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Effect of Acute Sympathectomy by Epidural Anesthesia on the Canine Coronary Circulation

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The effects of reversible sympathetic neural blockade of the canine myocardium under control conditions and in the presence of decreased coronary blood flow and after myocardial infarction were investigated in 17 dogs. A multiple-microsphere technique was used to measure distribution of blood flow in the myocardium. Epidural blockade was associated with the following changes in the ratio of endocardial to epicardial blood flow: under control conditions, no change; after 50 per cent decrease in coronary flow, 18 per cent increase in endocardial/epicardial ratio; after myocardial infarction at unrestricted coronary flow, 43 per cent ratio increase; after myocardial infarction and 50 per cent decrease in coronary flow, 76 per cent increase of endocardial/epicardial ratio. These effects appear to be independent of systemic factors, and may result from alterations in tone of transmural resistance vessels. In addition, cervicothoracic epidural blockade resulted in a decrease in systemic pressure and an increase in coronary vascular resistance as myocardial oxygen demand decreased. When systemic pressure was restored these effects were abolished. In the presence of myocardial infarction, epidural blockade had less effect on systemic pressure and left ventricular filling pressure was decreased. With decreased coronary flow, sympathetic blockade redistributed coronary blood flow, favoring the endocardium in both the normal and the infarcted heart. (Key words: Anesthetic techniques, epidural. Heart: blood flow, myocardial; coronary occlusion; endocardium; vascular pressures. Measurement techniques: radioactive tracers. Sympathetic nervous system: adrenergic transmission; anesthesia.)

IT HAS BEEN RECOGNIZED that the sympathetic nervous system may play an important role in the pathophysiology of myocardial infarction,[1,2] angina pectoris,[3] fatal cardiac arrhythmias,[4–6] and perhaps even the development of atherosclerosis.[7] The purpose of our investigation was to examine the effect of reversible sympathectomy induced by epidural cervical anesthesia on myocardial blood flow distribution during myocardial ischemia and infarction. This was done in the dog in order to determine whether such a procedure might be advantageous as a therapeutic measure in patients with acute myocardial infarction.

Upper thoracic epidural blockade interrupts cardiac afferent and efferent neural impulses at the level of the spinal cord, but leaves intact the parasympathetic reflexes that do not involve the cord.[8] We employed the technique developed by Lebeaux[9] to insert a chronic indwelling catheter into the cervical epidural space in the dog. This permitted us to test the effectiveness and the segmental extent of blockade in the conscious animal prior to studies of the coronary circulation. After an interval of two to three days, we examined the effect of acute blockade on regional distribution of myocardial blood flow using a multiple-radioactive-microsphere technique both in the presence and in the absence of myocardial infarction.

Materials and Methods

The study was performed on 17 healthy mongrel dogs weighing 15 to 25 kg. Preparation was in two stages; the first being epidural cannulation. We modified the epidural cannulation method of Lebeaux[9] to meet our requirements for a chronic preparation with the capability of limited segmental blockade involving the upper thoracic spinal segments.

The animals were anesthetized with thiopental, their tracheas intubated, and their lungs ventilated via a circle CO_2 absorption system using methoxyflurane and oxygen. The vertebral plate of either C7 or T1 was exposed via a paramedian incision. The epidural space was entered by drilling a 2-mm diameter hole through the lamina at the junction between the spinous process and the lateral process. A 19-gauge Teflon® catheter was passed through a 2-cm length of 16-gauge polyvinyl tubing so that the Teflon catheter protruded 1 cm. Stainless steel wire was then wrapped around the polyvinyl tube to secure it and to provide an anchoring shoulder. The Teflon catheter was advanced into the epidural space and the shoulder cemented to the bone using a rapid bonding adhesive (alpha-cyanoacrylate¶). A small quantity of saline solution was injected to test for leaks and to ensure that the catheter was patent.

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¶ Toagosei Chemical Industry Co., Ltd., Tokyo, Japan.

