Retrograde Radioisotope Myocardial Perfusion Patterns in Dogs


SUMMARY

A retrograde coronary vein injection technique for concentrating radioisotope in ischemic myocardial regions was evaluated in dogs. Potassium-43 in saline solution was injected into the coronary veins during complete closure of the coronary sinus. In the presence of coronary inflow obstruction, the venous potassium-43 was distributed mainly to the low pressure vessels in ischemic heart regions; i.e., the ratio of potassium-43 in the occluded-to-unoccluded areas ranged from 2:1 to 3:1 thirty seconds after retrograde injections. Krypton-85 in saline solution was injected under pressure into the coronary veins during partial closure of the coronary sinus. In the presence of inflow obstruction, the ratio of krypton-85 in the occluded-to-unoccluded areas ranged from 4:1 to 6:1 sixty seconds after retrograde injections; larger ratios may be expected after rapid washout of gas from the normally perfused region is nearly complete. Myocardial potassium-43 imaging techniques were applied to locate and measure the size of the ischemic heart region as a radioisotopic hot spot. Detection of hypoperfused areas of extremely small size may be accomplished by this technique.

Additional Indexing Words:
Myocardial imaging
Krypton-85

In efforts to assess regional myocardial ischemia in the presence of coronary artery disease, a variety of radioactive myocardial scanning techniques have been developed.1-11 In general, these methods are based on the premise that the myocardial distribution of radioisotope and coronary flow are identical once circulation after the radioisotope is injected at a site proximal to the coronary bed. A radioisotopic cold spot is then interpreted to represent a region of myocardial ischemia.

An alternate to the antegrade precoronary path for injecting radioisotope in the closed chest subject is available. Gregg and Dewald12 have shown that backward perfusion of the left ventricle from the coronary veins is possible. Harman et al.13 applied the principles of retrograde coronary perfusion by injecting a saline solution of krypton-85 into the coronary veins for the purpose of delivering radioisotope to the left ventricular tissues. After the injection, the krypton-85 washout phase was monitored precordially and accurate measurements of myocardial flow were made.

In the present study, we have taken a second look at the retrograde coronary route as an approach to concentrating radioisotope in the underperfused regions of a heterogeneously perfused heart. The retrograde approach was evaluated as a possible means of improving the reliability of the currently available precordial counting techniques for detecting myocardial ischemia.

Methods

Data were collected in experiments with 19 mongrel dogs ranging in weight from 17-24 kg. All animals were anesthetized with 30 mg/kg body weight of intravenously administered pentobarbital, secured in the right lateral decubitus position, intubated, and ventilated with a Harvard pump respirator. Right and left heart catheterizations were performed under fluoroscopic control with the following procedures: 1) A 8 French lumen, end hole catheter, with a 1.0 ml capacity, balloon mounted just proximal to the end hole, was inserted via the left jugular vein and advanced to the coronary sinus. The sinus catheter was employed to occlude the coronary sinus, inject saline solutions of radioisotope, and record sinus pressure. 2) A 7 Eppendorf catheter was passed via the left femoral artery and positioned in the thoracic descending aorta, from which point the systemic pressure was recorded. A 7 Eppendorf catheter was advanced from the left carotid artery to the left...
ventricle to record pressure. A left thoracotomy was performed at the fourth intercostal space and the pericardium incised.

The animals were grouped according to the procedures described in the following sections.

Group I (dogs 1-3): A Statham flow probe was implanted upon the aortic root to measure the left ventricular stroke volume. Snares for producing arterial occlusions were placed around proximal anterior descending artery in each animal. Dogs 1-3 and 4-9 (below) were employed in the sinus closure hemodynamic and retrograde potassium-43 injection studies described later.

Group II (dogs 4-6): The proximal portion of the anterior descending artery was dissected, ligated, canulated just distal to the ligature and perfused from the right femoral artery. The proximal circumflex artery was dissected free in order to implant a Statham a-c electromagnetic flow probe.

Group III (dogs 7-9): The proximal circumflex artery was cannulated and perfused from the right femoral artery. A Statham flow probe was positioned on the proximal anterior descending artery.

Group IV (dogs 10-13): Snares were placed around the proximal anterior descending artery in dogs 10 and 11 and around the proximal circumflex artery in dogs 12 and 13. The snares were employed to establish arterial occlusions during the myocardial scanning studies described later.

