Tonic Influence of the Sympathetic Nervous System on Myocardial Reactive Hyperemia and on Coronary Blood Flow Distribution in Dogs

PETER J. SCHWARTZ AND H. LOWELL STONE

SUMMARY In two groups of dogs we studied the effect of right and/or left stellectomy on myocardial reactive hyperemia (RH) and on coronary blood flow distribution. In the first group of 14 conscious dogs, the percent re-payment of flow debt produced by a 10-second occlusion of the left circumflex coronary artery was recorded with a Doppler ultrasonic flow probe and a hydraulic vascular occluder. The dogs were studied under control conditions, after right stellectomy and after left stellectomy and after administration of propranolol and phentolamine. Right stellectomy did not affect RH. RH was significantly increased by left stellectomy from 476 ± 71% to 622 ± 86% (+31%) at the spontaneous heart rate and from 407 ± 51% to 577 ± 106% (+42%) during pacing. Propranolol significantly reduced RH from 447 ± 25% to 390 ± 27% (-13%) at the spontaneous heart rate and from 456 ± 25% to 311 ± 24% (-32%) during pacing. Phentolamine significantly increased RH from 419 ± 63% to 517 ± 71% (+23%). Propranolol was effective after left stellectomy, whereas phentolamine was not effective after left stellectomy. In the second group of 14 anesthetized dogs with constant heart rate (15 μm) microspheres were injected twice into the left atrium. The first injection provided a control measurement; in nine dogs the second injection was made after left stellectomy. Left stellectomy significantly increased the left ventricular endocardial to epicardial ratio from 1.7 ± 0.03 to 1.23 ± 0.04. We conclude that the sympathetic nervous system has a tonic influence on coronary circulation and that left stellectomy increases the ability of the coronary bed to dilate and improves the endocardial perfusion.

UNILATERAL stellate ganglion blockade or ablation recently was found to produce marked changes in ventricular vulnerability to fibrillation1-2 and also to affect excitability of the ventricles.3 These studies suggested a tonic influence of the sympathetic nerves on cardiac function and avoided the shortcomings inherent in the use of nerve stimulation and autonomic drugs. The effect of tonic sympathetic nervous system activity on coronary flow and the distribution of flow across the ventricular wall remains an important unanswered question as stated by Berne.4 This study was designed to investigate the tonic effect of sympathetic activity on the coronary reactive hyperemic response to short-lasting occlusions and the distribution of coronary flow across the myocardial wall.

Myocardial reactive hyperemia (RH) is thought to depend on either hypoxia-induced release of vasoactive metabolites5 or myogenic relaxation of coronary vascular smooth muscle in response to loss of the stretch stimulus provided by arterial blood pressure.6,7 A possible role of cardiac sympathetic nerves in RH has been generally discounted,3,8-10 but the evidence in favor of this concept does not seem conclusive. Transmural distribution of coronary blood flow is affected by systolic extravascular pressure and by the resistance of the large tributary arteries.11 A lower tissue Po2 is present in the subendocardial layers of the left ventricle,12 which are known to be more vulnerable to ischemia than subepicardial layers.13 However, studies on the distribution of microspheres show that the endocardium has a higher blood flow than the epicardium [endocardial to epicardial ratio greater than 1] in animals with normal coronary arteries, as reported by most authors.11,13 Because redistribution of blood flow from the epicardium to the endocardium results from dilation of large intramural supply arteries,11 the sympathetic nerves may be implicated. Increases in sympathetic activity, as produced by stimulation of the left stellate ganglion (LSG)14 or duplicated by isoproterenol,15 decrease endo/epi ratio. In contrast, propranolol increases the endo/epi ratio,16,17 the effect being attributed primarily to the reduction in heart rate.18

Methods

Thirty-three mongrel dogs ranging in weight from 17 to 23 kg were used in this study. Of these, 19 were prepared for chronic studies and 14 were used in acute studies.

CHRONIC STUDIES

The dogs used for this portion of the study were free of heartworms and in good health prior to surgery. They were anesthetized with sodium pentothal (30 mg/kg, iv) and intubated. The level of anesthesia was maintained with a mixture of oxygen, nitrous oxide, and halothane. The left side of the thorax was entered through the 3rd intercostal space. The LSG, the ansa subclavia, and the rami communantes from T1 to T4 were identified. A length of nylon

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Supported in part by Grants HL-18798 and HL-14828 from the U.S. Public Health Service.

