapamil infusion increased to 3.7 ± 0.9 l/min/m² (p < 0.02) (fig. 2). The cardiac index increased in all but one patient, in whom it did not change. The mean resting left ventricular end-diastolic pressure decreased from 19.3 ± 8.1 to 14.5 ± 6.9 mm Hg (p < 0.006). The mean resting peak systolic left ventricular outflow tract gradient diminished from 17.5 ± 7.2 to 5.2 ± 4.5 mm Hg (p < 0.04) in all six patients with outflow obstruction. In patient 6, verapamil also eliminated the resting right ventricular outflow tract gradient of 45 mm Hg. The mean pulmonary artery pressure decreased from 26.3 ± 9.4 to 23.3 ± 6.3 (NS) after verapamil. The double product (LV systolic pressure × heart rate), an estimate of myocardial oxygen consumption, decreased after verapamil from 10,343 ± 3093 to 9243 ± 1899 mm Hg/min (NS).

Exercise Hemodynamics
At peak exercise after verapamil, cardiac index increased and left ventricular end-diastolic pressure and
peak systolic ejection gradient decreased (fig. 3). At maximal exercise in seven patients, verapamil increased cardiac index from $6.5 \pm 1.3$ to $7.8 \pm 1.8\, l/min/m^2$ ($p < 0.05$). Left ventricular end-diastolic pressure at maximal exercise decreased from $29.1 \pm 10.0$ to $19.3 \pm 10.4\, mm\, Hg$ ($p < 0.002$). In the five patients with obstructive disease, the left ventricular outflow tract gradient at peak exercise decreased from $31.2 \pm 10.5$ to $1.75 \pm 1.7\, mm\, Hg$ ($p < 0.04$). The mean pulmonary artery pressure at peak exercise decreased from $33.3 \pm 13.0\, mm\, Hg$ before verapamil to $25.7 \pm 12.2\, mm\, Hg$ after verapamil ($p < 0.001$).

In all patients, the exercise performance level increased (fig. 4). The total work performed on the bicycle increased from $1743 \pm 1152$ to $3168 \pm 1517\, kg-m$ ($p < 0.006$). Verapamil caused no significant change in the heart rate, pulmonary artery saturation or oxygen consumption at peak exercise (fig. 4).

Although there was only a small decrease in double product at peak exercise after verapamil (fig. 4), more work was performed in reaching that end point. Figure 5 depicts the decrease in double product at each stage of exercise before and after verapamil in patient 7. After verapamil, the double product at maximal exercise was nearly the same despite the greater total work performed. In addition, the double product generated at each stage of exercise was lower after verapamil.

**Echocardiographic Data**

Although verapamil induced no significant change in left ventricular shortening fraction, left ventricular end-diastolic dimension increased and left ventricular isovolumic relaxation time decreased in all but two patients (table 2). Left ventricular end-diastolic dimension increased from $3.2 \pm 1.0$ to $3.5 \pm 1.0\, cm$ ($p = 0.06$), and mean isovolumic relaxation time decreased from $52.6 \pm 17.4$ to $36.1 \pm 16.6\, msec$ ($p < 0.05$).

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**Figure 3.** Effect of verapamil on cardiac index, left ventricular end-diastolic pressure (LVEDP), systolic left ventricular (LV) outflow gradient and pulmonary artery mean pressure generated at maximal bicycle exercise. Values are mean ± SD.
Complications

Patient 5 developed sinus bradycardia and junctional escape rhythm at a stable rate shortly after verapamil infusion. PR interval prolongation occurred in all of the remaining patients after verapamil infusion (table 3). The mean PR interval was 142 ± 12 msec before verapamil and increased to 177 ± 24 msec (p < 0.01) after verapamil. Although the mean arterial blood pressure decreased after verapamil, no patient became symptomatic or had the infusion stopped because of hypotension. All patients received the same i.v. dose of verapamil, but their plasma verapamil levels varied widely (table 3). In addition, neither electrophysiologic effect (PR interval prolongation) nor hemodynamic effects (decreases in left ventricular end-diastolic pressure, left ventricular outflow tract gradient and isovolumic relaxation time) were related to the plasma verapamil concentration.

Discussion

Our study demonstrates that verapamil administered intravenously to children with hypertrophic cardiomyopathy decreases resting left ventricular outflow tract gradient and left ventricular end-diastolic pressure and increases cardiac output. In addition, our patients showed little change in mean resting heart rate after verapamil. The mean arterial blood pressure diminished from 82 ± 8.4 to 73 ± 7.5 (p < 0.05) after verapamil (fig. 1), but was not accompanied by symptoms of hypotension.

Supine bicycle exercise testing, performed to assess exercise tolerance and provoke an increase in left ventricular outflow tract gradient, yielded similar changes: maximal cardiac index, left ventricular outflow tract gradient and left ventricular end-diastolic pressure generated at exercise improved after i.v. verapamil.