Group V (dogs 14-19): No coronary arterial interventions were made in dogs 14 and 15 (control animals); snares were placed around the proximal anterior descending artery in dogs 16 and 17 and around the proximal circumflex artery in dogs 18 and 19. The snares were employed to produce arterial obstruction during the retrograde krypton-85 injection studies described later.

After the major surgical manipulations and prior to the insertion of all catheters, heparin (10 mg/kg body weight) was given intravenously and followed by repetitive doses of 2 mg/kg body weight every 30 min. The coronary sinus, aortic, and left ventricular catheters were connected to Statham strain gauge transducers. The Statham flow probes were connected to a Statham M4001 flowmeter. A sine wave pump was employed to obtain an in vitro calibration of the various flow probes. Flow and pressure were recorded with an Electronics for Medicine recorder. The ECG was monitored continuously throughout the experiment.

In dogs 1-9, the following systemic and coronary hemodynamic measurements were made 15 sec before and 3 min after sinus closure was established: 1) mean aortic pressure; 2) left ventricular end-diastolic pressure recorded at the highest amplifier gain and read during end expiration; 3) in dogs 4-9, coronary arterial inflow by the flowmeter method; 4) in dogs 1-3, the left ventricular stroke volume; and 5) heart rate.

The measurements mentioned above were made 1) in the absence of inflow obstruction and 2) after inflow obstruction was established for at least 3 min prior to complete sinus closure. These measurements were repeated during partial sinus closure sufficient to establish a peak systolic pressure of approximately 30-40 mm Hg.

In dogs 4-9, retrograde injections of potassium-43 were made as follows. The coronary cannula was clamped for 5 min, after which the coronary sinus was occluded. Five heart beats after sinus closure, 0.2 to 0.5 mCi of potassium-43 in 3.0 ml saline was injected into the sinus catheter over a 2 sec period. This injection was immediately followed by a 1.5 ml saline flush. The sinus balloon was deflated 5 sec after the saline flush. One minute after the retrograde injection, the heart was removed from the thorax. The anterior descending and circumflex myocardial regions were dissected according to the epicardial arterial anatomy.

Myocardial imaging with a rectilinear scanner was performed in dogs 10-13 after retrograde potassium-43 injections as follows: coronary inflow obstruction was established with closure of the anterior descending artery in dogs 10 and 11 and the circumflex artery in dogs 12 and 13; xylocaine (1 mg/kg body weight) was administered immediately after the arterial closures; electrocardioversion was required to terminate episodes of ventricular fibrillation in dogs 11 and 12. Five min after arterial closure, potassium-43 was injected into the coronary veins in the manner described earlier. Myocardial scanning was initiated 1 hr after the retrograde potassium-43 injection. The scanning technique has been described in a previous report. Direct measurements of the regional potassium-43 concentrations were made after the scanning procedure.

In dogs 14-19, retrograde injections of krypton-85 were made as follows. The coronary arterial snare was fastened for 5 min prior to partial sinus closure sufficient to elevate the peak sinus pressure to 30-40 mm Hg. Krypton-85 in 5.0 ml saline was injected into the sinus catheter over a 1-2 sec period; this was immediately followed by a 1.5 ml saline flush. The sinus balloon was deflated 5 sec after the saline flush. One minute after the retrograde injection, the heart was removed from the thorax. The anterior descending and circumflex myocardial regions were dissected according to the epicardial arterial anatomy and the tissue count rates measured in the manner described earlier.

**Results**

Measurements were made to assess the acute effects of coronary sinus occlusion on the systemic and coronary hemodynamics in nine dogs. These measurements were made in both the presence and absence of coronary inflow obstruction. The results are compiled in table 1; statistically significant changes did not occur. The baseline-to-3 min hemodynamic measurements during partial sinus closure in the presence of coronary inflow obstruction are summarized as follows: 1) mean aortic pressure (mm Hg), 85/85 (NS); 2) left ventricular end-diastolic pressure (mm Hg), 7.2/7.4 (NS); 3) coronary inflow (ml/min).
Table 1

<table>
<thead>
<tr>
<th>Without inflow obstruction</th>
<th>With inflow obstruction</th>
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<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td></td>
<td>15 sec</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
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</tr>
<tr>
<td>(dogs #1–9)</td>
<td>87 ± 6</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
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<td>(dogs #1–9)</td>
<td>5.9 ± 1.6</td>
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<tr>
<td>Cor. INFLOW (ml/min)</td>
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</tr>
<tr>
<td>(dogs #4–9)</td>
<td>34.8 ± 4.1</td>
</tr>
<tr>
<td>LVSV (ml)</td>
<td></td>
</tr>
<tr>
<td>(dogs #1–3)</td>
<td>12.7 ± 2.4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
</tr>
<tr>
<td>(dogs #1–9)</td>
<td>112 ± 7</td>
</tr>
</tbody>
</table>

*All values given are means ± standard deviations.