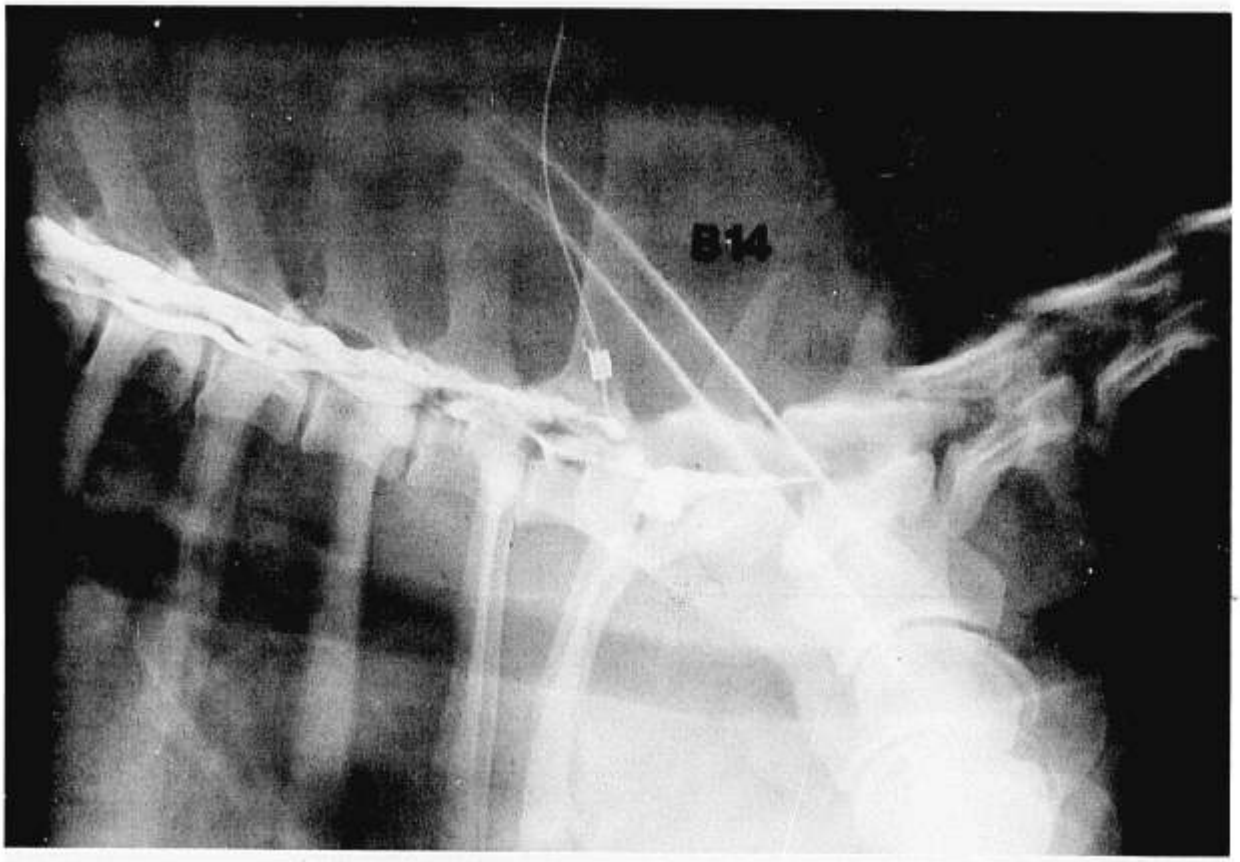

FIG. 1. Lateral peridurogram of dog (B 14) after epidural injection of 2 ml 60 per cent Na diatrizoate (Hypaque®) through epidural catheter cemented into lamina of first thoracic vertebra. Contrast spreads in extradural space from sixth cervical to sixth thoracic vertebrae.

The wound was then closed with the catheter secured by sutures and tape.

Before recovery from anesthesia, the position of the catheter and the extent of spread of the anesthetic agent to be injected were ascertained by roentgenography using a small volume of water-soluble radiopaque dye (Hypaque®, 60–75 per cent, or metrizamide, 300 mg I/ml) (fig. 1). The volume of contrast medium injected was that which was found to provide adequate spread over the cervical and upper thoracic segments, and ranged between 1.5 and 3 ml.[10] On the day following recovery of the animal, the peridurogram was repeated and the dose of contrast medium was adjusted as required to ensure complete spread into the upper thoracic segments. The extent and effectiveness of a brief period of blockade were confirmed by injecting the same volume of chlorprocaine, 2 per cent, and observing loss of pain sensation in front limbs (C6–8, T1, T2); loss of spontaneous motor power in front limbs (C6–8, T1, T2); Horner's syndrome, unilateral and bilateral (T1–3); and abdominal breathing (T2–13).

Observations were made at 5-min intervals for the first 15 min and then every 10 min until full recovery (usually 90 min). The onset of sympathetic blockade appeared within 5 min of injection and was complete in 10 min.

