Different Relations Between Infarct Size and Occluded Bed Size in Barbiturate-Anesthetized Versus Conscious Dogs

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The relation between infarct size and occluded bed size in barbiturate-anesthetized (n = 32) and conscious (n = 34) dogs was compared using models of the left anterior descending (n = 43) and circumflex (n = 23) coronary arteries with 2 day old infarcts. Infarct and occluded bed (postmortem coronary arteriography) masses were measured by computerized planimetry of weighed left ventricular rings. For either type of occlusion, infarcts were larger in anesthetized than in conscious dogs (56 versus 33% occluded bed, $p < 0.001$), with greater slopes of the linear regressions between infarct size and occluded bed size ($p < 0.001$) and less epicardial sparing ($p < 0.05$) on topographic mapping. Although arterial and left atrial pressures were similar in the two groups, heart rates were higher in the anesthetized dogs, both before (127 versus 88 beats/min, $p < 0.001$) and after (151 versus 109 beats/min, $p < 0.001$) occlusion.

Myocardial blood flow distribution (radioactive microspheres, n = 33) favored the epicardium in anesthetized dogs, with lower endocardial-epicardial flow ratios pre- and postocclusion. Also, the level of total plasma catecholamines (radioenzymatic assay) was higher in barbiturate-anesthetized (n = 5) than in conscious (n = 5) dogs. Increasing the heart rate in conscious dogs (n = 18) to that of the anesthetized group (139 beats/min) by pacing produced larger infarcts and greater linear regression slopes, as seen in anesthetized dogs. Decreasing the heart rate in anesthetized dogs (n = 7) to that of the conscious group (98 beats/min) by sinoatrial node destruction and pacing resulted in smaller infarcts and lower linear regression slope, as seen in conscious dogs. Thus, the larger infarcts in barbiturate-anesthetized dogs appeared to be related mainly to the tachycardia, although transmural maldistribution of flow and increased circulating catecholamines might have contributed.

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Anesthetized and conscious dog models are commonly used to study the effect of therapies on myocardial infarct size. Coronary occlusion is done either 1) under barbiturate anesthesia, with the chest opened (1), or 2) in the fully awake or mildly sedated animal, after recovery from surgery (2–8). Events in the early hours after coronary occlusion determine the extent of ultimate myocardial necrosis (9) and infarct size in anesthetized dogs might differ from that in conscious dogs because of the combined effects of anesthesia and surgical trauma.

The primary aim of this study was to examine the linear regressions and topographic relations between infarct size and occluded bed size, defined by stereoscopic postmortem coronary arteriography, in barbiturate-anesthetized (1) and conscious (2–7) dogs with left circumflex or anterior descending occlusions. Previous studies (1–8) showed that comparison of the slopes and intercepts of linear regressions after permanent coronary occlusion is a sensitive approach for detecting the effect of therapy during acute infarction. Also, the arteriographic method of defining occluded bed size was shown to be reproducible (1–5,7,8,10) and permitted mapping of infarcts (1–5,7,8), flow (1–5,7,8,11) and mechanical abnormalities (12) in relation to a fixed anatomic reference.

The analysis of infarct size relative to occluded bed size recognizes that: 1) coronary anatomy is variable and results in a wide range of occluded bed and infarct sizes despite occlusions at similar anatomic locations, but a direct relation exists between infarct size and occluded bed size; 2) infarcts are smaller than the occluded beds, leaving variable rims of uninfarcted myocardium in the occluded beds; and 3)

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small occluded beds, less than 10 to 20% of left ventricular mass, are usually associated with no infarcts (1,2). This last fact has an important "dilution" effect on group comparisons of infarct mass (in grams or as percent of left ventricular mass). Because of this effect, larger numbers of dogs are needed to detect effects of therapy than are needed to compare linear regressions (2–5,7,8).

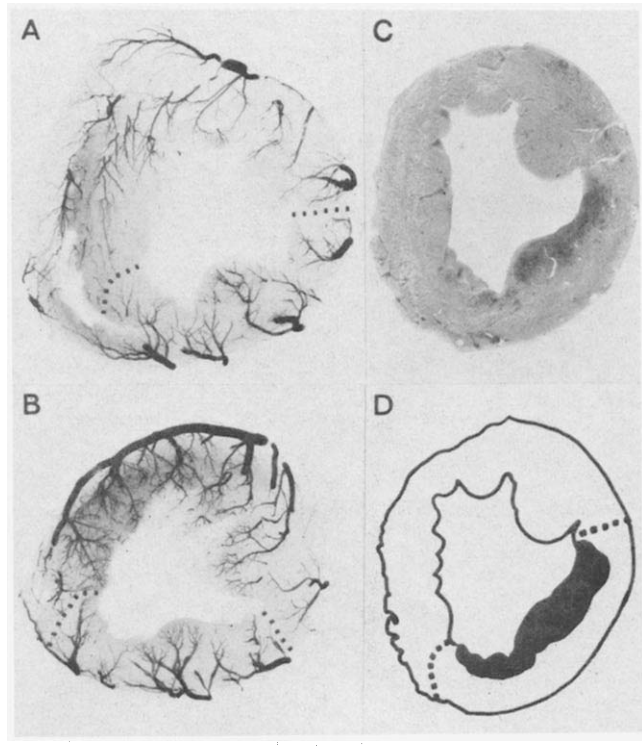
A secondary aim was to clarify some possible mechanisms for differences in infarct size between barbiturate-anesthetized and conscious dog models.

Methods

Experimental procedure. Experiments were done in 116 healthy mongrel dogs weighing 14 to 20 kg. The first 82 dogs were randomized for coronary artery occlusion under barbiturate anesthesia (n = 41) or in the conscious state (n = 41) and for measurement of infarct size 2 days after occlusion (2,11). All dogs were instrumented under general anesthesia (intravenous sodium pentobarbital, 30 mg/kg body weight) and through a left lateral thoracotomy with 1) a plastic occluder snare around the left anterior descending or circumflex artery distal to the first diagonal or marginal branch, and 2) plastic catheters in the external jugular vein, right common carotid artery and left atrium. The time required for instrumentation and chest closure averaged 60 minutes (range 50 to 70). In the anesthetized group, occlusion was produced 60 minutes (range 50 to 70) after barbiturate was given and 30 minutes before the chest was closed. A second dose of intravenous barbiturate (5 mg/kg) was given 2 to 3 hours after occlusion to maintain anesthesia. In the conscious group, occlusion was performed 7 to 10 days after surgery in 36 survivors, with the dogs standing in a sling, and 30 minutes after intravenous morphine (0.3 mg/kg) for analgesia and light sedation. In both groups, left atrial and aortic pressures (Statham P23Db) and lead II of the electrocardiogram were recorded continuously on a multichannel recorder (Gould) for 10 minutes before and 4 hours after occlusion. Five minutes after occlusion, all dogs received intravenous lidocaine (1 mg/kg) to suppress ventricular arrhythmias. Arterial blood gases and results on hemograms were within the normal range in all dogs, with no difference between groups.