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Original manuscript received January 19, 1976; accepted for publication November 18, 1976.
monofilament suture was placed around the caudal portion of the ganglion near the entry of the T3 ramus and a second piece of suture was placed around the ansa subclavia at the cranial part of the ganglion. Both monofilament sutures were buried subcutaneously near the vertebralae on the left side. Care was exercised to make certain that the sutures remained loose around the ganglion to prevent undue tension on it.

The heart was exposed through the 5th intercostal space. The left circumflex coronary artery was dissected free of surrounding tissue from its origin for approximately 2.5–3 cm. Usually sufficient lengths of artery were obtained for the implantation of the flow probe and hydraulic occluder without sacrificing large epicardial branches. Great care was exercised in the dissection of this vessel to maintain the adventitia intact; and, in so doing, adipose tissue surrounding the vessel was not removed. A Doppler ultrasonic flow probe was placed around the vessel and secured in place. A hydraulic vascular occluder was placed around the vessel distal to the flow probe. A solid state pressure transducer (Konigsberg, model P-20) was positioned in the left ventricular cavity through an incision in the left ventricular apical dimple. A polyvinyl catheter was passed through the left atrial appendage to the left atrium and secured in place. Stainless steel electrodes were sutured to the right atrium about 2 cm apart. All lead wires and the left atrial catheter were brought out of the chest and tunneled to the dorsal surface of the neck where they exited from the skin. The chest incision was closed and the dog was allowed to recover.

Studies were started 3–4 weeks after implantation. Recordings of the left circumflex coronary artery flow velocity, left ventricular pressure, left atrial pressure, and the electrocardiogram (lead 2) were made on an eight-channel Beckman direct-writing oscillograph. The derivative of left ventricular pressure (dP/dt) was obtained by an analog differentiator with a time constant of 0.01 second and a linear frequency response to 65 Hz. This signal was recorded on the direct-writing oscillograph. The electrocardiogram was used to trigger a cardiotachometer for measurement of heart rate. The signals also were recorded on magnetic tape (Ampex FR-1300) for later analysis. The stainless steel electrodes were connected to a Grass S4 stimulator through an isolation unit. Pulse duration was set at 5 msec with voltage high enough to be able to sustain a paced heart rate. Four 10-second occlusions of the left circumflex were made at 10-min intervals. Two occlusions were repeated with the heart paced at 150 beats/min. Thus, at least six trials were made during each experiment. For most of the dogs three experiments were performed under each of the conditions under study, with the experiments separated by at least 2–3 days. In one of these experiments, both under control conditions and after bilateral stellectomy, the six trials were repeated after administration of propranolol (1 mg/kg) or phentolamine (1 mg/kg). α-Adrenergic blockade was tested by the intravenous injection of phenylephrine. Flow debt, reactive hyperemic flow, and repayment of flow debt were calculated as described by Coffman and Gregg.

Flow debt = control flow rate × duration of occlusion.

Reactive hyperemic flow = (integral of the flow curve during reactive hyperemia) − (control flow rate × duration of reactive hyperemia).

Percent repayment of flow debt = (reactive hyperemic flow/flow debt) × 100. [For simplicity, the percent repayment will be referred to in text and tables as reactive hyperemia (RH).]

When the control study had been completed, the dogs were anesthetized a second time in the same manner. The right chest was entered through the 3rd intercostal space. The right stellate ganglion (RSG) was dissected free, isolated in the same manner as the LSG, and then completely excised.

Two weeks after the removal of RSG, the experiments were repeated as under control conditions. At the end of the last experiment, the dogs were anesthetized with sodium pentothal (30 mg/kg, iv) and the nylon monofilament suture around the LSG was exposed. Both sutures were pulled simultaneously, culminating in the destruction of the LSG. After 6 days, a sequence of three experiments was repeated, including one with propranolol (12 trials). At this point, both stellate ganglia had been removed; this resulted in an almost complete (from a functional point of view) cardiac sympathetic denervation.

In three dogs the study began after right stellectomy (RSGx), and in one, after left stellectomy (LSGx). Two dogs were studied under control conditions and after RSGx. For technical reasons, it was not possible to continue the study with LSGx. In two dogs LSGx was performed without prior RSGx.

When the dogs were killed the left circumflex coronary artery was injected with acrylic and allowed to harden. The cross-sectional area was calculated from the dimension of this acrylic cast. Velocity of flow was converted to volume flow by multiplying the velocity by the cross-sectional area.