To forestall the possibility that granulation tissue might obstruct the epidural catheter, the second-stage measurement of regional myocardial blood flow was carried out within 72 hours of inserting the epidural catheter. Carbonated lidocaine, 2 per cent, was used to produce blockade. Blood levels of lidocaine were measured 20 min after injection. Measurements of myocardial blood flow were made under four conditions: 1) with resting coronary flow; 2) with coronary flow decreased by 50 per cent; 3) with resting coronary flow after epidural sympathetic blockade; 4) with coronary flow decreased by 50 per cent during epidural blockade. For this portion of the study the dogs were anesthetized with chloralose–urethane (75:550 mg/kg) and succinylcholine, 10 mg. Their tracheas were intubated and their lungs ventilated to maintain a P_{CO_2} of 40 torr and a P_{O_2} of at least 70 torr (whenever P_{O_2} decreased below this level, oxygen was added to the inspired air). An additional two doses of succinylcholine, 10 mg, were usually given during the course of the study.

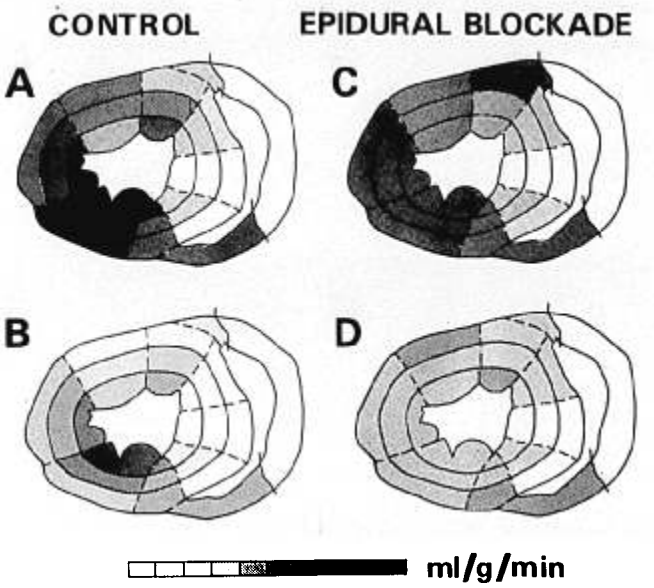

FIG. 2. A typical transverse slice of myocardium from a dog with septal myocardial infarction (clear area). *A*, normal flow; *B*, decreased flow; *C*, epidural blockade with normal flow; *D*, epidural blockade with decreased flow. A shading code indicates the flow in each piece of myocardium (range: white 0.00–0.38 to black 3.42–3.80 ml/g/min).

The heart was exposed through a small thoractomy incision. Our purpose was to obtain controlled coronary flow in the left coronary artery or its circumflex branch. This was achieved by passing a thin metal cannula through the right carotid artery into the origin of the left coronary artery, or, when this vessel was short, into the circumflex branch. Arterial blood passed through one lumen of this cannula from a constant-flow pump with an interposed air trap so that flow in the cannula was phasic and similar to that present in unperfused vessels. Arterial blood for the pump came from a reservoir maintained at 37 C and fed continuously from the right femoral artery. The cannula was sealed in place by a special clamp designed to avoid interrupting the nerve fibers that travel along the coronary artery. Coronary arterial pressure was measured at the tip of the cannula through the second lumen: pressures were also measured in the left atrium and aorta using Statham 23 Db transducers. Pressures and lead II of the electrocardiogram were recorded on a DR 8 Electronics for Medicine® recorder. The cannula was specially constructed so that its total volume was less than 1 ml, which resulted in a blood flow velocity of more than 50 cm/sec during diastole even at the lowest flows. This rapid velocity was necessary to maintain mixing of the radioactive microspheres, which were injected directly into the cannula. Three protocols were then followed: Group A, flow determinations without blood transfusion; Group B, flow determinations with blood transfusion; Group C, flow determinations after myocardial infarction.

For Group A (n = 5), following placement of the coronary cannulas, pump flow to the coronary artery was adjusted so that coronary arterial pressure was similar to aortic pressure. When the preparation was stable, the first set of labelled microspheres was injected and coronary arterial, atrial, and aortic pressures were recorded. Following this, the vascular resistance due to autoregulation was assessed by stopping flow for 15 sec to produce ischemia and recording the decrease in pressure when flow was restored. This was quantitated as a reactivity index (RI) using the formula:

$$RI = \frac{P_1 - P_2}{CF}$$

where P_1 is the coronary mean diastolic pressure before the stop flow, P_2 is the coronary diastolic pressure after the stop flow, and CF is coronary flow per 100 mg of perfused tissue. The perfused area was assessed by dye injection as described below.