Abbreviations: MAP = mean aortic pressure; LVEDP = left ventricular end-diastolic pressure; Cor. = coronary; LVSV = left ventricular stroke volume; HR = heart rate.

38.2/37.6 (NS); 4) left ventricular stroke volume (ml), 10.6/10.9 (NS); 5) heart rate (beats/min), 114/113 (NS).

Direct in vitro counting techniques were employed to measure the potassium-43 concentrations, i.e., C(43K) = counts per minute per gram of tissue, in the ischemic and nonischemic left ventricular, right ventricular, and atrial regions of hearts removed from the thorax 30 sec after coronary vein injections. The results for the individual animals are reported in table 2. When the anterior descending artery was occluded, the anterior descending-to-circumflex C(43K) ratio ranged from 2:1 to 4:1. In the absence of inflow obstruction, the circumflex-to-anterior descending C(43K) was approximately 1.3:1. The latter observation is consistent with the possibility that larger portions of isotope are delivered to the coronary veins nearest the sinus catheter.

Myocardial scans were made 1 hr following retrograde potassium-43 injections in the acutely ischemic canine heart. The scans shown in figure 1 were made from dogs 10 and 11 during closure of the anterior descending artery. Figure 2 depicts the scans made from dogs 12 and 13 during closure of the circumflex artery. All scans clearly show a well-delineated radioisotopic hot spot over the ischemic region.

Table 2

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Artery closed</th>
<th>Atrial C (43K) (CPM/gm) 10^-7</th>
<th>RV C (43K) (CPM/gm) 10^-7</th>
<th>AD C (43K) (CPM/gm) 10^-7</th>
<th>CX C (43K) (CPM/gm) 10^-7</th>
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<td>1.2</td>
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<td>7</td>
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<td>0.8</td>
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<tr>
<td>8</td>
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<tr>
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<td>6.6</td>
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<td>1.3</td>
<td>35.3</td>
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<tr>
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<td>CXA</td>
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<td>2.2</td>
<td>9.1</td>
<td>46.4</td>
</tr>
<tr>
<td>13</td>
<td>CXA</td>
<td>1.0</td>
<td>1.0</td>
<td>13.8</td>
<td>52.9</td>
</tr>
</tbody>
</table>

Abbreviations: C(43K) = 43K tissue concentration; CPM/gm = counts per minute per gram; RV = right ventricle; AD = anterior descending; CX = circumflex; ADA = anterior descending artery; CXA = circumflex artery.

*C(43K) measurements were made 1 hr after retrograde 43K injections; measurements in dogs 1–9 were made 30 sec after injection.

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region. After scanning, direct in vitro counting techniques were employed to measure the regional C(43K); the results are reported in table 2. The ischemic area-to-nonischemic area C(43K) ratios in dogs 10-13 ranged from 3.5:1 to 5:1 and were relatively high compared to the ratios found in dogs 4-9 when measurements were made 30 sec after the retrograde potassium-43 injections. The higher ratios in dogs 10-13 may possibly reflect flow related regional differences in the rate of myocardial potassium-43 loss.

Direct in vitro counting techniques were employed

Figure 1

Myocardial scans of dog 10 (part a) and dog 11 (part b). These animals were prepared with occlusions of the proximal anterior descending artery. Apex of heart is at the 5 o'clock position. The boundary of the heart, indicated by the dotted line, was determined from a teleroentgenogram.
to measure the krypton-85 tissue concentrations, i.e., $C(\text{Kr}) = \text{counts per minute per gram of tissue}$, in the ischemic and nonischemic left ventricular regions 1 min after coronary vein injections during partial sinus closure. The results are given in table 3. The ischemic area-to-nonischemic area $C(\text{Kr})$ ratios in dogs 16-19 ranged from 4:1 to 6:1. The distribution of krypton-85 was nearly uniform in the absence of inflow obstruction (dogs 14 and 15).