To reduce experimental variability, the data were grouped in the following way: the first trials of the control sessions were averaged and compared with the average of the first trials of the experimental sessions (after RSGx or LSGx) and so on with the second, third, and fourth trial of every session. Data were analyzed by Student’s t-test for paired observations. All values are expressed as means ± se.

**ACUTE STUDIES**

Fourteen mongrel dogs were used for this portion of the study. The dogs were anesthetized with α-chloralose (80 mg/kg, iv), intubated, and ventilated with a Harvard respirator. The heart was exposed on the right side and the sinoatrial node crushed. Pacing electrodes were sutured to the right atrium and pacing of the heart was begun at 162 beats/min. The right chest was closed and the dog was turned for exposure of the heart from the left side. The heart was exposed and catheters were placed in the left atrium and coronary sinus. An electromagnetic flow probe was carefully placed around the left circumflex artery. Ligatures were placed around the LSG. Both femoral arteries were cannulated. A catheter-tip pressure transducer (Millar) was passed into the left ventricle and a woven dacron catheter was positioned in the thoracic aorta to measure pressure.
After dissection of the coronary artery, both cervical vagi were cut to increase sympathetic activity. The dogs were allowed to stabilize for 1 hour while blood gases were determined with an Instrumentation Laboratories model 213 blood gas analyzer. The arterial pressure catheter was connected to a Statham P23Db pressure transducer zeroed to the midsternal line. The electromagnetic flow probe was connected to a Zepeda flowmeter. All signals were recorded on an eight-channel Beckman recorder. Continuous recordings of the electrocardiogram, left ventricular pressure, the first derivative of left ventricular pressure, arterial pressure, heart rate, and left circumflex coronary artery flow were made as described previously. The zero flow signal was determined before and after each injection of microspheres. Blood samples were taken from the arterial catheter and the coronary sinus catheter prior to each microsphere injection. The dog's body temperature was maintained at 37 ± 0.5°C during the course of the experiment. The flow probe was calibrated with the dog's blood at the termination of the experiments.

After the stabilization period the distribution of coronary flow across the myocardium was determined by the injection of carbonized microspheres into the left atrium. The microspheres (3M Co.) were 15 ± 5 μm in size, labeled with either 14C or 85Sr. The size distribution of the microsphere was determined by microscopic examination. The microspheres were drawn up into a syringe and mixed well before injection, as described previously. A total of approximately 8.5 x 10⁶ microspheres was injected. The microspheres were flushed into the atrium with saline. A second injection of microspheres was made 45 minutes after the first after ablation of the LSG in nine dogs while five dogs served as controls. Again, blood samples were taken from both the artery and coronary sinus. 21 After the second injection of microspheres, the hearts were killed and the hearts were removed and washed free of blood. The hearts were divided into left ventricular free wall, septum, and right ventricular free wall. The left ventricular free wall was further divided from base to apex into samples of 1-3 g. Each small sample was cut into equal epicardial and endocardial portions and placed in counting vials. The samples were weighed and counted in a 7.6 cm Nal well-type scintillation detector (Searle Analytic). The samples were counted for 10 minutes to establish a proper counting efficiency. The radioactivity from each sample was expressed as activity per gram of sample and the counts in each sample were corrected for nuclide interaction. The endocardial to epicardial ratio for each sample was determined. The samples comprising the central portion of the left ventricular free wall were used in the analysis of the data in each dog. The average value for the control and experimental periods was obtained by using the same location on the free wall and number of samples from each subject.

Myocardial oxygen consumption was calculated from the left circumflex coronary artery flow and the arteriovenous oxygen content difference. Statistical analysis was performed using a paired t-test.

### Results

#### EXPERIMENTS IN CONSCIOUS DOGS

Of the 19 dogs instrumented and completely studied in the control condition, one died of postsurgical complications after the right stellectomy, and technical failures in two dogs made the continuation of the study impossible. In two other dogs that were eventually killed because of an acute infection, RH decreased by 27% after bilateral stellectomy. The results reported here are based, therefore, on 14 dogs in which the various devices implanted performed well for the necessary periods of time, ranging from 50 to 65 days following surgery. In one of these dogs the LSG was damaged and, therefore, ablated in the first surgical session. The percentage of dogs that could not participate in the entire study is comparable with those reported in previous investigations.10

**Effect of RSGx**

In five dogs (24 experiments and 88 trials), RSGx did not affect RH (Tables 1 and 2; Fig. 1). The decrease from 486 ± 45% to 460 ± 40% (−5%) was not statistically significant. RSGx had a minor effect on blood pressure (−4%) but significantly decreased heart rate (−17%) and mean coronary flow (−17%). By contrast, dP/dt increased significantly (+13%).