Pump coronary flow was then decreased to 50 per cent of its control value and after 15 min, to allow stabilization of pressures, the second set of microspheres was injected and reactivity measured again. Coronary flow was then returned to its control value.

Segmental neural blockade of the thoracic segments was then established by injecting the predetermined volume (carbonated lidocaine, 2 per cent) into the epidural catheter. Vascular pressures were continuously recorded, and when they had stabilized at a new level (usually after 10 to 15 min), the third set of microspheres was injected, pressures were measured, and the new reactivity index determined. Coronary flow was then decreased to 50 per cent of control, the measurements were repeated, and the fourth set of microspheres was injected. A blood sample for estimation of blood lidocaine concentration was drawn 20 min after the epidural injection.

The protocol for Group B (n = 8) was similar to that for Group A with the exception that following epidural blockade, blood from a donor dog was infused into a femoral vein until aortic pressure was similar to that present during the pre-blockade period. The purpose of this intervention was to lessen the effect on the heart of decreased afterload. Systemic pressure decreased by 41 per cent after epidural blockade in Group A, dogs not receiving transfusion, but in Group B, dogs receiving transfusions, this decrease was limited to 20 per cent.

In Group C (n = 4) dogs, myocardial infarction was produced by occlusion of the first septal penetrating artery of the left coronary artery. The infarcted area

was confined to the septum. Its presence was confirmed by injection of dye at the completion of the procedure and by identification of the area that received the fewest microspheres (fig. 2). The protocol otherwise was the same as for Group A dogs.

Radioactive microspheres** 15 μm ± 5 μm in diameter, were labelled with one of four isotopes, ^{125}I, ^{141}Ce, ^{85}Sr, ^{91}Nb. They were suspended in whole blood before injection. Microscopic inspection revealed homogeneous distribution and no aggregation. Following agitation the microspheres were injected into the high-velocity-flow cannula over six to ten cardiac cycles with pressure monitoring (to avoid pressure artifacts arising from uneven pressure during injections). The sequence for injection was determined by a random number program.

At the completion of the study the dogs were killed with pentobarbital and the perfusion mass of the cannulated coronary artery determined by injecting Evans blue dye at arterial pressures. The heart was removed and fixed in formalin. After a period of 48 hours of fixation the heart was cut into five coronal sections; the dyed areas were separated and cut into five segments. These pieces were divided into three layers: epi-, mid- and endocardium. Epicardial vessels were removed and the dyed pieces coded and weighed. Each section contained 800–1,200 spheres of each type of microsphere. The pieces were then counted using a Bio-gamma†† counting system. Corrections were made for spectral overlap and for differences in half-lives of the nucleides. Since total flow was known, regional flow to a piece could be calculated as the proportion of counts in that piece to total counts times flow. In addition to calculating average flow for all of the pieces in a region, histograms of flow distribution were plotted for each injection to determine whether low- or high-flow areas, which might indicate a faulty microsphere injection technique, were present. Animals showing uneven flow distribution under resting conditions were excluded from the series. All statistical analyses of the data were based on recognized computer programs.[11] $P < 0.05$ was regarded as significant.

In some instances myocardial oxygen consumption (MV_{O_2}) was measured during the four measurement periods. In these animals splenectomy was performed before the procedure to assure a constant arterial blood hematocrit. When circumflex perfusion was carried out coronary venous blood was obtained from a local surface vein selected by injecting dye into the coronary cannula. Oxygen content was measured

