Distribution of Coronary Artery Flow to the Canine Right Atrium and Sinoatrial Node

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SUMMARY We assessed segmental distribution of blood flow to the right atrium and the region of the sinoatrial node using microspheres (7–10 μm) in 20 anesthetized dogs. Mean right atrial flow averaged 83 ± 7 (SE) ml/min × 100 g, which was 56% of the left ventricular blood flow. The distribution of right atrial flow was not homogeneous. For example, flow to anterior right atrial segments including the segment containing the sinus node was greater (105 ± 8 ml/min × 100 g) than mean right atrial flow. Following ligation of the sinus node artery, perfusion of the segment containing the sinus node decreased by only 36%. Relative preservation of perfusion to the sinus node following sinus node artery ligation may explain why ligation of the sinus node artery does not alter heart rate. Furthermore, we also found that cannulation and pump perfusion of the sinus node artery at pressures 10 and 50 mm Hg greater than systolic pressure did not alter the distribution of right atrial flow. Thus, because cannulation and perfusion of the sinus node artery do not artifactually distort regional right atrial blood flow, we conclude that this should be a useful method for evaluating responsiveness of the sinus node to various interventions.

THE SINOATRIAL node with its dominant effect on cardiac pacemaker function occupies a preeminent position in the control of heart rate in man and many animals. Located in close proximity to the dominant atrial artery, the sinus node artery, it is easily accessible for experimental interventions. In numerous studies of the pharmacology of sinus node automaticity, the sinus node artery is used to deliver drugs, hormones, and other chemical agents to the sinus node. The responses of the sinus node to these interventions must be related to the pattern and extent of perfusion of the atrium from the sinus node artery and other atrial arteries.

Ligation of the sinus node artery has been shown not to alter the rate of sinus node discharge. In addition, the response of the sinus node to pharmacological interventions is quantitatively different with various experimental methods for sinus node artery perfusion. To find an explanation for these observations we assessed total and regional atrial blood flow under a variety of conditions: during normal perfusion, after transient occlusion of the sinus node artery, and during various methods of sinus node perfusion.

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Methods

PREPARATION OF ANIMALS

Twenty adult mongrel dogs of both sexes weighing 15–25 kg were anesthetized with intravenous α-chloralose (50 mg/kg) and urethane (500 mg/kg). The dogs were ventilated via a cuffed endotracheal tube with room air and supplemental oxygen using a volume respirator adjusted to maintain normal arterial blood gases and pH. Periodically the lungs were hyperinflated to prevent atelectasis.

The left chest was opened. A cannula was placed in the left atrium for injections of microspheres, and the chest was closed. Catheters were placed in the brachial and right and left femoral arteries for withdrawal of reference arterial blood samples and measurement of pressure. Arterial pressure was measured with a Statham P23Db strain gauge leveled at the midchest. The electrocardiogram was recorded from standard limb leads and heart rate was calculated with a tachometer. All signals were recorded on a direct-writing recorder. A right thoracotomy was performed and the right coronary artery and its distal branch supplying the region of the sinus node (hereafter referred to as the sinus node artery) were identified. If the sinus node artery did not arise from the right coronary artery, the dog was not included in the study. This occurred in 5% of the dogs studied. All dogs were treated with heparin. 500 U/kg. iv.

SINUS NODE ARTERY CANNULATION AND PERFUSION

In 17 dogs the sinus node artery was cannulated with polyethylene tubing (outside diameter = 0.09–0.21 cm).
and perfused by an infusion pump (Holter model RL175) with autologous blood obtained from the femoral artery. Perfusion pressure was monitored with a strain gauge joined to a T-connector. A second T-connector placed distal to the pump allowed withdrawal of reference blood samples for the sinus node artery pump injections after pump mixing, but before sinus node perfusion. Flow in the perfusion pump was adjusted to achieve a mean pressure in the sinus node artery perfusion system that was 10 mm Hg higher than systolic arterial pressure. In some studies, perfusion pressure in the sinus node artery was increased to a value 50 mm Hg greater than systolic pressure by increasing pump flow.