Since heart rate, which is a major determinant of mean coronary flow, was reduced by RSGx, the study was repeated keeping the heart rate constant by atrial pacing. RH was unaffected by RSGx plus pacing. The increase from 453 ± 47% to 456 ± 56% (+1%) was insignificant. Pacing suppressed the decrease in mean coronary flow produced by RSGx (from 46 ± 17 to 47 ± 16 ml/min at

### Table 1 - Effect of Unilateral Stellectomy, and α- and β-Blockade on Reactive Hyperemia

<table>
<thead>
<tr>
<th>No. of dogs</th>
<th>Experiments</th>
<th>Trials</th>
<th>Reactive hyperemia (%)</th>
<th>Change (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSGx</td>
<td>5</td>
<td>24</td>
<td>486 ± 45</td>
<td>460 ± 40</td>
<td>−5</td>
</tr>
<tr>
<td>RSGx + P</td>
<td>5</td>
<td>25</td>
<td>453 ± 47</td>
<td>456 ± 56</td>
<td>+1</td>
</tr>
<tr>
<td>LSGx</td>
<td>5</td>
<td>16</td>
<td>476 ± 71</td>
<td>622 ± 86</td>
<td>+51</td>
</tr>
<tr>
<td>LSGx + P</td>
<td>3</td>
<td>9</td>
<td>407 ± 51</td>
<td>577 ± 106</td>
<td>+42</td>
</tr>
<tr>
<td>β-Blockade</td>
<td>4</td>
<td>4</td>
<td>447 ± 25</td>
<td>390 ± 27</td>
<td>−13</td>
</tr>
<tr>
<td>β-Blockade + P</td>
<td>4</td>
<td>4</td>
<td>456 ± 25</td>
<td>311 ± 24</td>
<td>−32</td>
</tr>
<tr>
<td>α-Blockade</td>
<td>7</td>
<td>14</td>
<td>419 ± 63</td>
<td>517 ± 71</td>
<td>+23</td>
</tr>
<tr>
<td>α-Blockade + P</td>
<td>5</td>
<td>10</td>
<td>368 ± 21</td>
<td>423 ± 34</td>
<td>+13</td>
</tr>
</tbody>
</table>

RSGx = right stellectomy; LSGx = left stellectomy; P = pacing; NS = not significant. All values are means ± se.
CIRCULATION RESEARCH VOL. 41, No. 1, JULY 1977

TABLE 2  
Effect of Unilateral Stellectomy on Reactive Hyperemia and Other Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Left stellectomy</th>
<th>Control</th>
<th>LSGx</th>
<th>Change (%)</th>
<th>Significance</th>
<th>Right stellectomy</th>
<th>Control</th>
<th>RSGx</th>
<th>Change (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH</td>
<td>476 ± 71%</td>
<td>622 ± 86%</td>
<td>+31</td>
<td>P &lt; 0.005</td>
<td></td>
<td>486 ± 45%</td>
<td>460 ± 40%</td>
<td>-5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>89 ± 9</td>
<td>80 ± 9</td>
<td>-10</td>
<td>P &lt; 0.05</td>
<td></td>
<td>106 ± 7</td>
<td>88 ± 3</td>
<td>-17</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>140 ± 9</td>
<td>130 ± 7</td>
<td>-7</td>
<td>NS</td>
<td></td>
<td>137 ± 5</td>
<td>131 ± 5</td>
<td>-4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>dP/dt_{max}</td>
<td>3132 ± 180</td>
<td>3172 ± 290</td>
<td>+1</td>
<td>NS</td>
<td></td>
<td>2994 ± 345</td>
<td>3394 ± 287</td>
<td>+13</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>MCF</td>
<td>36 ± 7</td>
<td>32 ± 4</td>
<td>-11</td>
<td>NS</td>
<td></td>
<td>41 ± 9</td>
<td>34 ± 7</td>
<td>-17</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

LSGx = left stellectomy; RSGx = right stellectomy; RH = reactive hyperemia; HR = heart rate (beats/min); BP = blood pressure (mm Hg); dP/dt_{max} = first derivative of left ventricular pressure (mm Hg/sec); MCF = mean coronary flow (ml/min); NS = not significant. All values are mean ± SE.