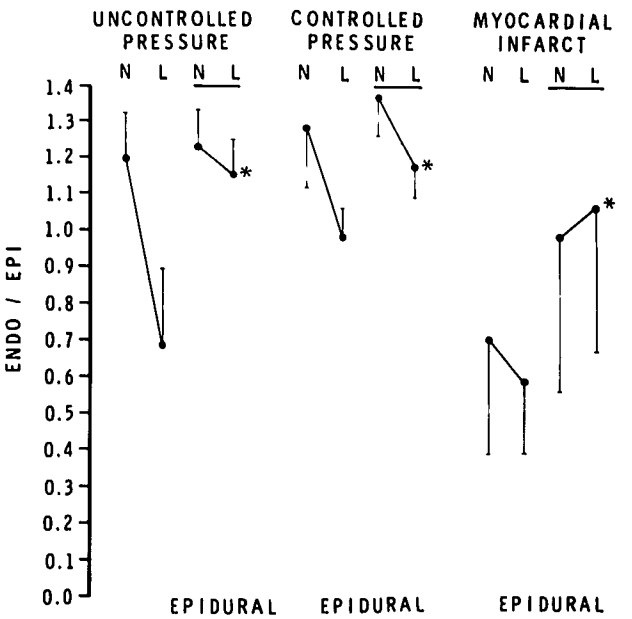

FIG. 3. Change in endocardial/epicardial ratio during normal (N) and low (L) coronary flow (lines join the two flow states). The line under N or L indicates the presence of sympathetic blockade. Bars indicate one standard error of the mean. Asterisks(*) indicate a significant change in ratio following epidural blockade compared with control with the same coronary flow.

using the polarographic method described by Sabatier *et al.*[12] Blood-gas tensions were measured using an IL® electrode system and blood lidocaine concentrations by gas chromatography.[13]‡‡

Results

Epidural blockade results in a profound redistribution of myocardial blood flow (fig. 2). Decreasing coronary flow and diastolic pressure (Group A) tended to redistribute flow to the epicardium, with a resultant decrease in the endocardial/epicardial ratio (fig. 3). These results are similar to those previously reported.[14] Following epidural blockade the pattern was similar. However, when the paired differences were analyzed at decreased flows following blockade, endocardial flow was always higher and epicardial flow lower than control, and the endocardial/epicardial ratio increased by 66 per cent ($P < .05$).

Blockade in Group B, in which systemic pressure was augmented by transfusion, had a result similar to that in Group A, with the differences in regional flow persisting when systemic pressure was augmented. The endocardial/epicardial ratio at decreased flow was significantly improved following blockade, with an increase of 18 per cent.

** 3M Company, Minneapolis, Minnesota.
†† Beckman Ltd., Fullerton, California.

‡‡ Lidocaine concentrations were measured by Astra, Framingham, Massachusetts 01701.

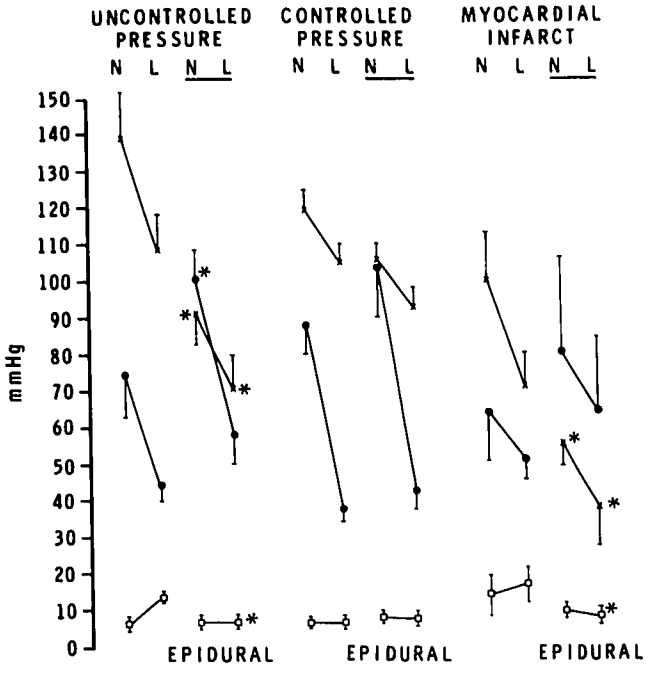

FIG. 4. Aortic systolic pressure (×), coronary diastolic pressure (○) and left atrial pressure (□) during normal (*N*) and low (*L*) coronary flow (lines join these two flow states). The line under *N* or *L* indicates the presence of epidural blockade. Bars indicate one standard error of the mean. An asterisk (*) indicates a significant change in pressure following sympathectomy compared with control with the same coronary flow.

Myocardial infarction (Group C) resulted in lower endocardial blood flow, reflecting in part that the area of infarction was more extensive in the endocardium than in the epicardium, with an endocardial/epicardial ratio of 0.70 ± .21. Decreasing flow further decreased this ratio. Epidural blockade decreased epicardial flow and increased endocardial flow significantly. The endocardial/epicardial blood flow ratio was increased by 43 per cent in infarcted hearts at high coronary flow rates, and by 76 per cent at low coronary flow rates (fig. 3).