**PROTOCOL**

Measurements of atrial and ventricular blood flow were obtained by using radioactive microsphere techniques.

1. To assess the importance of the sinus node artery as a source of right atrial perfusion, total and regional right atrial flow were measured in all dogs during normal perfusion and 5 minutes after temporary occlusion of the sinus node artery with an atraumatic neurosurgical clamp. In these dogs microspheres were injected into the left atrium. The effect of cannulation and perfusion of the sinus node artery on the distribution of atrial flow was assessed by comparing the distribution of microspheres with left atrial injections during normal perfusion (1) and with pump perfusion (2).

2. To determine the amount of blood supplied to the region of the sinus node via the sinus node artery and the amount supplied via other vascular channels, in five dogs the sinus node artery was cannulated and two differently labeled batches of microspheres were injected simultaneously; one isotope was injected directly into the left atrium, the other into the cannulated, pump-perfused sinus node artery. The effect of cannulation and perfusion of the sinus node artery on the distribution of atrial flow was assessed by comparing the distribution of microspheres with left atrial injections during normal perfusion (1) and with pump perfusion (2).

3. In seven dogs we assessed the effect of increasing pump perfusion pressure from 10 to 50 mm Hg above systemic systolic pressure on total and regional right atrial blood flow. In these experiments, the sinus node artery was cannulated and pump-perfused and perfusion pressure was increased by increases in pump flow. Microsphere injections were made proximal to the pump after hemodynamic parameters during perfusion had been stable for 5 minutes.

4. We assessed the effect of the alterations in the distribution of flow that resulted from changes in perfusion pressure on the pharmacological responses of the sinus node to injections of acetylcholine and norepinephrine into the cannulated sinus node artery and constant flow pump perfusion. In these studies, the sinus node artery was cannulated, pump perfusion was established, and microspheres were injected proximal to the perfusion pump. The pump was then removed and a direct injection of differently labeled spheres was delivered from a hand syringe in 1.0-ml volume over 30 seconds. Since no mixing of blood with spheres occurs with the latter injections, no reference flow could be obtained. Therefore, in these studies the relative regional distribution of perfusion was estimated by calculating the regional distribution of microspheres as a percentage of the total number of spheres injected.

**PHARMACOLOGICAL STUDIES**

The response of the sinus node to pharmacological agents was assessed by injecting acetylcholine, 10 and 50 µg, and norepinephrine, 0.1 and 0.5 µg, into the sinus node artery perfusion system. The drugs were diluted in normal saline to volume of 0.1 ml and injected in 1 second by hand upstream from the infusion pump to avoid increases in sinus node artery pressure. The sinus node response was taken as the peak change in heart rate that occurred within 30 seconds after injection.

**MEASUREMENT OF BLOOD FLOW**

We used microspheres 7-10 µm in diameter and labeled with 85Sr, 86Sr, 51Cr, and 141Ce. For each flow measurement we used between $1.3 \times 10^8$ and $3.0 \times 10^8$ tracer microspheres suspended in 0.5 ml of saline. Before injection, the vial containing the microspheres and 1 drop of polysorbate 80 (Tween 80) were vigorously agitated for 4 minutes. Microscopic examination showed that 98% of the spheres were completely dispersed. Occasional groups of 3-5 spheres were observed. Starting 1 minute before injection and continuing until 3 minutes after injection, blood was withdrawn simultaneously with Harvard pumps from the right brachial and femoral arteries at 2.06 ml/min into glass syringes. The microspheres were injected over a 15-second period and the cannula was flushed with 5 ml of saline at 37°C during the subsequent 20 seconds.