150 beats/min), suggesting that it was merely dependent on the change in heart rate.

In one of these five dogs the RSG was ablated after LSGx; this resulted, therefore, in a bilateral stellectomy. LSGx only slightly reduced RH also in this dog; this indicated that the lack of effect on RH of RSGx was independent of the sequence of experimental conditions.

**Effect of LSGx**

In five dogs (16 experiments and 60 trials) LSGx significantly increased RH, in comparison to the values after RSGx (three dogs) and to control values (two dogs), from 476 ± 71% to 622 ± 86% (+31%) (Tables 1 and 2; Fig. 1). There were minor changes in blood pressure, dP/dt, and mean coronary flow. The decrease in heart rate was small but significant and the study was repeated in three dogs while heart rate was kept constant by arterial pacing: RH was found to be increased more, from 407 ± 51% to 577 ± 106% (+42%).

The dog in which ablation of the LSG in the first surgical session did not permit the recording of control values was the one constantly showing the largest RH (811 ± 52%).

The peak hyperemic flow was 123 ± 11 ml/min before removal of the LSG and fell to 106 ± 4 ml/min (–14%). The decrease in the peak flow response to a 10-second occlusion was not significant.

**Effect of β-Blockade**

In four dogs (four experiments and 28 trials), propranolol (1 mg/kg) significantly reduced RH from 447 ± 25% to 390 ± 27% (–13%) (Tables 1 and 3; Fig. 1). Propranolol significantly decreased dP/dt and mean coronary flow. The decreases in heart rate and blood pressure were not significant but it must be noted that the reduction in heart rate (–16%) is smaller than that expected, probably because in two of the dogs in which propranolol was tested the RSG had been ablated. As with RSGx, the reduction in mean coronary flow was no longer present when heart rate was kept constant by atrial pacing. Pacing, however, did not abolish the effect of propranolol on RH, which was actually potentiated: RH was decreased from 456 ± 25% to 311 ± 24% (–32%).

The opposite effect produced by LSGx and propranolol prompted us to investigate whether the drug still could influence RH in a heart largely deprived of sympathetic innervation as in bilaterally stellectomized dogs. In two dogs after bilateral stellectomy, propranolol significantly decreased (–29%) when the heart rate was kept constant by pacing. Also, with spontaneous heart rate, propranolol reduced RH, but to a lesser degree (–10%).

**Effect of α-Blockade**

In seven dogs (14 experiments and 42 trials) phentolamine (1 mg/kg) significantly increased RH in comparison to control values, from 419 ± 63% to 517 ± 71% (+23%) (Tables 1 and 4; Fig. 1). There were no significant
Table 3  Effect of Propranolol on Reactive Hyperemia and Other Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous HR</th>
<th>Pacing</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
</tr>
<tr>
<td>RH</td>
<td>447 ± 25%</td>
<td>390 ± 27%</td>
</tr>
<tr>
<td>HR</td>
<td>91 ± 5</td>
<td>76 ± 7</td>
</tr>
<tr>
<td>BP</td>
<td>134 ± 5</td>
<td>126 ± 6</td>
</tr>
<tr>
<td>dP/dt_max</td>
<td>3508 ± 113</td>
<td>3010 ± 133</td>
</tr>
<tr>
<td>MCF</td>
<td>37 ± 13</td>
<td>30 ± 12</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. All values are mean ± se.

Table 4  Effect of Phentolamine on Reactive Hyperemia and Other Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous HR</th>
<th>Pacing</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>RH</td>
<td>419 ± 63%</td>
<td>517 ± 71%</td>
</tr>
<tr>
<td>HR</td>
<td>91 ± 7</td>
<td>113 ± 12</td>
</tr>
<tr>
<td>BP</td>
<td>134 ± 2</td>
<td>116 ± 17</td>
</tr>
<tr>
<td>dP/dt_max</td>
<td>3171 ± 262</td>
<td>3474 ± 272</td>
</tr>
<tr>
<td>MCF</td>
<td>28 ± 3</td>
<td>30 ± 2</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. All values are mean ± se.

changes in heart rate, blood pressure, dP/dt_max, or mean coronary flow after phentolamine blockade during spontaneous rhythm. With pacing, a small but significant increase in dP/dt_max was found (2,906 mm Hg/sec to 3,363 mm Hg/sec) after blockade. With heart rate kept constant by pacing in five dogs (10 experiments and 30 trials), phentolamine still significantly increased RH from 368 ± 21% to 423 ± 34% (+15%). Apparently α-blockade was duplicating the effects of LSGx; this suggested interference with the effects of neural activity passing through the LSG. In two dogs phentolamine was used after LSGx. In them, α-blockade did not modify RH during spontaneous heart rate. However with pacing, there was a slight, but not significant, decrease in RH.