Studies in adults with hypertrophic cardiomyopathy have demonstrated improvement in exercise capacity after long-term oral verapamil therapy.3,5 There have been no previous reports of the acute effects of verapamil on exercise hemodynamics in patients with hypertrophic cardiomyopathy. Our patients demonstrated a marked increase in work performance after verapamil, yet the heart rate and pulmonary artery saturations at maximal exercise were not significantly different from the pre-verapamil values. The increase in work performance after verapamil was accompanied by an improved utilization of myocardial oxygen, as reflected by the rate-pressure product24 (fig. 5).

The influence of training on exercise capacity was minimized by acquainting the patient with the ergometer before testing. The possible placebo effect of verapamil was not evaluated in this study. However, the

Table 2. Echocardiographic Changes After Verapamil

<table>
<thead>
<tr>
<th>Pt</th>
<th>Before</th>
<th>After</th>
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<td>3.7</td>
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<td>0.44</td>
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<td>3.8</td>
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<tr>
<td>9</td>
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<td>0.45</td>
<td>3.3</td>
<td>3.5</td>
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<td>15</td>
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<tr>
<td>Mean</td>
<td>0.45</td>
<td>0.44</td>
<td>3.2 ± 1.0</td>
<td>3.5 ± 1.0</td>
<td>52.6 ± 17.4</td>
<td>36.1 ± 16.6</td>
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<td>± SD</td>
<td>±0.08</td>
<td>±0.09</td>
<td>±1.0</td>
<td>±1.0</td>
<td>±17.4</td>
<td>±16.6</td>
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</tbody>
</table>

*p < 0.05 vs pre-verapamil.
patients were not aware of how much exercise they had performed before verapamil, and no patient was encouraged to exercise past exhaustion.

All patients appeared to exercise to the same degree of exhaustion in both exercise tests, by subjective assessment and as documented by similar decreases in pulmonary artery saturation at maximal supine exercise (39 ± 14% before verapamil and 43 ± 9% after verapamil) and similar increase in oxygen consumption at maximal supine exercise (656 ± 105 ml O₂/min/m² before verapamil and 725 ± 146 ml O₂/min/m² after verapamil).

With regard to the possibility that the improved exercise performance after verapamil could have been due to a training effect, Stamford et al.25 showed that with repeat exercise testing on the same day, one would expect similar maximal oxygen consumptions (as seen in our patients) and a diminished exercise endurance rather than the marked increase in endurance that we observed in our patients (fig. 4). In addition to the marked increase in work performance after i.v. verapamil, we also observed a significant decrease in exercise-induced left ventricular outflow tract gradient and a marked decrease in both the peak exercise left ventricular end-diastolic pressure and the mean pulmonary artery pressure. The diminution in both peak exercise pulmonary artery pressure and left ventricular end-diastolic pressure in our patients after verapamil may explain why dyspnea on exertion is one of the major symptoms that improves with chronic verapamil therapy.

Even though numerous studies have suggested that the primary pharmacologic effect of verapamil on the heart is to inhibit calcium flux across the myocardial muscle cell membranes,8, 26-31 how this inhibition of calcium flux results in the beneficial hemodynamic effects observed in our patients with hypertrophic cardiomyopathy is unclear. Verapamil has been shown in vivo32, 33 to depress myocardial contractility, which could explain the decrease in left ventricular outflow tract obstruction in our patients who had outflow tract obstruction. However, there was no evidence of depressed myocardial function after verapamil, in that cardiac index increased and echocardiographically determined left ventricular shortening fraction remained stable. Others have shown that verapamil does not alter left ventricular contractility in either healthy middle-aged men34 or patients with cardiomyopathy.7 Therefore, it seems unlikely that depression of myocardial contractility is the major mechanism responsible for the verapamil-induced decrease in left ventricular outflow tract gradient observed in this and other studies.

In addition to ventricular outflow tract obstruction and hypercontractile myocardial function, patients with hypertrophic cardiomyopathy also have impaired diastolic function.6, 7, 35-38 Prolonged isovolumic relaxation,6, 36, 38 diminished rapid diastolic filling rates,6, 7, 35-38 prolonged rapid diastolic filling period7, 36, 37 and increased chamber stiffness35 have all been reported in patients with hypertrophic cardiomyopathy. Verapamil has been shown to improve several indexes of left ventricular filling and relaxation, including isovolumic relaxation time,6 regional left ventricular dimension,6 rate of left ventricular posterior wall thinning,6 peak filling rate and time to peak filling rate.7 Our patients also had better diastolic function, as documented by decreases in left ventricular isovolumic relaxation times, resting left ventricular end-diastolic pressure, mean pulmonary artery pressure and left ventricular end-diastolic pressure generated at exercise. Although we did not document a statistically significant increase in echocardiographically determined left ventricular end-diastolic dimension, left ventricular end-diastolic dimension increased in eight of nine patients. Also, the decrease in left ventricular outflow gradient after verapamil may be due to improved diastolic filling and a concomitant increase in left ventricular chamber or outflow tract size.