Measurement of infarct size and occluded bed size. The 66 dogs surviving 2 days were reanesthetized and given a lethal dose of intravenous potassium chloride. The heart was removed, washed and weighed. Infarct size and occluded bed size were measured as described previously (2). Stereoscopic postmortem coronary arteriography was performed on all fresh hearts using simultaneous pressure-controlled injections of the three coronary arteries and the occluded vessel with a barium sulfate-gelatin mass. Monastral dyes (Du Pont Company) were added to the injectates to facilitate sampling for flow. After injection, hearts were packed with gauze to preserve diastolic proportions and fixed in 10% buffered formalin for 48 hours. Each heart was then radiographed in two perpendicular planes and filling of vessels proximal and distal to the occlusion was confirmed on all arteriograms. Beginning at the level of the occlusion, 11 transverse sections were made, giving 10 sections (5 to 7 mm in thickness) below the occlusion. All sections were radiographed with metallic markers to facilitate orientation, and anatomic boundaries between occluded and unoccluded vascular beds were marked on paired coded radiographs by two observers with no knowledge of the gross appearance of the sections (Fig. 1). The overlap of vessels across boundary markings was minimal (upper sections 1 to 2 mm, apical section 1 to 3 mm). Boundaries drawn by two observers differed by 1 to 2 mm, whereas those made by the same observers had to be shifted by 1 to 3 mm in 5% of the cases, mainly in the septal region of the first few sections. Inter- and intraobserver differences in marking the boundaries were negligible (<1% occluded bed, as percent of left ventricular mass) and were resolved

Figure 1. Delineation of anatomic boundaries of occluded bed and infarct. **A** and **B,** Boundaries of the occluded bed (**dotted lines**) in left ventricular ring radiographs of two slices from a heart after postmortem coronary arteriography performed after left circumflex occlusion. **C,** Infarct in the left ventricular ring corresponding to the slice shown in **panel A**. **D,** Superimposed outlines of the left ventricular ring, occluded bed and infarct from the slice shown in **panels A** and **C**.



by consensus. The average interobserver error in the 66 hearts was 1 mm (±1 SD).

Left ventricular transverse sections were weighed and outlines of the sections and infarcts drawn on plastic overlays, without knowledge of interventions. Markings of the occluded bed were copied on these outlines. Area and dimensions of the infarct, occluded bed and whole section were measured by computerized planimetry (HP 9835A computer and 9874A digitizer), and infarct and occluded bed masses were computed for each section and each left ventricle as described previously (2,7,11). The mass of infarcted myocardium was expressed as percent of occluded bed mass. Topographic maps of the infarct and occluded bed in each section were plotted from linear and angular measurements (Fig. 2); average maps were generated by computer for corresponding sections in different groups and data reduced to five equally spaced sections (7).

Measurement of regional myocardial blood flow. Flow was measured in 20 anesthetized and 20 conscious dogs with left circumflex (n = 20) or anterior descending (n = 20) artery occlusion, using 7 to 10 μm diameter microspheres labeled with cerium-141, ruthenium-103, chromium-51 or scandium-46 (New England Nuclear) and suspended in 20% dextran and 0.01% polysorbate 80 (Tween 80). As described previously (2,7,11), the microspheres were sonicated for 5 minutes before use; 4×10^6 microspheres (20 μCi) were injected into the left atrium and flushed by 5 ml saline solution over 10 seconds; and reference arterial blood was withdrawn (2.06 ml/min) on a calibrated pump for 30 seconds before and 2.5 minutes after each injection. Measurements were made 5 minutes before occlusion and at 30 minutes and 4 hours after occlusion. After quantitation of infarct and occluded bed size, transmural myocardial samples (2 to 3 g) were taken from three regions of the left ventricular sections: infarct center, infarct margin and uninfarcted lateral "border" regions (normal-appearing zone within marked boundaries and 1 to 5 mm away from the infarct margin) of the occluded bed as well as from the center of the nonoccluded bed. Samples were divided into inner and outer halves, which were weighed and counted for radioactivity in a gamma scintillation counter (Tracor Northern 2250).

Flow (ml/min per g) was computed as follows: flow = $(C_M \times R/C_R)$, where C_M = corrected counts per gram in myocardial samples, R = withdrawal rate of reference blood and C_R = counts in reference blood. Flows were analyzed before and after correction for microsphere loss (13–15). Correction was made by dividing flow in each region by the corresponding ratio of preocclusion flow in ischemic and nonischemic regions (4,5,16).

Catecholamines. Plasma catecholamines were measured in five anesthetized and five conscious dogs using the radioenzymatic assay of Peuler and Johnson (17). Arterial and venous blood were sampled hourly for the first 4 hours after anterior descending artery occlusion.

Pacing experiments. In 34 other instrumented dogs, pacing wires were sutured to the right ventricle and connected to a pacemaker (Medtronic 5330, atrioventricular sequential, demand, 3 mA). First, 22 conscious dogs were paced at the average heart rate of the anesthetized group (139 beats/min); circumflex (n = 11) or anterior descending (n = 11) artery occlusion was made and pacing continued for 4 hours after occlusion. Second, 12 barbiturate-anesthetized dogs were paced, after sinoatrial node destruction, at the average rate of the conscious group (98 beats/min) and pacing continued for 4 hours after anterior descending artery occlusion. The sinoatrial node was located by applying dry ice (CO_2 snow, −76°C) to the right atrium, further cooled until the heart rate was persistently below 60 beats/min and then crushed with a clamp and plicated to ensure destruction (necrosis confirmed by subsequent histologic study in each case). In both experiments, infarct and occluded bed sizes were measured 2 days later.

Histology. Histologic sections of samples from central regions of the occluded beds were made in the same planes as the planimetrically measured top surfaces, stained with hematoxylin-eosin and total histologic necrosis was assessed morphometrically and expressed as percent of the sample area. Histologic criteria for necrosis included pyknosis, karyorrhexis, karyolysis, fiber fragmentation, polymorphonu-

Figure 2. Actual computer map of the infarct, occluded bed and left ventricular (LV) ring at the papillary muscle level. The center of the inner endocardial contour was computed. **Points** along inner and outer contours are at 5° intervals. Linear measurements were made along or between selected radii as well as between appropriate pairs of points within the occluded bed. Radii were drawn at intersections of the inner perimeter with the infarct and occluded bed (**large dots**) so that angular extents of the infarct (α) and lateral rims of the uninfarcted myocardium within the occluded bed (β_1 and β_2) could be measured. Intersections of the occluded bed boundaries with the outer perimeter and the right ventricle with the left ventricular ring (A and P) were also recorded (**large dots**). Data from corresponding rings of all hearts within a group were used to compute the average map for that group.