After each study the dog was killed with an injection of potassium chloride. The heart was excised and the right atrium removed in its entirety. The atrium was opened along a line bisecting the atrial appendage and coursing along the atrioventricular groove so that the epicardial surface was exposed. Figure 1 shows the atrium as viewed from its epicardial surface with the anterior surface of the atrium to the right and the posterior wall and interatrial septum to the left. Using the origin of the sinus node artery and the inferior and superior vena cava as reference points, the atrium was divided into 16 segments [average weight = 0.67 ± 0.3 (SE) g]. Transmural right and left ventricular myocardial samples (average weight = 1.0 ± 0.5 g and 2.0 ± 0.5 g, respectively) were also taken. The segments were weighed to the nearest milligram, placed in glass tubes containing 10% formalin, and counted for 5 minutes in a 3-inch well-type gamma counter. The reference blood samples were divided into samples so that the counting geometry was similar to that of the atrial samples. To perform isotope separation, standard techniques were used.

The blood flow, sample weight, and atrial location of each segment were punched on cards and subsequent analysis was then performed with the PDP 11 computer.
Flow, sinus node, anterior atrial, posterior atrial, atrial appendage).

Control 2 (injection of microspheres into the left atrium)

SNA cannulated and pump perfused (injection of microspheres into the perfusion pump)

Table 1  Atrial Blood Flow Distribution

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Sinus node segment</th>
<th>Anterior atrial segments</th>
<th>Posterior atrial segments</th>
<th>Atrial appendage segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Flow</td>
<td>% of control total flow</td>
<td>Flow</td>
<td>% of control total flow</td>
<td>Flow</td>
</tr>
<tr>
<td>Control 1</td>
<td>20</td>
<td>82.0 ± 7*</td>
<td>104.8 ± 12*</td>
<td>105.5 ± 8**</td>
<td>66.1 ± 6*</td>
</tr>
<tr>
<td>SNA occluded</td>
<td>20</td>
<td>63.8 ± 5</td>
<td>68.8 ± 6</td>
<td>65.0 ± 5</td>
<td>63.0 ± 7</td>
</tr>
<tr>
<td>Control 2</td>
<td>5</td>
<td>118.0 ± 12*</td>
<td>157.8 ± 11*</td>
<td>164.9 ± 11*</td>
<td>102.9 ± 16*</td>
</tr>
<tr>
<td>SNA cannulated</td>
<td>5</td>
<td>48.6 ± 5</td>
<td>90.8 ± 5</td>
<td>107.7 ± 5</td>
<td>17.3 ± 7</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se; flow values are in ml/min × 100 g; SNA = sinus node artery; bracketed measurements were obtained simultaneously; n = number of dogs.

* P < 0.05, significance level of pairwise comparisons (control flow vs. intervention) for each of the five segment groups (total atrial flow, sinus node, anterior atrial, posterior atrial, atrial appendage).
† P < 0.01 (segment flow compared to control total flow).
‡ P not significant (segment flow compared to the anterior atrial segment flow).
§ Pump perfusion was at 10 mm Hg > than systolic pressure.

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REGIONAL DISTRIBUTION OF RIGHT ATRIAL BLOOD FLOW

Under control conditions, right atrial flow was 83 ± 7 ml/min × 100 g. Perfusion of transmural segments of the right and left ventricles measured simultaneously was 116 ± 12 and 150 ± 10 ml/min × 100 g, respectively. Thus, right atrial flow per gram was 72% of right ventricular perfusion and 55% of left ventricular perfusion. Flow to the right atrium was not uniformly distributed (Table 1). Blood flow to the six anterior atrial segments, including the segment that contained the sinoatrial node, was greater (106 ± 9 ml/min × 100 g) than flow to the atrial appendage or the posterior atrial wall segments (79 ± 10 and 66 ± 6 ml/min × 100 g, respectively). Flow to the sinus node segment was not significantly different from the mean flow to the total anterior wall segments.

EFFECTS OF TEMPORARY OCCLUSION OF THE SINUS NODE ARTERY

Heart rate was unchanged by sinus node artery occlusion (175 ± 6 and 169 ± 6 beats/min before and after pump perfusion was at 10 mm Hg > than systolic pressure.
Effects of altering sinus node perfusion pressure on responses of the sinus node to pharmacological interventions

The effects of norepinephrine and acetylcholine injections into the sinus node artery perfusion system at different perfusion pressures are shown in Figure 4. The response to norepinephrine injections was not altered by changing perfusion pressure, but the response to a large dose of acetylcholine was more pronounced if the acetylcholine was injected when perfusion pressure was greater.