Because the transmural distribution of blood flow of the left ventricle can be altered by changes in endoventricular pressure, heart rate, autoregulatory tone, and oxygen consumption, we examined those variables in the three groups. In Group A a decrease in coronary flow from 135 ± 21 to 60 ± 9 ml 100 g/min during the preblockade period resulted in significant decreases in coronary arterial diastolic pressure (75 ± 12 to 45 ± 5 torr) and aortic pressure (140 ± 12/98 ± 9 to 109 ± 9/74 ± 11 torr), left atrial pressure increased (6.9 ± 0.8 to 13.9 ± .4 torr), and heart rate was unchanged (154 ± 8 to 155 ± 8 beats/min) (fig. 4). The reactivity index decreased (0.25 ± .08 to .05 ± .03), indicating a decrease in autoregulatory tone. In addition, myocardial oxygen consumption decreased from 6.20 to 4.02 ml/100 g/min (fig. 5).

When epidural blockade was induced and coronary flow was the same as during control, coronary diastolic pressure increased (101 ± 8 torr), and aortic systolic pressure decreased (93 ± 10 torr) significantly (fig. 4), without significant change in left atrial pressure, heart rate, reactivity index, or myocardial oxygen consumption (fig. 5). When coronary flow was decreased, aortic pressure decreased significantly to 70 ± 10 torr, left atrial pressure did not increase as it had during control and was significantly lower (6.8 ± .5 torr, fig. 4) and the reactivity index increased significantly to 0.59 ± .17, indicating an increase in autoregulatory tone (fig. 5).

The increase in coronary diastolic pressure observed following epidural blockade could be explained by either the decrease in systemic pressure with a decrease in myocardial oxygen demand or as a direct result of sympathetic denervation. We therefore designed the

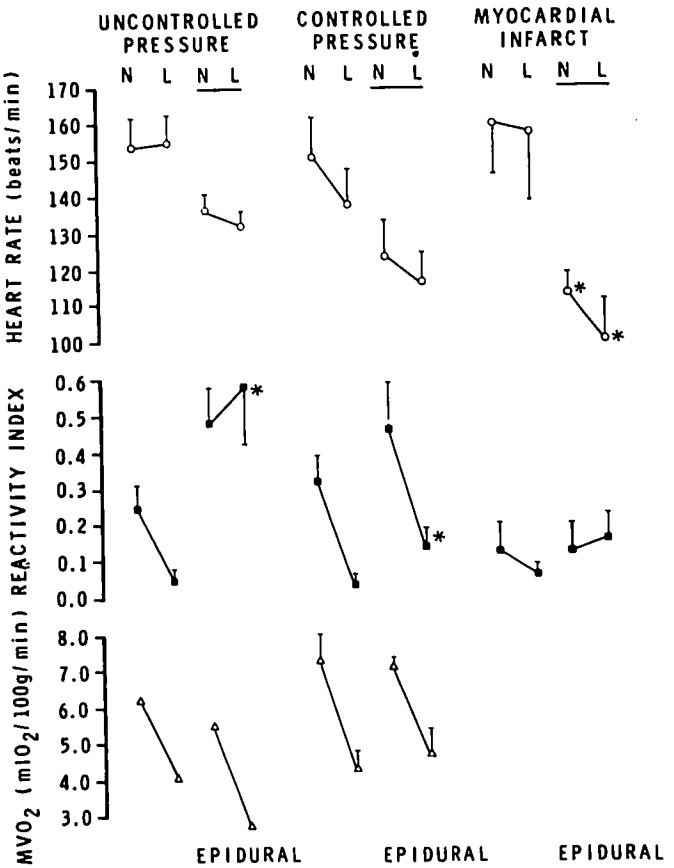

FIG. 5. Heart rate (○), reactivity index (■) and myocardial oxygen consumption (MV_{O_2}) (△) during normal (*N*) and low (*L*) coronary flow (lines join the two flow states). The line under *N* or *L* indicates the presence of sympathetic blockade. Bars indicate one standard error of the mean. An asterisk (*) indicates a significant change in the variable following epidural blockade compared with control with the same coronary flow.