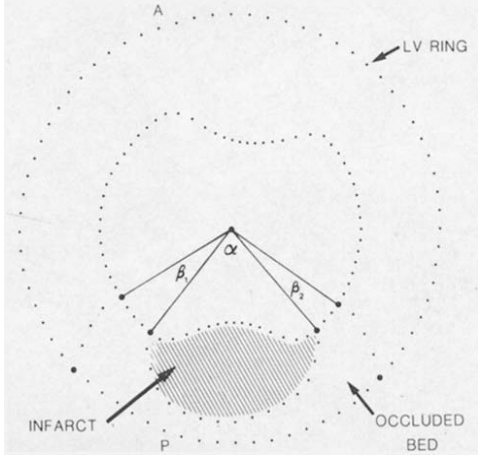


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Table 1. Occluded Bed and Infarct Sizes in Barbiturate-Anesthetized and Conscious Dogs

Coronary Occlusion Group	Infarct Mass (g)	Occluded Bed Mass (g)	LV Mass (g)	Occluded Bed/LV (%)	Infarct/ Occluded Bed (%)
Circumflex					
Anesthetized (n = 17)	16 ± 2	31 ± 2	87 ± 6	36 ± 2	50 ± 3†
	(2–24)	(17–43)	(52–145)	(23–47)	(0–65)
Conscious (n = 26)	13 ± 2	35 ± 3	84 ± 3	40 ± 2	32 ± 4
	(0–37)	(9–78)	(56–128)	(17–59)	(0–55)
Anterior descending					
Anesthetized (n = 15)	13 ± 2	19 ± 2	79 ± 6	23 ± 2	67 ± 4†
	(0–31)	(6–40)	(50–131)	(7–30)	(25–88)
Conscious (n = 8)	10 ± 3	22 ± 3	81 ± 6	27 ± 5	38 ± 7
	(0–25)	(8–39)	(52–104)	(10–54)	(0–63)
Total group					
Anesthetized (n = 32)	14 ± 1	25 ± 2*	83 ± 4	29 ± 2†	56 ± 3§
	(0–31)	(6–43)	(50–145)	(7–47)	(0–88)
Conscious (n = 34)	12 ± 2	32 ± 2	83 ± 3	37 ± 2	33 ± 3
	(0–37)	(8–78)	(52–128)	(10–59)	(0–63)

*$p < 0.05$, †$p < 0.01$, §$p < 0.001$, respectively, comparing anesthetized with conscious groups or subgroups. Values in parentheses represent range. Values are mean ± SEM. LAD = left anterior descending artery; LC = left circumflex artery; LV = left ventricle.

clear cell infiltration, loss of fiber cross striations and deep eosinophilic appearance of fibers (9). More than two criteria had to be present before the tissue was classified as necrotic. The percent of visual necrosis determined by planimetry agreed with the percent of histologic necrosis (visual = 0.97 histologic + 5.89; r = 0.95, n = 50, $p < 0.001$), in agreement with previous studies (2–5,7).

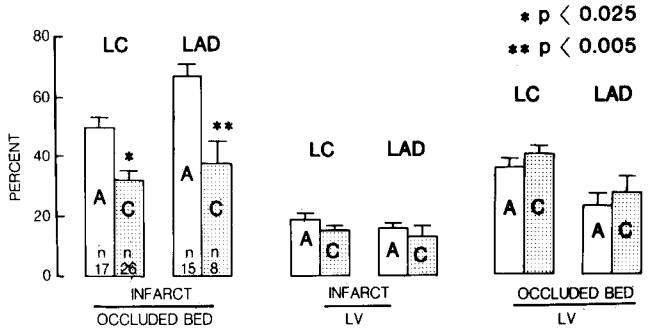
Statistics. The following statistical methods were used: 1) analysis of variance (ANOVA) for the significance of differences within and among groups; 2) linear regression analysis by the least square fit method, and the significance of r values and slopes by ANOVA; 3) the 2 × 2 chi-square (with ANOVA) for significance of differences in event frequency between groups; 4) ANOVA for the two postocclusion flows within groups; and 5) repeated measures ANOVA for hemodynamic changes. Results are given as mean ± standard error. The level of statistical significance was $p < 0.05$.

Results

Infarct size as percent of occluded bed size. The infarct data for barbiturate-anesthetized versus conscious groups and left circumflex versus left anterior descending coronary artery occlusion subgroups are summarized in Table 1. The larger occluded bed in the conscious group was probably related to the greater mortality in the anesthetized group (9 of 41 versus 2 of 36, chi-square = 4.21, $p < 0.05$). Infarct size as percent of occluded bed was greater in the anesthetized than in the conscious dogs (Fig. 3) for the entire group (56 versus 33%, $p < 0.001$), the circumflex subgroup (49 versus 32%, $p < 0.025$) and the anterior descending subgroup (66 versus 37%, $p < 0.005$). This difference between groups was also present when hearts with small occluded beds (<20% left ventricular mass) or hearts with no infarct were excluded. Thus, excluding hearts without an infarct, infarct size as percent of occluded bed for anesthetized and conscious subgroups was 49 ± 3 versus 36 ± 3% ($p < 0.01$) for circumflex artery infarcts and 66 ± 4 versus 43 ± 5% ($p < 0.005$) for anterior descending artery infarcts.

Relation between infarct size and occluded bed size. For each of the four subgroups, infarct size (as percent of left ventricle) was directly related to the size of the occluded bed (as percent of left ventricle) over a wide range of values (Fig. 4). More important, the slopes of the regressions (but not horizontal axis intercepts) were greater in barbiturate-anesthetized than in conscious subgroups with either circumflex artery occlusion (0.97 versus 0.83, $p < 0.001$) or anterior descending artery occlusion (0.94 versus 0.79, $p < 0.001$). These results indicate that for similar occluded

Figure 3. Two day old infarcts, as percent of occluded bed, are larger in barbiturate-anesthetized (A) compared with conscious (C) dogs with either left circumflex (LC) or left anterior descending (LAD) coronary artery occlusion. LV = left ventricle.



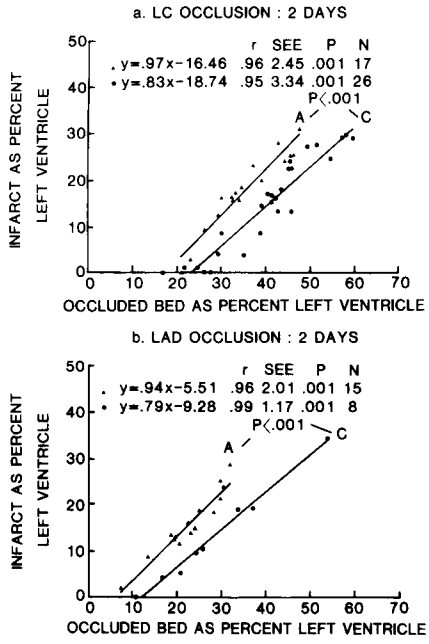


Figure 4. Linear regressions between infarct size and occluded bed size. The slope in anesthetized (A) dogs is greater ($p < 0.001$) than that in conscious (C) dogs with either left circumflex (LC) or left anterior descending (LAD) coronary occlusion. Horizontal intercepts were greater ($p < 0.05$) for left circumflex (**panel a**) than left anterior descending occlusions (**panel b**), indicating that left anterior descending infarcts are larger than left circumflex infarcts in both anesthetized and conscious states. Horizontal intercepts within left circumflex (**panel a**) or left anterior descending (**panel b**) subgroups were similar ($p > 0.05$).

bed sizes, infarcts were larger in the anesthetized dogs, regardless of the type of occlusion.