Effects of direct injection compared to pump perfusion on atrial blood flow distribution

The percentage of the total spheres delivered to the segment containing the sinus node was 5.8 ± 1.9% with pump perfusion and 9.3 ± 1.7% with direct injections. The average percentage of total counts for each isotope delivered to the combined anterior atrial segments and the overall distribution of counts were similar with either method. Although with direct injections a greater percentage of radioactivity appeared to localize in the segment containing the sinus node, these differences were not statistically significant (Table 3).

Discussion

Although there have been many studies of regional right and left ventricular blood flow, little attention has been given to regional atrial blood flow. Domenech and coworkers noted that atrial flow per gram was significantly less than right or left ventricular flow. Our studies confirm these results, and furthermore demonstrate that blood flow is not uniformly distributed to the right atrium. Specifically, the blood flow to the anterior segments and to the segment containing the sinus node is about 30% higher than flow to the remainder of the right atrium. It should be noted, however, that although the sinus node was localized to a single atrial segment weighing about 0.6 g, we cannot be certain that blood flow to the segment is representative of flow to the sinus node, since flow within the segment could be heterogeneous.

Our studies also demonstrate that the sinus node artery contributes about two-thirds of the flow to the sinus node region. After occlusion of the sinus node artery, however, flow to the region of the sinus node decreases by only one-third.
The response to 50 ng of acetylcholine, however, is significantly increased at the higher perfusion pressure.

There are no significant differences in the tachycardia produced by norepinephrine at either dose level. There are no significant differences in the regional distribution of right atrial flow. Increases in systemic systolic pressure do not alter the distribution of flow to the anterior atrial segments or flow to the segment that contains the sinus node. Increasing the sinus node artery perfusion pressure to 50 mm Hg above systemic systolic pressure also does not significantly alter perfusion to these segments but may alter the pharmacological responses to chronotropic agents.

Several experimental techniques to study the effect of physiological and pharmacological interventions on sinus node automaticity require cannulation of the sinus node artery. The first technique developed was direct injection of drugs into the sinus node artery. This technique causes an abrupt increase in pressure in the sinus node artery which in turn causes bradycardia. Another technique that avoids this problem involves pump perfusion of the sinus node artery. Our data indicate that sinus node artery perfusion at a pressure 10 mm Hg greater than systemic systolic pressure does not alter the distribution of flow to the anterior atrial segments or flow to the segment that contains the sinus node. Increasing the sinus node artery perfusion pressure to 50 mm Hg above systemic systolic pressure also does not significantly alter perfusion to these segments but may alter the pharmacological responses to chronotropic agents.

Use of the pump perfusion technique to study sinus node function requires considerably larger drug doses than are needed to achieve comparable responses with the direct injection method. When direct injection of spheres into the sinus node artery was compared with injection during pump perfusion, the relative distribution of spheres to the segment containing the sinus node tended to be greater during direct pressure injection although the differences did not achieve statistical significance. Although these studies do not demonstrate redistribution of flow to the sinus node segment as an explanation for the differences observed in pharmacological studies utilizing these two techniques, it is possible that flow within the sinus node segment itself is nonuniform. Direct injections could result, therefore, in a greater flow to the sinus node itself, though total flow to the sinus node segment might not increase significantly. Differences in transit time or volume of drug distribution may also contribute to these findings.

In summary, this study has demonstrated that right atrial flow is inhomogeneously distributed and tends to be greater in the anterior atrial segments and in the atrial segment containing the sinus node. There is a dual blood supply to the region of the sinus node in the dog, and after ligation of the sinus node artery, perfusion to the region of the sinus node is relatively well preserved. Sinus node artery cannulation and perfusion at pressures that are 10 mm Hg greater than systemic systolic pressure do not alter the regional distribution of right atrial flow. Increases in
perfusion pressure were not shown to alter the distribution of flow but may alter the pharmacological response to some chronotropic agents.

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