**Discussion**

The possibility of retrograde myocardial perfusion from the coronary veins was first reported by Gregg and Dewald. These investigators observed that the...
retrograde flow from a coronary artery, opened to atmospheric pressure distal to its proximal occlusion, was greatly increased following closure of the coronary sinus. They also noted a large increase in the peripheral pulse pressure of an acutely occluded left coronary ramus within a few heart beats after abrupt sinus closure. Approximately 4-8 cardiac cycles following closure of the sinus, the epicardial arterial vessels distal to an occlusion were deeply cyanotic. Assuming the intraluminal oxygen consumed by the arterial wall was negligible, the rapid appearance of intense cyanosis in the occluded arterial vessels was consistent with a sizable and brisk intermixing of arterial and capillary, and perhaps, venous blood. The observations presented here suggest the presence of an oscillating to-and-fro component of flow in the ischemic myocardial region following closure of the coronary sinus. Possible mechanisms for the biphasic flow pulse include: 1) the retrograde myocardial compression of a large intramural vascular blood volume which increases following outflow obstruction and 2) the retrograde pumping of venous blood into the ischemic bed by the normally perfused regions. Further discussion of the latter mechanism follows.

After sinus closure, the coronary venous inflow delivered by the normally perfused region distends the coronary veins and greatly elevates the venous systolic pressure which approaches and occasionally exceeds the peak systolic left ventricular pressure. During this time, a portion of the venous blood volume may leave through the Thebesian veins into the ventricular and atrial chambers and thus limit the extent of venous engorgement. In the presence of arterial occlusion, another portion of the venous blood may be forced backward into the ischemic bed as a consequence of the pressure gradient generated between the coronary veins and the peripheral channels of the occluded artery. The compliant epicardial arterial network beyond the central occlusion would appear to be a ready recipient of a retrograde flow pulse delivered through the low resistance vasodilated arterioles of an acutely ischemic myocardial region. Poor contractility of the ischemic myocardium would presumably heighten the magnitude of the retrograde flow pulse arising at the coronary vein level. During diastole, the distended channels of the ischemic bed undergo passive decompression and thereby return blood delivered during the preceding systole to the venous circulation. This forward component of flow completes the cycle of a biphasic capillary perfusion. A superimposed unidirectional component of retrograde capillary flow is possible if arteriolar-to-Thebesian vein shunts are opened and drained by the heart chambers.

Although the backflow of unmodified, unoxygenated coronary venous blood would appear to be valueless in preserving the viability of ischemic myocardium, it does provide a vehicle for the delivery of potassium-43 to the ischemic bed. In the presence of inflow obstruction, potassium-43 injected into the coronary veins during sinus closure is distributed mainly to the ischemic regions (table 2). The hemodynamics, described above, are in accordance with the pattern of myocardial potassium-43 distribution in the heterogeneously perfused heart, i.e., the normally perfused myocardium pumps a portion of the venous pool of potassium-43 into the ischemic zones.

The greatest difference between the potassium-43 tissue concentration in the ischemic and nonischemic regions is undoubtedly obtained in preparations with abrupt and complete closure of a left coronary ramus. Under these conditions, both vasodilation and diminished contractility in the ischemic region favor the retrograde delivery of potassium-43 to the occluded vessel. In the presence of lesser degrees of inflow obstruction, the regional differences in the potassium-43 tissue concentration would, in theory, be less striking. In the absence of inflow obstruction, the retrograde potassium-43 uptake by the homogeneously perfused left ventricle was nearly uniform (table 2). Gregg and Dewald have reported that abrupt closure of the coronary sinus results in an increase in

Table 3

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Artery closed</th>
<th>Atrial C (K) CPM/gm</th>
<th>RV C (K) CPM/gm</th>
<th>AD C (K) CPM/gm</th>
<th>CX C (K) CPM/gm</th>
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</thead>
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<td>14</td>
<td>NONE</td>
<td>5</td>
<td>5</td>
<td>55</td>
<td>59</td>
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<td>19</td>
<td>81</td>
<td>410</td>
</tr>
<tr>
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<td>CXA</td>
<td>10</td>
<td>12</td>
<td>60</td>
<td>368</td>
</tr>
</tbody>
</table>

C(K) = K tissue concentration. All other terms are defined in footnote of table 2.
the size of the heart during diastole, a significant decrease in the arterial inflow to the normally perfused regions, and marked cyanosis of the left ventricle. The latter observation does not, of course, assess the adequacy of tissue oxygenation in the deeper subendocardial zones of the left ventricle. The factor(s) responsible for cyanosis was (were) not determined in this study. One possibility is a selective reduction or reversal of flow in the subepicardium. A theoretical schema is given below to support this argument.