No infarcts developed in five dogs with a small occluded bed (range 9 to 27% of the left ventricle), in one dog in the anesthetized group (circumflex artery occlusion) and four dogs in the conscious group (anterior descending artery occlusion in one and circumflex artery occlusion in three). The intercepts of the linear regressions on the occluded bed axis in Figure 4 (but not the slopes) were greater ($p < 0.05$) for circumflex than for anterior descending occlusion in anesthetized (17.0 versus 5.9%) and conscious subgroups (22.5 versus 11.7%), indicating that anterior descending infarcts were also larger than circumflex infarcts, as reported previously (1).

Infarct topography. Infarct geometry was significantly different for barbiturate-anesthetized and conscious dogs with either anterior descending or circumflex infarcts (Fig. 5). Average computer-generated maps of infarct and occluded bed in five equally spaced left ventricular sections, from base to apex, revealed the following differences between anterior descending and circumflex infarcts: 1) infarct locations were different (anterior versus posterior by angular coordinates), although both showed clockwise rotation of the infarct from base to apex relative to the anatomic landmark of the junction of the anterior left ventricular free wall and the right ventricle; 2) anterior descending infarct areas increased toward the apex whereas circumflex infarct areas decreased; 3) the area of uninfarcted myocardium in the occluded bed was greater for circumflex than for anterior descending infarcts, as reported previously (1); and 4) anterior descending infarcts became more transmural toward the apex while circumflex infarcts were more transmural at the base. More important, for either type of occlusion, the following differences between infarcts in anesthetized and conscious dogs were found: 1) greater infarct size (as percent of occluded bed) in anesthetized dogs in each left ventricular ring from base to apex ($p < 0.05$); 2) less uninfarcted myocardium in the occluded bed of anesthetized dogs (48 ± 3 versus $67 \pm 3\%$, $p < 0.001$); 3) less lateral and subepicardial thicknesses of noninfarcted myocardium in the occluded bed of anesthetized dogs (Table 2); and 4) greater angular extent of infarcts in anesthetized dogs, reflecting greater endocardial extent. There was no difference in frequency of "transmurality" of the infarcts in anesthetized versus conscious groups using definitions of greater than 50% wall thickness (75 versus 63%, NS) or 100% wall thickness (38 versus 35%, NS). Also, for anesthetized versus conscious groups, the average infarct area over the five levels differed in the epicardial (1.5 versus 0.5 cm^2, $p < 0.01$) but not the endocardial (1.8 versus 1.3 cm^2, $p < 0.1$) half. Furthermore, the average percent increase in infarct area (as percent of occluded bed) in anesthetized dogs over that in conscious dogs was greater in the epicardial than in the endocardial half (266 versus 38%, $p < 0.025$), with no difference between circumflex and anterior descending infarcts.

Hemodynamics. The hemodynamic changes in barbiturate-anesthetized and conscious groups are summarized in Figure 6. Heart rate was higher in anesthetized than in conscious groups ($p < 0.001$), both before occlusion (127 ± 4 versus 88 ± 2 beats/min) and for 4 hours after occlusion (151 ± 4 versus 109 ± 3 beats/min). In both groups, heart rate increased after occlusion ($p < 0.001$). Mean arterial pressure in the two groups was similar, both before (117 ± 2 versus 111 ± 2 mm Hg) and after (111 ± 2 versus 111 ± 2 mm Hg) occlusion, and did not change after occlusion in either group. Mean left atrial pressure increased ($p < 0.001$) after occlusion in both anesthetized (6.6 ± 0.2 versus 14.6 ± 0.5 mm Hg) and conscious (6.8 ± 0.2 versus 13.5 ± 0.5 mm Hg) groups, but there was no difference in pre- and postocclusion values between the two groups. Within either group, the hemodynamic changes were similar for the two types of occlusion. However, postocclusion heart rate with circumflex artery occlusion was slightly less than with anterior descending artery occlusion in both anesthetized (145 versus 157 beats/min, $p < 0.1$) and conscious (105 versus 115 beats/min, $p < 0.01$) subgroups.

Regional myocardial blood flow. Regional perfusion data in 33 dogs with a detectable infarct (circumflex, n =

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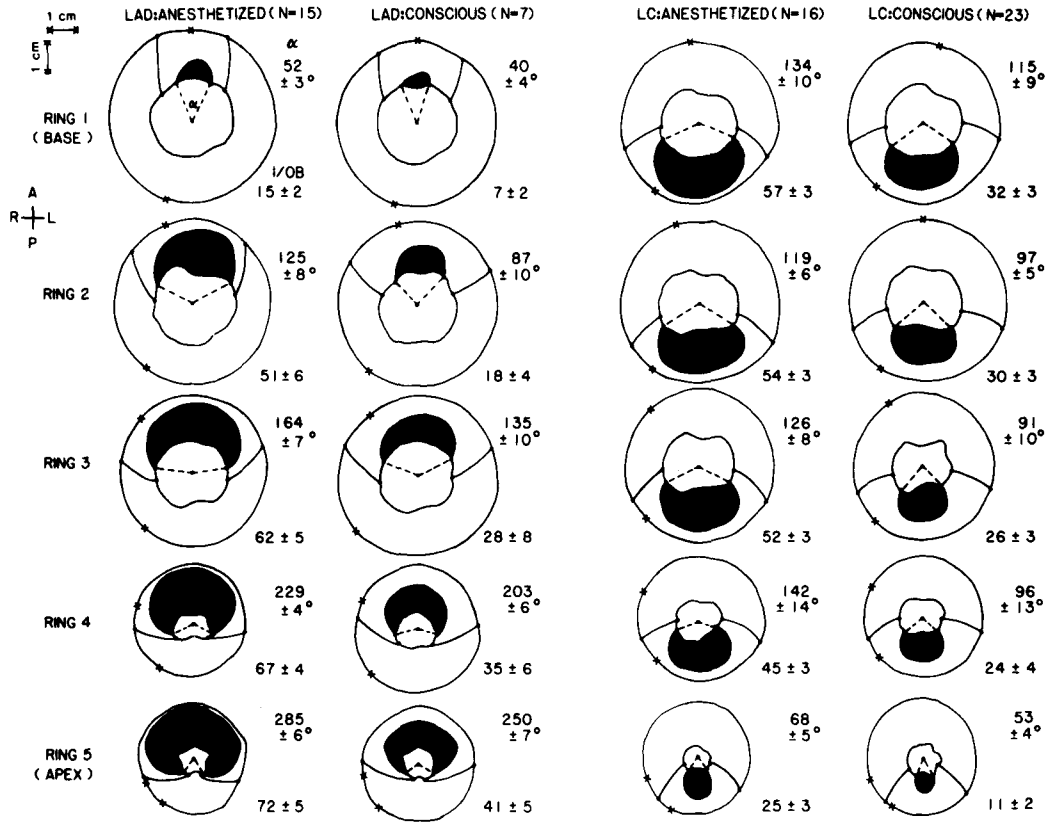

Figure 5. Average computer-generated maps for barbiturate-anesthetized and conscious dogs with left anterior descending (LAD) and left circumflex (LC) coronary occlusion. Infarct mass as percent of occluded bed (I/OB) is indicated by numbers (mean ± SEM) at the **lower right** of each map. Angular extent of the infarct (α), in degrees, is shown at the **upper right** of each map. **Asterisks** on epicardial contours indicate anatomic locations of junctions of the left and right ventricles.