ACUTE EXPERIMENTS

In nine dogs the transmural coronary blood flow distribution was determined by measuring the left ventricular subendocardium-subepicardium ratio of distribution of radioactive microspheres before and after left stellectomy (Table 5). LSGx significantly increased the endo/epi ratio from 1.17 ± 0.03 to 1.23 ± 0.04; this finding indicates a better perfusion of the subendocardium. Heart rate was kept constant by atrial pacing; and blood pressure, dP/dt, mean coronary flow, and O2 consumption were almost unchanged.

In the five control dogs in which no experimental procedures were conducted between the first and second injection of microspheres, the endo/epi ratio remained practically unmodified and showed only a slight decrease, from 1.12 ± 0.24 to 1.11 ± 0.24.

Discussion

MYOCARDIAL REACTIVE HYPEREMIA

To evaluate the possible role of the sympathetic nervous system in the phenomenon of RH, the following steps were considered important: (1) to measure RH before and after surgical denervation, the number of dogs being of secondary importance with respect to the number of trials and sessions in each condition, in order to minimize individual variability from day to day; (2) to compare surgical denervation with pharmacological blockade in order to gain insights into the mechanisms involved and to verify if the latter can duplicate the former, as often is assumed; (3) to perform the entire study under conditions of spontaneous and paced heart rate since both surgical and pharmacological interventions on the sympathetic innervation
alter, by reducing heart rate, hemodynamic parameters of possible importance such as mean coronary flow; (4) to study conscious dogs and thus avoid the shortcomings associated with anesthesia.

Vasodilation in response to a metabolite produced by even mild degrees of anoxia and the myogenic properties of vascular smooth muscle are presently the factors most often implicated in the production of RH. The involvement of any neural mechanism has been practically discarded on the basis of several experimental data, none of which seems conclusive. Olsson and Gregg found that atropine and guanethidine increased RH. This effect was considered to be dependent only on heart rate increases, but the experiments were not repeated during cardiac pacing. Gregg et al. studied five dogs with cardiac neural ablation and the degree of reactive hyperemic response (300-700%) was considered comparable to that found in normal dogs (500 ± 200%). These experiments suffer, however, from the lack of internal controls and, with such large variation in individual control values, changes produced by denervation in each dog could not be excluded. Eikens and Wilcken found that propranolol reduced the percent repayment from 471 ± 21% to 325 ± 28% (a reduction of 31%), a change strikingly similar to that obtained in our experiments with pacing (Table 3). These authors attributed this reduction to the lower preclosure mean coronary flow.

Right stellectomy, the LSG being either intact or sectioned, did not affect RH. Decreases in mean coronary flow and in heart rate were prevented in the experiments with pacing while RH remained unaffected by RSGx. The increase in dP/dt observed after RSGx confirms the suggestion that after unilateral stellectomy a baroreceptive reflex increases the sympathetic activity running through the contralateral stellate ganglion. Due to the predominant innervation of the left ventricle by fibers passing through the LSGx, this would result, as observed, in an actual increase in contractility.

In contrast, LSGx significantly increased RH. Hemodynamic changes that might explain this finding were not present and the decrease in mean coronary flow was similar to that associated with RSGx and unmodified RH, and with propranolol and reduced RH. Thus, a lower level of mean coronary flow, per se, does not influence RH. This is at variance with the suggestion offered by Eikens and Wilcken to explain the reduction in RH produced by propranolol.

RSGx performed after LSGx resulted in a minor decrease in RH. The dog in which LSGx was performed initially was the one showing the largest RH. The difference between the effect of RSGx and LSGx is therefore extremely likely to be independent of the sequence of ablation. A possible explanation for the difference observed is that the circumflex coronary artery is predominantly innervated by the LSG. The cardiac sympathetic nerves mediate both α- and β-adrenergic effects and their section, of course, interferes equally with both of them. The increase in RH produced by LSGx, which represents "the ability of coronary bed to dilate," suggested that a vasoconstrictor activity (possibly of the α type) was dominant. This suggestion was confirmed by finding that α-blockade increased RH as did LSGx, although to a lesser degree. The difference in magnitude is probably due to the fact that whereas LSGx completely interrupts all the fibers passing through the ganglion, α-blockade may often be less than 100% effective. An additional important finding was that α-blockade after LSGx was no longer effective.