Johnson and DiPalma\textsuperscript{14} have shown that a systolic tissue pressure gradient exits from the high pressure subendocardial to the low pressure subepicardial zones of the left ventricular wall. During systole, in animals with coronary sinus occlusion, the high tissue pressure in the subendocardium (as high as 2.5 times the peak systolic left ventricular pressure\textsuperscript{15}) may vigorously squeeze blood into the epicardial and subepicardial veins. On the other hand, the relatively low systolic tissue pressure in the subepicardium (i.e., values approaching atmospheric pressure in the open chest dog\textsuperscript{16}) is less effective, if at all, in emptying the mural vessels against the elevated venous pressure. Consequently, these conditions could, in theory, result in a plethora of the subepicardial capillaries with poorly oxygenated blood, i.e., the systolic retrograde pressure gradient generated between the coronary veins and capillaries in the subepicardial zones could impede the systolic outflow from the deeper zones and perhaps transiently reverse flow in the capillaries of the more superficial subepicardial areas.

In this study we have observed a definite decrease in the mean aortic pressure and coronary inflow during a 3 min period of complete sinus closure in the dog (table 1). In contrast, the mean aortic pressure and coronary inflow were not altered for 3 min following partial sinus closure sufficient to raise the peak sinus pressure to 30-40 mm Hg; there was no apparent cyanosis of the left ventricle nor increase in heart size. It is not known whether brief periods (e.g., 10 sec) of complete sinus closure in man can be performed with a reasonable degree of safety and thus its clinical application is subject to serious question. On the other hand, temporary partial sinus closure in the dog appears to be a benign intervention and its possible application to facilitate the retrograde delivery of a diffusible radioisotope is discussed below.

Complete sinus closure was performed in the potassium-43 studies in order to minimize the antegrade distribution of recirculating potassium-43. The problem of recirculation is considerably reduced with the use of radioactive inert gases which are largely cleared by the lung.\textsuperscript{18} The retrograde potassium-43 myocardial perfusion patterns serve well, however, as an estimate of the initial distribution of isotope after retrograde injections; the data demonstrate the possibility of developing a large radioisotopic concentration gradient between an ischemic and nonischemic heart region when diffusible inert gases such as krypton-85 and xenon-133 are used. For example, the rapid injection of an inert gas saline solution superimposed upon the myocardial drainage must necessarily elevate the venous pressure in the presence of partial sinus closure and preferentially drive isotope into the low pressure vessels of an ischemic region. Rapid washout of gas from the normally perfused region may then isolate a large residual pool of isotope in the slowly cleared ischemic area. This hypothesis was tested with retrograde krypton-85 injections in four dogs; the average ischemic area-to-nonischemic area ratio of krypton-85 in tissue ranged from 4:1 to 6:1 60 sec after retrograde injections. In theory, this approach allows selective radioisotopic labeling of both poorly perfused viable and infarcted tissues. Other techniques\textsuperscript{19-10} have been proposed to localize radioisotope in areas of myocardial infarction.

With present techniques for measuring regional myocardial perfusion using a scintillation camera, xenon-133 injections are made proximal to arterial constrictions; thus, the initial distribution of the radioisotope favors the normally perfused myocardial region\textsuperscript{16} and the isotope-poor ischemic region is seen as a radioisotopic cold spot, providing the ischemic mass is sufficiently large. As a consequence of the relatively low concentration of detectable isotope in the ischemic zone, the performance of the precordial counting techniques for measuring blood flow\textsuperscript{7,8} in this region may be impaired, if not inadequate. On the other hand, accurate measurements of flow in underperfused regions of extremely small size may be expected when the ischemic myocardium is isolated as a radioisotopic hot spot. The retrograde injection approach is one possible solution for this problem; however, further evaluation and development of this technique is required before it can be considered a clinically useful tool.

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