17; anterior descending, n = 16) from conscious (n = 16) and barbiturate-anesthetized (n = 17) groups is summarized in Table 3. For these dogs, the occluded bed size was similar in the two groups (35.9 ± 1.9 versus 40.2 ± 2.3% left ventricle, NS) and the infarct was larger in the anesthetized group (49.6 ± 3.2 versus 32.0 ± 3.7% occluded bed, $p < 0.005$). The numbers of paired endocardial and epicardial samples pooled in each region for the two groups were, respectively, infarct center, 84 and 76; infarct margin, 168 and 152; border region, 156 and 136; normal unoccluded region, 108 and 96. In the remaining seven dogs without an infarct (four conscious, three anesthetized), the occluded bed size averaged 13.5 ± 1.6% of the left ventricle. Their 30 minute postocclusion myocardial flow averaged 0.72 ± 0.04 ml/min per g in the center of the occluded bed and 1.01 ± 0.03 ml/min per g in the center of the nonoccluded region.

Preocclusion flows were lower in infarcted than in noninfarcted regions, suggesting microsphere loss (Table 3). Because changes in flow were similar before and after correction for microsphere loss, only uncorrected data are shown. In both groups, postocclusion flow in the occluded bed was lower than preocclusion flow ($p < 0.001$), showed gradients from lateral to central regions and epicardial to endocardial regions and did not change between 30 minutes and 4 hours. However, the transmural distribution favored the endocardium more in conscious than in barbiturate-anesthetized dogs. Thus, after circumflex artery occlusion, endocardial flow in the center of the occluded bed at 30 minutes was less in the anesthetized than in the conscious group (0.04 ± 0.01 versus 0.08 ± 0.01 ml/min per g, $p < 0.05$). By 4 hours, both endocardial and epicardial flows in the center of the occluded bed were less in the anesthetized group. In contrast, the pre- and postocclusion endocardial-epicardial flow ratios in all regions were less ($p < 0.05$) in anesthetized than in conscious dogs (Table 4). Thus, the flow ratios in the two groups 4 hours after occlusion were, respectively, 0.36 versus 0.47 ($p < 0.05$) at the infarct center, 0.55 versus 0.72 ($p < 0.05$) at the infarct margin and 0.63 versus 0.80 ($p < 0.05$) at the uninfarcted border region. Similar differences in myocardial flow and flow ratio were found in most regions with anterior descending occlusion (Tables 3 and 4). Infarct size was inversely related to flow in both groups.

Table 2. Topographic Infarct Data in Barbiturate-Anesthetized and Conscious Dogs

Ring	Infarct/ LV (%)	Infarct/ Occluded Bed (%)	Angular Extent (α°)	Thickness of Noninfarcted Rim (mm)		
				Left	Right	Epicardial
LAD Anesthetized (n = 15)						
1	2 ± 1*	15 ± 2*	52 ± 3*	5.5 ± 0.4*	6.0 ± 0.1*	9.0 ± 0.5
2	19 ± 3*	51 ± 6*	125 ± 8*	3.8 ± 0.5*	5.0 ± 0.4*	2.8 ± 0.4*
3	25 ± 4*	62 ± 5*	164 ± 7*	3.2 ± 0.4*	3.5 ± 0.3*	2.1 ± 0.2*
4	37 ± 3*	67 ± 4*	229 ± 4*	2.5 ± 0.2*	2.0 ± 0.2*	1.5 ± 0.2*
5	53 ± 6*	72 ± 5*	285 ± 6*	1.2 ± 0.1*	1.4 ± 0.1*	0.7 ± 0.1*
LAD Conscious (n = 7)						
1	1 ± 1	7 ± 2	40 ± 4	8.5 ± 0.1	7.0 ± 0.2	9.5 ± 0.5
2	10 ± 4	18 ± 4	87 ± 10	6.3 ± 0.5	6.5 ± 0.5	6.0 ± 0.4
3	12 ± 6	28 ± 8	135 ± 10	6.5 ± 0.6	7.0 ± 0.6	6.0 ± 0.5
4	15 ± 6	35 ± 6	203 ± 6	4.2 ± 0.3	4.0 ± 0.5	6.2 ± 0.4
5	25 ± 8	41 ± 5	250 ± 7	3.7 ± 0.2	3.2 ± 0.3	4.5 ± 0.3
LC Anesthetized (n = 16)						
1	18 ± 2*	57 ± 3*	134 ± 10*	3.2 ± 0.4*	4.2 ± 0.3*	1.9 ± 0.1*
2	18 ± 2*	54 ± 3*	119 ± 6*	3.5 ± 0.2*	3.0 ± 0.2*	3.0 ± 0.2*
3	19 ± 2*	52 ± 3*	126 ± 8*	4.2 ± 0.2*	4.5 ± 0.4*	3.9 ± 0.2*
4	19 ± 2*	45 ± 3*	142 ± 14*	3.2 ± 0.2*	3.5 ± 0.3*	3.4 ± 0.2*
5	6 ± 3*	25 ± 3*	68 ± 5*	3.0 ± 0.2*	2.4 ± 0.1*	4.2 ± 0.2*
LC Conscious (n = 23)						
1	15 ± 2	32 ± 3	115 ± 9	7.5 ± 0.4	6.5 ± 0.3	5.0 ± 0.5
2	13 ± 3	30 ± 3	97 ± 5	6.5 ± 0.5	6.5 ± 0.5	5.5 ± 0.4
3	11 ± 2	26 ± 3	91 ± 10	6.0 ± 0.4	6.0 ± 0.5	6.1 ± 0.3
4	10 ± 2	24 ± 4	96 ± 13	4.3 ± 0.4	5.0 ± 0.3	5.0 ± 0.4
5	3 ± 2	11 ± 2	53 ± 4	4.0 ± 0.3	3.0 ± 0.1	7.0 ± 0.4

*$p < 0.05$, significance of difference between corresponding rings in anesthetized and conscious groups for left anterior descending and left circumflex artery infarcts, respectively. Values are mean ± SEM. Abbreviations as in Table 1.

Plasma catecholamines. The level of total catecholamines in venous blood was higher than in arterial blood, but both levels were greater in barbiturate-anesthetized than in conscious dogs before and after anterior descending artery occlusion (Table 5). This difference in catecholamines in the two groups was related to higher levels of epinephrine in the anesthetized dogs. Thus, the venous levels of epinephrine in the anesthetized and conscious dogs were 705 ± 89 versus 144 ± 29 ng/liter before occlusion ($p < 0.001$) and 730 ± 124 versus 106 ± 23 ng/liter after occlusion ($p < 0.005$). There was no difference in norepinephrine or dopamine levels in the two groups. The infarct (as percent of occluded bed) in these anesthetized dogs was larger than in the conscious dogs (48 versus 25%, $p < 0.05$).