Propranolol decreased RH. When heart rate was kept constant by pacing, preventing the reduction in mean coronary flow, the effect was even more marked. β-Blockade leaves unopposed the α-vasoconstrictor effect and it is not surprising that this results in a decreased RH. The opposite effect of LSGx and propranolol are, therefore, understandable. Unfortunately, too often β-blockade is still assumed to duplicate cardiac sympathetic denervation.

Coronary artery occlusion, through excitation of cardiac sympathetic afferent fibers, elicits a reflex increase in cardiac sympathetic efferent activity. This cardiocardiac sympathetic reflex, which is partially responsible for the arrhythmias associated with coronary artery occlusion, may contribute to the sympathetic effect on RH by increasing the vasoconstrictor tone.

Szentivanyi and Juhasz-Nagy reported that section of the coronary sympathetic vasomotor fibers, in acute experiments, diminishes or abolishes RH. According to Berne, however, this finding is suggestive of unresponsive vessels in deteriorating preparations. Our data in two acutely infected dogs support Berne's opinion, since a decrease in RH following bilateral stellectomy was observed.

The emerging concept of the cardiac sympathetic nerves representing a limiting factor for reactive hyperemia and the capability of the coronary bed to dilate, should not lead to the unjustified conclusion that coronary vasoconstriction of clinical importance may result from increased sympathetic activity.

MYOCARDIAL BLOOD FLOW DISTRIBUTION

Microspheres injected into the left atrium distribute systematically and, because of their size, are trapped in precapillary vessels in their first transit through the circulation. The 15-μm microspheres give a good estimate of flow distribution and have been used to study regional myocardial blood flow. It was found in our series of dogs that LSGx significantly increased the endo/epi ratio of distribution of microspheres. This effect was not associated with, and therefore was independent of, changes in blood pressure, dP/dt, mean coronary flow, and O2 consumption. These changes were probably minimized by the fact that we kept heart rate constant by atrial pacing. Thus, the interruption of the tonic activity present in the cardiac sympathetic nerves remains as the major factor responsible for the observed increase in the endo/epi ratio. Theoretically, this may be due to either an increase in endocardial perfusion or to a decrease in epicardial perfusion.
sympathetic nervous system has a
to a combination of both. The latter possibility
seems to be more likely since total flow from the circum-
flex artery did not change. It may be deduced that the
resistance to flow through subendocardial vessels has de-
creased, thus—with inflow constant—there would be a
greater portion of flow to the endocardium.
Luchida and Ueda44 used electrical stimulation of the
LSG and reduced the endo/epi ratio of myocardial blood
flow distribution. In their experiments, however, the
hemodynamic parameters were not controlled and the
results may have been partially dependent on, for in-
stance, an increase in left ventricular pressure or con-
tractility.
Propranolol has been found to increase the endo/epi
ratio; but this effect was associated with reductions in
heart rate.16, 17 Since the endocardial flow occurs mainly in
diastole, a decrease in heart rate may be expected to
increase flow. In fact, Gross and Winbury16 found that
when heart rate is kept constant, propranolol does not
modify the endo/epi ratio. However, they also found that
a decrease in heart rate, per se, does not change the endo/
epi ratio unless there is an associated increase in coronary
resistance, which is thought to be a result of metabolic
autoregulation. Therefore, a pure β-blocking action does
not seem to increase the endo/epi ratio of coronary blood
flow distribution.
Stellectomy interrupts both α- and β-adrenergic activi-
ty. Since the net effect was an increase in the endo/epi
ratio without hemodynamic changes, one may speculate
that interruption of a dominant α-activity was the causative
factor for the observed changes. A possible site of
action could be the intramural supply arteries. Interrup-
tion of a dominant α-constrictor activity would dilate
them, resulting in a redistribution of blood from the epi-
cardium to the endocardium.11
The significant change in endo/epi ratio was not large—
probably because of some limiting factors of our experi-
mentai conditions: (1) The heart was paced at 162 beats/
min to reduce the hemodynamic changes associated with
stellectomy, but at the same time the short diastolic inter-
val also reduced the possibility of greatly increasing endo-
cardial flow. (2) The changes in endo/epi ratio were not
obtained by electrical stimulation but were dependent on
the level of spontaneous activity present in the cardiac
sympathetic nerves. (3) Only part of the cardiac sympa-
thetic innervation was ablated since a unilateral left stel-
llectomy was performed. It is therefore likely that our
results have actually underestimated the tonic influence of
sympathetic nerves in limiting endocardial flow.