Although resting PR interval increased in all of our patients, a single episode of sinus bradycardia was the only potentially serious side effect noted. However, children with serious conduction system disease or the combination of elevated left ventricular end-diastolic pressure (> 20 mm Hg) and severe left ventricular outflow tract obstruction (resting gradient ≥ 50 mm Hg) were excluded from the study, as verapamil is contraindicated in these patients.38

Finally, despite the administration of similar i.v. doses of verapamil, the patients had a wide range of plasma verapamil levels. The range of plasma levels

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### Table 3. Relationship of Plasma Verapamil Level to Electrophysiologic and Hemodynamic Effects

<table>
<thead>
<tr>
<th>Pt</th>
<th>Postinfusion verapamil level (ng/ml)</th>
<th>Postinfusion norverapamil level (ng/ml)</th>
<th>ΔPR interval (msec)</th>
<th>ΔResting LVEDP (mm Hg)</th>
<th>ΔResting LVOT (mm Hg)</th>
<th>ΔIVR (msec)</th>
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</thead>
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</table>

Abbreviations: ΔPR = change in resting PR interval; ΔLVEDP = change in resting left ventricular end-diastolic pressure; ΔLVOT = change in resting systolic left ventricular outflow tract gradient; ΔIVR = change in isovolumic relaxation time.
was considerably greater than in normal adult volunteers,\textsuperscript{39} which suggests greater variability in the metabolism of verapamil among children. We do not yet know what the relationship is between the i.v. dose used in this study and the presently recommended oral dose of the drug. As with other drugs that have a high hepatic extraction from the portal blood, there will probably be great individual variation in plasma level for a given oral dosage. Drug levels in children receiving this medication should be carefully monitored to determine the ideal dose schedule for prolonged oral therapy.

In conclusion, our data in nine children with obstructive or nonobstructive hypertrophic cardiomyopathy indicate that i.v. verapamil markedly improves resting and exercise hemodynamics and has few side effects. The effects of chronic verapamil administration in children with hypertrophic cardiomyopathy are unknown and are presently under investigation. Adequate chronic therapy may require rigorous monitoring of blood levels of the drug. Should chronic administration of oral verapamil result in continued improvement of hemodynamic and symptomatic status as it has in adults, it may be an extremely effective therapeutic agent for hypertrophic cardiomyopathy in children.

Acknowledgment

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References

33. Newman RK, Bishop VS, Peterson DF, Leroux EJ, Horwitz LD:
The Effects of Reperfusion and Retrograde Coronary Flow Bleeding After Coronary Occlusion on Induced Electrical Instability in the Dog

B.A. Jones-Collins, M.D., and R.E. Patterson, M.D.

SUMMARY Reperfusion achieved by streptokinase infusion early after myocardial infarction (MI) is now being performed in patients, but the effect on electrical instability of increasing or decreasing perfusion in the region at risk for MI is unknown. Accordingly, 34 dogs were randomized to control (13 dogs), reperfusion (11 dogs) and retrograde bleeding (10 dogs) groups. All dogs underwent coronary artery occlusion (23 of the left anterior descending and 11 of the circumflex artery). In the control dogs, occlusion was permanent. In the reperfused dogs, the occlusion was released at 2 hours. In the retrograde bleeding dogs, retrograde flow bleeding distal to the occlusive tie was continued for 2 hours after coronary occlusion. Four days later, all dogs underwent a standard right ventricular pacing protocol. Induced arrhythmias were scored: ventricular fibrillation was assigned the highest score, followed by sustained ventricular tachycardia, nonsustained ventricular tachycardia and repetitive ventricular response. Arrhythmias provokable later in diastole were assigned higher scores than those provokable early in diastole. Infarct size was not different in the three groups (35%, 28% and 39% of the area at risk in control, reperfusion and retrograde bleeding groups, respectively). However, the electrical instability index was lower in the reperfusion group than in the other two groups (e.g., electrical instability index $A$ at 200 beats/min: $p < 0.005$ for reperfusion vs control; $p < 0.01$ for reperfusion vs retrograde bleeding). Retrograde bleeding did not alter the electrical instability index from the control state. These results suggest that despite no significant reduction in infarct size, reperfusion after infarction may reduce electrical instability.

Reperfusion after 2 hours of coronary occlusion and retrograde drainage of collateral flow during the first 2 hours of occlusion were selected as interventions expected to decrease and increase ischemic injury, respectively. Electrical instability was defined for the purpose of this study by the ease of induction of ventricular arrhythmias by programmed right ventricular stimulation.

Methods

Animal Preparation

Thirty-eight foxhounds of either sex, weight 19–37 kg, underwent thoracotomy. Four had a “sham” operation in which the left anterior descending coronary artery was dissected, but not occluded. The 34 other dogs received an acute occlusion, 23 of the left anterior descending and 11 of the circumflex coronary artery. The dogs were randomized into three groups: control (13 dogs), reperfusion (11 dogs) and retrograde bleeding (10 dogs). Lidocaine was given as a 60-mg i.v. bolus before occlusion, and was continued as a 3-mg/min continuous infusion throughout the surgical and
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