Effect of pacing. Of the 22 paced conscious dogs, 18 survived 2 days (10 with circumflex artery occlusion, 8 with anterior descending artery occlusion). Their infarct was larger than in the previous unpaced conscious dogs (48.3 ± 6.8 versus 32.9 ± 2.8% occluded bed, $p < 0.025$). The slope of the linear regressions in the paced conscious dogs was also greater than in the unpaced conscious dogs with circumflex occlusion (1.28 versus 0.83, $p < 0.001$; Fig. 7) or anterior descending occlusion (1.03 versus 0.79, $p < 0.001$; Fig. 8). Furthermore, the slope was similar to that of previous anesthetized dogs with circumflex occlusion (1.28 versus 0.97, NS) or anterior descending occlusion (1.03 versus 0.94, NS).

Of the 12 anesthetized dogs with sinoatrial node destruction and pacing at the slower rate of the conscious group, 7 survived 2 days. Their infarct (as percent of occluded bed) was smaller than that in the previous anesthetized subgroup with anterior descending occlusion (33.2 ± 6.5 versus 66.5 ± 3.8%, $p < 0.001$) and similar to that in the corresponding previous conscious subgroup (33.2 ± 6.5 versus 37.6 ± 7.1%, NS). The slope of the linear regression was less in the anesthetized group with sinoatrial node destruc-

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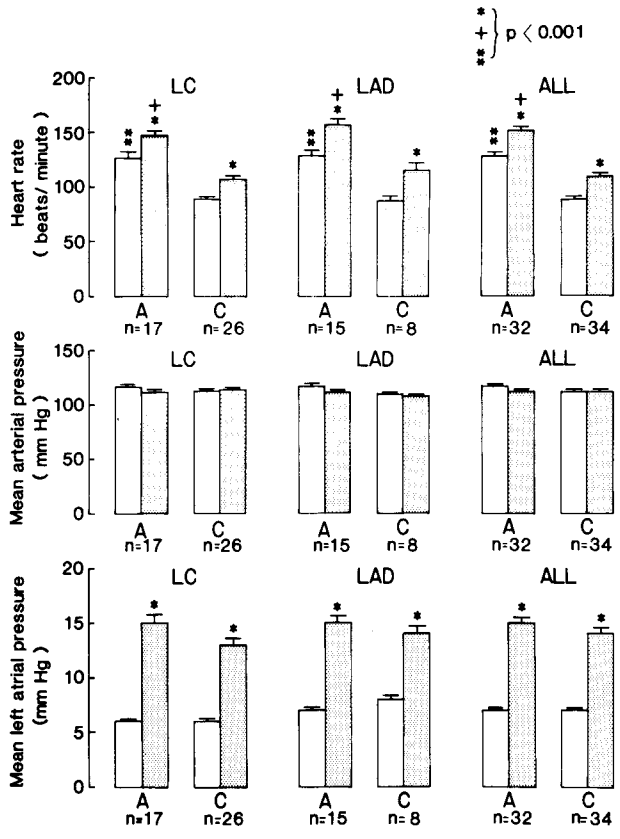

Figure 6. Hemodynamics in barbiturate-anesthetized (A) and conscious (C) groups. Preocclusion values (**clear bars**) and average values for the 4 hours after occlusion (**stippled bars**) are shown for the left circumflex (LC) and left anterior descending (LAD) occlusion groups. * = $p < 0.001$, comparing pre- and postocclusion values within anesthetized or conscious groups; ‡ = $p < 0.001$, comparing preocclusion values in anesthetized and conscious groups; + = $p < 0.001$, comparing postocclusion values in anesthetized and conscious groups.

tion than in the previous anesthetized subgroup with anterior descending occlusion (0.63 versus 0.94, $p < 0.005$) but similar to that in the previous conscious subgroup with anterior descending occlusion (0.63 versus 0.79, NS; Fig. 8).

Discussion

There are two major findings in this study. First, infarct size measured relative to occluded bed size was larger in barbiturate-anesthetized than in conscious dogs with either left circumflex or left anterior descending coronary artery occlusion. This difference was reflected in greater infarct mass as percent of occluded bed, greater slope of linear regression between infarct mass and occluded bed mass (each as percent of left ventricle) and less uninfarcted myocardium at subepicardial and lateral regions of occluded beds in the anesthetized group. Mean arterial and left atrial pressures were similar in the two groups but pre- and postocclusion heart rate was 39 to 44% higher in the anesthetized group. Flow data in 33 dogs with infarction revealed lower endocardial flow in the center of the occluded bed and lower pre- and postocclusion endocardial-epicardial flow ratios in anesthetized than in conscious dogs. Also, plasma catecholamine data in 10 dogs revealed higher levels in anesthetized than in conscious dogs. Second, conscious dogs paced at the higher heart rate of the barbiturate-anesthetized group had an infarct size similar to that in the anesthetized group. Conversely, when heart rate in barbiturate-anesthetized dogs was decreased to that of the conscious group by sinoatrial node destruction, infarct size was similar to that in the conscious group.

Cardiovascular changes in barbiturate-anesthetized dogs. The extent to which general anesthesia and surgical trauma can alter cardiovascular responses to physiologic and pharmacologic stimuli has been reviewed (18). It is generally recognized that barbiturate anesthesia induces tachycardia (18–22). The heart rate in anesthetized dog models (1,9,11) is consistently higher than in conscious dog models (2–8,10,11). Manders and Vatner (22) found that a single dose of intravenous barbiturate (30 mg/kg sodium pentobarbital) given to nine trained dogs increased heart rate from 80 to 160 beats/min at 2.5 minutes, which then decreased to 109 beats/min by 30 minutes. In those studies (22), barbiturate anesthesia had minor effects on cardiac output, arterial pressure and total peripheral resistance, but produced important decreases in stroke volume and myocardial contractility. The decrease in contractility was due to incomplete left ventricular emptying rather than to a decrease in end-diastolic size. The decrease in stroke volume was associated with a smaller left ventricular end-diastolic diameter and a larger end-systolic diameter. Rushmer (20) and Van Citters et al. (21) also noted decreased end-diastolic size during anesthesia, suggesting that the effect of tachycardia in decreasing end-diastolic size outweighs the myocardial depressant effect, which would tend to increase it. Manders and Vatner (22) also found that 1) reductions in end-diastolic diameter and coronary resistance did not occur when heart rate was controlled; 2) barbiturate did not cause tachycardia after bilateral section of carotid and aortic nerves, suggesting that tachycardia associated with barbiturate anesthesia is not only vagolytic but is also mediated through the baroreceptor reflex; and 3) left ventricular end-diastolic pressure increased, suggesting altered diastolic compliance (23) or shape.