Conclusion

These two groups of experiments demonstrate that the
sympathetic nervous system has a tonic influence on coro-
nary circulation. The cardiac sympathetic nerves exert a
continuous restraint on the capability of the coronary bed
to dilate and on the endocardial perfusion. This effect is
likely to depend on a coronary vasoconstrictor activity of the
α-receptor type.34, 35 Recently we found that LSG
blockade markedly reduces the number of ectopic beats
associated with short-lasting coronary artery occlusion
in dogs.6 The favorable effect produced by LSGx on RH and
endocardial blood flow distribution may contribute,
together with the decrease in ventricular vulnerability14 and
excitability13 produced by LSGx, in explaining this result.
Recent experiments by Feigl46 indicate that "blood flow to
the heart, like that to other vascular beds, is potentially
under autonomic as well as metabolic control. " This state-
ment was based on data obtained with electrical stimula-
tion. Our experiments, in which we observed the effects of
simply removing part of the cardiac sympathetic innerva-
tion, confirm and extend Feigl's concept and indicate that
the coronary circulation is actually under autonomic
as well as metabolic control.

Acknowledgments

We are grateful to G. E. Todd for expert technical assistance. We wish to
thank Dr. Keith Morgan of the Division of Nuclear Medicine for his
assistance with the microsphere study.

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The Canine Heart As an Electrocardiographic Generator
Dependence on Cardiac Cell Orientation

L. Vincent Corbin, II, and Allen M. Scher

SUMMARY Traditionally it is assumed that during cardiac depolarization the macroscopic current generators that produce electrocardiographic voltages can be represented as a uniform double-layer source, coincident with the macroscopic boundary between resting and depolarized cardiac fibers as measured with extracellular electrodes ("uniform" hypothesis). A segment of this boundary is thus considered as a current dipole oriented perpendicular to the boundary. We present evidence that, contrary to the above, the effective dipoles largely parallel the long axes of cardiac fibers ("axial" hypothesis). Calculated potentials in volume conductors differ markedly in the two cases. The magnitudes of rapid local "intrinsic" deflections also differ markedly. In our experiments, potential fields produced by stimulation at several cardiac sites and measured magnitudes of intrinsic deflections during normal depolarization and that caused by stimulation support the axial hypothesis and are incompatible with the uniform hypothesis. Our results suggest that axial orientation of sources is sufficiently strong so that predictions assuming the uniform hypothesis would be seriously in error, although the axial theory alone does not exactly describe all the measured potentials. Axial orientation of current generators must be considered in quantitative prediction of electrocardiographic potentials. Further study of the geometry of the intracellular depolarization boundary and its relation to fiber direction and to the frequency of lateral intercellular junctions is required to describe the generators exactly.

THE ELECTROCARDIOGRAM (ECG) is of great utility in physiology and in cardiac diagnosis, but its shape has not been quantitatively predictable from a knowledge of intracardiac events. Such prediction, known as the electrocardiographic "forward" problem (usually dealing with ventricular depolarization and the QRS complex), has appeared feasible on the basis of available knowledge of (1) cellular electrical changes associated with depolarization of cardiac cells; (2) the sequence of these changes in the heart (pathway of depolarization); (3) geometry and conductivity of the torso and its contents; and (4) the physical theory describing current flow in three-dimensional, bounded, inhomogeneous conductors like the torso.<ref>18-21</ref> If the forward problem were solved, it would greatly strengthen the scientific basis of electrocardiography. Although all necessary information seems available, past attempts to solve the forward problem during ventricular depolarization<ref>19-23</ref> appear to us either qualitative and very difficult to evaluate or, when body surface maps that can be compared with real body surface maps have been produced, the studies do not show good agreement between the two. An explanation for failure to solve the forward problem may, we believe, be found in myocardial cellular anatomy, the electrophysiology of cardiac cell-to-cell conduction, and the manner in which cardiac cells generate external currents. These are the subject of this paper.

Cardiac cells are long and narrow (about 15 μm in diameter by 70 μm in length, with considerable variabil-
Tonic influence of the sympathetic nervous system on myocardial reactive hyperemia and on coronary blood flow distribution in dogs.
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Circ Res. 1977;41:51-58
doi: 10.1161/01.RES.41.1.51

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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