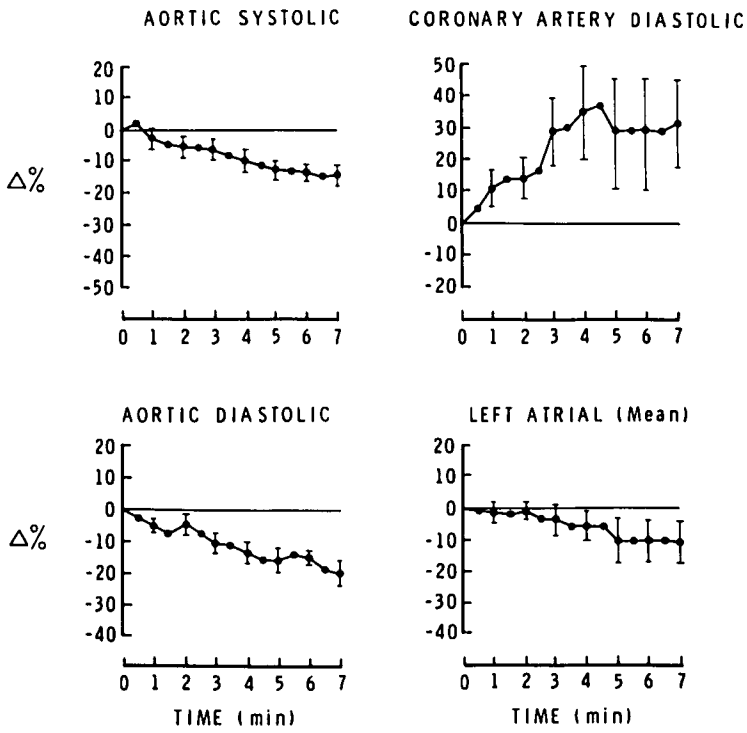

FIG. 6. Acute changes in hemodynamics after induction of epidural blockade, expressed as percentage differences from control values. Dots are means and bars represent one standard error of the mean. See text for absolute values in torr.

next series of experiments so as to minimize the decrease in aortic pressure following blockade by a transfusion of blood. It is of interest that tachycardia did not accompany a decrease of aortic pressure in these animals, suggesting that the baroreceptor response was blocked.

Control values obtained for Group B were similar to those of Group A at both levels of coronary flow. The decrease in coronary flow was slightly less (normal flow 135 ± 22, decreased flow 67 ± 10 ml/100 g/min), and left atrial pressure did not increase with a decrease in coronary blood flow (fig. 4).

Following epidural blockade and transfusion of blood the decrease in aortic pressure (fig. 4) was no longer significant (control 120 ± 5/84 ± 8, following blockade 105 ± 5/67 ± 6 torr). Exact matching of pressures was not accomplished. The same trends in the postblockade period observed in Group A were observed in Group B, but were not significantly different from control at both levels of flow. The exception to this was the increase in the reactivity index at decreased flow (control .04 ± .01 compared with .14 ± .05 postblockade, fig. 5). The persistence of this increase in tone may reflect either our inability to prevent completely the decrease in aortic pressure by transfusion or that sympathetic blockade removed a dilator component to coronary vascular tone so that reactivity was increased.

The size of myocardial infarction in the Group C dogs and its location is shown in figure 2. Infarction was produced 30 min before control measurements and one hour before epidural blockade was induced. The animals remained relatively stable throughout the study, and arrhythmias were infrequently observed; none of the animals in this group received a transfusion. Aortic pressure was somewhat lower than that in the non-infarcted dogs, so coronary flow during control was also lower, 118 ± 16 ml/100 g/min, decreased flow, 76 ± 4 ml/100 g/min. Left atrial pressure was increased (13.8 ± 5.8, 16.3 ± 5.3 torr) at both flows, and the reactivity index was low at normal flow. MV_{O_2} was not measured in this group. Coronary flow could not be decreased to the same extent as in Groups A or B without precipitating a marked increase in left atrial pressure.

Epidural blockade significantly decreased aortic pressure (55 ± 6/26 ± 4, 38 ± 11/18 ± 6 torr) and heart rate. At decreased flows blockade decreased left atrial pressure to 8.2 ± 1.8 torr and increased the reactivity index to 0.16 ± .07. Thus, in the infarcted animal, epidural blockade produced systemic hypotension, a decrease in heart rate, and an increase in coronary arterial tone.

With induction of epidural blockade, aortic systolic (115 ± 11 torr) and diastolic pressures (78 ± 10 torr) decreased immediately by 15 ± 3 and 20 ± 5 per cent, respectively, over a 7-min period (fig. 6). Coronary diastolic pressure (66 ± 11 torr) increased by 32 ± 14

per cent with a constant coronary flow, indicating an increase in coronary vascular resistance. Left atrial pressure (8.1 ± 1.3 torr) decreased by 12 ± 6 per cent.