Effect of tachycardia on myocardial perfusion in barbiturate-anesthetized dogs. In theory, tachycardia can decrease absolute flows by shortening diastolic perfusion time. The positive inotropic effect resulting from more frequent contractions is more prominent in the anesthetized than in the conscious dog (24). In experiments without coronary occlusion, Cobb et al. (25) found that barbiturate anesthesia, together with thoracotomy and pericardiectomy in 13 dogs, produced a sustained increase in heart rate (71 versus 156

Table 3. Regional Myocardial Blood Flow (ml/min per g) in 2 Day Infarcts

	Left Circumflex Artery				Anterior Descending Artery			
	Conscious (n = 9)		Barbiturate (n = 8)		Conscious (n = 7)		Barbiturate (n = 9)	
	Endo	Epi	Endo	Epi	Endo	Epi	Endo	Epi
Infarct center								
Pre-O	0.90 ± 0.05*†	0.83 ± 0.04*	0.75 ± 0.02*	0.81 ± 0.02*	0.81 ± 0.05*†	0.76 ± 0.04*	0.64 ± 0.04*	0.79 ± 0.04*
Post-O								
30 min	0.08 ± 0.01†	0.17 ± 0.02	0.04 ± 0.01	0.15 ± 0.01	0.05 ± 0.01†	0.14 ± 0.02	0.02 ± 0.01	0.10 ± 0.04
4 h	0.09 ± 0.01†	0.19 ± 0.01†	0.05 ± 0.01	0.14 ± 0.01	0.06 ± 0.01†	0.14 ± 0.03	0.03 ± 0.01	0.11 ± 0.05
Infarct margin region								
Pre-O	0.95 ± 0.05*†	0.87 ± 0.04*	0.79 ± 0.03*	0.84 ± 0.03*	0.91 ± 0.05*†	0.83 ± 0.06*	0.77 ± 0.04*	0.81 ± 0.07*
Post-O								
30 min	0.18 ± 0.02	0.25 ± 0.02	0.14 ± 0.01	0.28 ± 0.02	0.13 ± 0.02	0.18 ± 0.03	0.08 ± 0.02	0.20 ± 0.05
4 h	0.21 ± 0.02	0.29 ± 0.03	0.18 ± 0.02	0.33 ± 0.02	0.15 ± 0.02	0.25 ± 0.04	0.10 ± 0.03	0.23 ± 0.06
Border region								
Pre-O	1.09 ± 0.05*†	0.98 ± 0.05†	0.94 ± 0.02*	0.97 ± 0.03*	0.98 ± 0.05*	0.89 ± 0.03*	0.81 ± 0.08*	0.85 ± 0.06*
Post-O								
30 min	0.61 ± 0.04	0.72 ± 0.05	0.58 ± 0.02	0.84 ± 0.02	0.56 ± 0.06	0.76 ± 0.05	0.44 ± 0.05	0.72 ± 0.06
4 h	0.60 ± 0.05	0.75 ± 0.05	0.57 ± 0.02	0.90 ± 0.02	0.64 ± 0.05	0.81 ± 0.07	0.49 ± 0.08	0.67 ± 0.10
Normal center region								
Pre-O	1.11 ± 0.04†	0.98 ± 0.03†	1.12 ± 0.03	1.09 ± 0.03	1.11 ± 0.04	0.94 ± 0.03	1.01 ± 0.06	0.96 ± 0.05
Post-O								
30 min	1.14 ± 0.05	0.94 ± 0.05	1.06 ± 0.03	1.01 ± 0.03	1.12 ± 0.05	0.99 ± 0.08	1.08 ± 0.05	1.02 ± 0.08
4 h	1.15 ± 0.06	0.95 ± 0.05	0.98 ± 0.02	0.95 ± 0.02	1.08 ± 0.06	0.95 ± 0.10	1.06 ± 0.08	1.03 ± 0.04

*$p < 0.001$, significance of difference between pre- and postocclusion flows within each subgroup; †$p < 0.05$, significance of difference between endocardial or epicardial flows between conscious and barbiturate-anesthetized subgroups. Values are mean ± SEM. Endo = endocardial; Epi = epicardial; O = occlusion.

Table 4. Endocardial-Epicardial Blood Flow Ratios in 2 Day Infarcts

	Left Circumflex Artery		Left Anterior Descending Artery	
	Conscious (n = 9)	Barbiturate (n = 8)	Conscious (n = 7)	Barbiturate (n = 9)
Infarct center				
Pre-O	1.08 ± 0.04*	0.92 ± 0.02	1.07 ± 0.05*	0.93 ± 0.02
Post-O				
30 min	0.47 ± 0.02*	0.26 ± 0.01	0.37 ± 0.02*	0.20 ± 0.02
4 h	0.47 ± 0.02*	0.36 ± 0.01	0.43 ± 0.03*	0.27 ± 0.02
Infarct margin region				
Pre-O	1.09 ± 0.04*	0.94 ± 0.03	1.08 ± 0.05*	0.95 ± 0.03
Post-O				
30 min	0.73 ± 0.02*	0.53 ± 0.01	0.71 ± 0.03*	0.42 ± 0.02
4 h	0.72 ± 0.02*	0.55 ± 0.02	0.63 ± 0.03*	0.45 ± 0.02
Border region				
Pre-O	1.11 ± 0.05*	0.97 ± 0.02	1.09 ± 0.04*	0.94 ± 0.03
Post-O				
30 min	0.86 ± 0.05*	0.68 ± 0.02	0.74 ± 0.02*	0.61 ± 0.02
4 h	0.80 ± 0.04*	0.63 ± 0.02	0.79 ± 0.03	0.73 ± 0.02
Normal center region				
Pre-O	1.14 ± 0.03*	1.03 ± 0.03	1.14 ± 0.03*	1.05 ± 0.03
Post-O				
30 min	1.21 ± 0.05*	1.05 ± 0.03	1.12 ± 0.04	1.06 ± 0.03
4 h	1.21 ± 0.05*	1.03 ± 0.02	1.14 ± 0.03*	1.05 ± 0.03

*$p < 0.05$, significance of difference between ratios for each time interval in conscious and barbiturate-anesthetized subgroups. Values are mean ± SEM. Abbreviations as in Table 2.

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Table 5. Total Plasma Catecholamines (ng/liter) During Acute Infarction in Barbiturate-Anesthetized and Conscious Dogs

	Preocclusion		Postocclusion*	
Group	Venous	Arterial	Venous	Arterial
Conscious (n = 5)	837 ± 73	380 ± 49	690 ± 106	470 ± 76
Anesthetized (n = 5)	1,258 ± 51	1,048 ± 128	1,342 ± 148	891 ± 158
p value	0.005	0.005	0.01	0.05

*Average level for 4 hours after left anterior descending coronary artery occlusion. Values are mean ± SEM.

beats/min). This was associated with increases in epicardial (0.75 versus 1.08 ml/min per g) and endocardial (0.83 versus 1.11 ml/min per g) flow (7 to 10 μm microspheres), but the increase was less in the endocardium than in the epicardium, an effect attributed to tachycardia (25). Using 15 μm microspheres in tranquilized dogs with atrial pacing, Neill et al. (26) found that the endocardial-epicardial flow ratio in the left ventricular free wall and septum decreased from 1.39 to 1.27 and 1.17 as heart rate increased from 73 to 151 and 193 beats/min, respectively. Bishop et al. (27), using 15 μm microspheres, found that endocardial-epicardial flow ratios in barbiturate-anesthetized and thoracotomized dogs were less than in conscious dogs (1.04 versus 1.28). Thus, more frequent systolic compressions cause transmural maldistribution of flow (25), but the effect is greater in barbiturate-anesthetized, open chest dogs.

Tachycardia also causes disproportionately greater distribution of flow away from the endocardium toward the epicardium in ischemic regions after coronary artery occlusion (22). Using both 7 to 10 μm and 15 ± 5 μm microspheres in open chest, barbiturate- (and chloralose-) anesthetized dogs with left anterior descending artery ligation, Becker (28) found that incremental increases in heart rate by atrial pacing (118 versus 141 versus 165 beats/min) resulted in a decrease in endocardial-epicardial flow ratio in nonischemic (1.08, 1.06 and 1.02, respectively) and ischemic (0.42, 0.38 and 0.30, respectively) regions. These changes in ischemic endocardial-epicardial ratios were associated with marked increases in epicardial ST segment elevation. Becker (28) concluded that tachycardia accentuates endocardial-epicardial maldistribution in ischemic regions and might account for the harmful effect on infarction. This conclusion is supported by the findings of Shell and Sobel (29), who showed that increasing heart rate after left anterior descending occlusion in conscious dogs increased creatine kinase infarct size. They concluded that the greater infarct size was related to increased heart rate, which increases myocardial oxygen demand and consumption (30). However, Shell and Sobel did not measure flow.

Although transmural gradients of flow have been documented in conscious and barbiturate-anesthetized dog models similar to those used in this study (22), comparisons between the two models using similar occlusions were not made. Recently, Becker et al. (1) showed that infarcts in barbiturate-anesthetized dogs were not only larger after anterior descending than after circumflex artery occlusion, but postocclusion flows were 50% lower after anterior descending occlusion. The endocardial-epicardial flow ratios at about 20 minutes, calculated from results of Becker et al. (1),

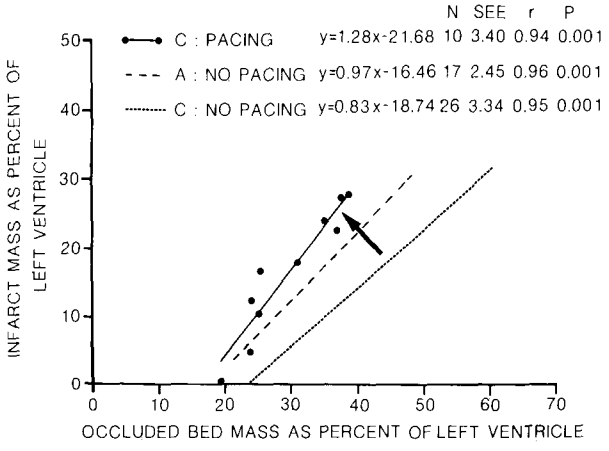

Figure 7. Linear regressions for 2 day old circumflex artery infarcts in paced conscious (C) dogs; regressions for unpaced conscious and barbiturate-anesthetized (A) dogs are shown for comparison. **Arrow** indicates upward shift in slope ($p < 0.001$) of the linear regression for paced conscious compared with the unpaced conscious subgroup. **Horizontal axis** intercepts were similar ($p > 0.05$).

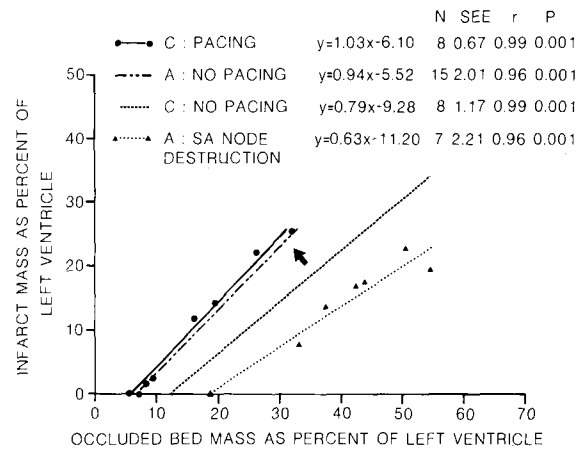

Figure 8. Linear regressions for 2 day old anterior descending artery infarcts in paced conscious (C) dogs and barbiturate-anesthetized (A) dogs with sinoatrial (SA) node destruction; regressions for unpaced conscious and anesthetized dogs are shown for comparison. **Arrow** indicates upward shift in slope ($p < 0.001$) of the linear regression in paced conscious dogs compared with the unpaced conscious group. Only **horizontal axis** intercepts for the paced conscious versus "anesthetized, sinoatrial node destruction" subgroups were different ($p < 0.05$).

were similar for anterior descending and circumflex occlusions (0.35 versus 0.37) in the center ischemic region. In this study, corresponding values for the ratios at 30 minutes with the two types of occlusion were also similar for anesthetized (0.20 versus 0.26) and conscious (0.37 versus 0.47) dogs. However, flow ratios were less in anesthetized than in conscious dogs after either type of occlusion. Thus, tachycardia in barbiturate-anesthetized dogs affected the transmural distribution of flow after either type of occlusion. Another possible explanation for regional differences in flow in the barbiturate-anesthetized group is a greater degree of vasoconstrictor tone. Thus, Templeton et al. (23) demonstrated withdrawal of coronary vasoconstrictor tone mediated by the alpha-adrenergic system in conscious but not anesthetized dogs. In this study, differences in ischemic flows between the two groups were small. The suspicion that the stress of thoracotomy in the anesthetized group might be associated with increased catecholamine levels was confirmed. However, the elevation was primarily due to increased epinephrine levels, whereas norepinephrine and dopamine levels were similar in the two groups. Although epinephrine tends to increase coronary flow, this effect was probably outweighed by the tachycardia.

Infarct size in the barbiturate-anesthetized dog model. In this study, the greater infarct size in anesthetized compared with conscious groups was reflected in the greater slope of the linear regressions for subgroups with circumflex or anterior descending infarcts. In contrast, the larger anterior descending infarcts in both groups were reflected in smaller intercepts on the occluded bed axis of the linear regressions, as reported by Becker et al. (1). Infarct topography was also different in the two groups. For both circumflex and anterior descending infarcts, the endocardial extent of the infarcts was greater and the epicardial rim of uninfarcted myocardium less in the anesthetized group. However, the increase in infarct area with barbiturate, compared with that in the conscious group, was greater in the epicardial than in the endocardial half of the occluded bed, suggesting that the diversion of flow toward the epicardium was sufficient to affect endocardial extension of infarction but insufficient to prevent epicardial extension in the anesthetized group. This was probably due to the overwhelming effect of increased oxygen consumption associated with tachycardia, as suggested by the pacing experiments.

Limitations. Despite differences in infarct size as percent of occluded bed, slopes of linear regressions for infarct versus occluded bed size and infarct topography between barbiturate-anesthetized and conscious dogs in this study, infarct size as percent of left ventricle was not statistically different ($p < 0.1$). Although this finding supports the notion that analysis of infarct size relative to occluded bed size is a more sensitive approach, it also suggests that the effect might be small and therefore easily masked unless infarcts relative to occluded beds are measured. This might explain why the difference in infarct size has been overlooked despite evidence of physiologic differences between the two models.

Conclusions. The barbiturate-anesthetized dog model was associated with tachycardia, a larger infarct relative to the anatomic occluded bed size and altered infarct topography with less epicardial and lateral sparing compared with the conscious dog. These differences were noted in infarcts after both circumflex and anterior descending coronary artery occlusion. The greater infarct size in the barbiturate-anesthetized model appeared to be related mainly to the tachycardia, probably mediated by increased myocardial oxygen consumption, although transmural maldistribution of flow associated with tachycardia and higher levels of circulating catecholamines might have contributed.

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