As a measure of the instantaneous piece-to-piece variation in coronary blood flow, we calculated the coefficient of variation of flow[15] for the three groups and the effect of epidural blockade on this variable. The data presented are for approximately 100 pieces of the left ventricle in which flow was measured. Results were similar for epicardium, mid-layer, and endocardium. Epidural blockade did not alter this index, but myocardial infarction *per se* did increase the variability in flow (control 13.3 ± 6.5, infarction 40.7 ± 7.0 per cent).

The highest plasma level of lidocaine recorded was 3.24 μg/ml; the average was 2.32 ± 0.12 μg/ml.

Discussion

The purpose of this investigation was to determine the effects of upper thoracic sympathectomy by epidural anesthesia on the canine coronary circulation. We used a potent local anesthetic in order to ensure complete blockade of all neural modalities in the thoracic segments. Sympathectomy in the presence of a fixed coronary flow and controlled pressures resulted in a redistribution of coronary blood flow favoring the endocardium. The endocardial/epicardial ratio was significantly greater following epidural blockade. The increase in endocardial/epicardial blood flow ratio after epidural blockade was greatest in the most compromised hearts, that is, at low coronary flow rates after acute myocardial infarction (fig. 3). An important mechanism under neural control, which influences the transmural distribution of coronary blood flow, must therefore exist.

Hoffman and Buckberg[16] have reviewed the determinants of transmural distribution of coronary blood flow. They propose that they are determined by the ratio of supply and demand, *i.e.*, diastolic pressure time divided by systolic pressure time. In our study, when pressures were controlled, we observed alterations in the endocardial/epicardial ratio without significant change in the determinants of the Buckberg index,[17] namely, heart rate and systemic pressure. This suggested that neural tone can modify distribution, and that it is an important but minor determinant of transmural distribution. This is in accord with the findings of Schwartz and Stone[18] who also used a multiple-microsphere technique, and who found that the endocardial/epicardial blood flow ratio was decreased by sympathetic stimulation, but increased by 5 per cent after excision of the left stellate ganglion. Becker *et al.*[19] have also reported increases of endocardial flow following administration of propranolol or nitroglycerin. Winbury[20] has proposed that the site of the associated change in resistance might be located in the transmural penetrating arteries.

There is other evidence that suggests that the sympathetic nerves may play a role in transmural distribution. Uchida and Ueda[21] observed that stellate ganglion stimulation decreases endocardial flow with shunting of coronary flow to the epicardium. Uchida and Murao[22] have proposed that this redistribution is mediated through afferents travelling through the A δ fibers. The efferent side of the reflex arc is served by the upper four or five thoracic segments, as has been shown by Randall *et al.*[23] In contrast to this view, Buckberg and Ross[24] reported that the effects of isoproterenol, a potent β stimulant, on coronary flow distribution could be totally predicted by the effect on the DPTI/STPI ratio. It is probable that the minor effects of sympathetic stimulation were overlooked in their data.

The hemodynamic effects of epidural blockade we observed are similar to those found in man by Hackel *et al.*[25] and in the monkey by Sivarajan *et al.*[26]; that is, a decrease in preload and afterload with a consequent decrease in overall coronary blood flow as cardiac work decreases. When we restored systemic pressures by transfusion and maintained cardiac work, we saw no effect of epidural blockade on coronary vascular resistance. This implies that the resting sympathetic tone in the animals we studied was minimal. We observed similar changes in the presence of myocardial infarction.

Forrester *et al.*[27] have reviewed what they consider to be the desirable hemodynamic state for a patient with an acute myocardial infarction and the aims of optimal therapy. In the presence of left heart failure with an adequate aortic diastolic pressure, it is considered desirable to decrease left ventricular filling pressure and systemic pressures in order to improve endocardial blood flow and decrease MV_{O_2}. In all dogs, with myocardial infarction, we observed a significant decrease in left atrial pressure and a decrease in heart rate after epidural blockade; both of these hemodynamic changes would act to decrease MV_{O_2}. Sympathectomy redistributed coronary blood flow to the endocardium with an improvement in the endocardial/epicardial ratio, both in infarcted and uninfarcted hearts. The improvement of distribution to the endocardium was particularly striking at low flow rates after acute infarction.

Our data suggest that sympathetic blockade achieved through epidural anesthesia might be a useful adjunct to the treatment of acute myocardial infarction through improved endocardial blood flow and a decrease in the determinants of MV_{O_2}. Any additional benefit from the relief of cardiac pain by segmental epidural blockade remains to be assessed.[28]

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