Coronary Blood Flow Measurements in the Presence of Arterial Obstruction

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ABSTRACT

As an approach to delivery of inert gas to the myocardium in the presence of coronary artery obstruction, Kr\textsuperscript{85} in saline was injected into a catheter in the coronary venous system of intact anesthetized dogs. Isotope delivered at the level of the great cardiac vein was selectively localized in the region of myocardium subserved by the vein and the left anterior descending artery. Similarly, injection at the coronary sinus level was attended by localization of isotope to the area perfused by the circumflex branch of the left coronary artery. Precordial counting of isotope delivered in this retrograde manner yielded coronary blood flow values that closely corresponded to those derived from coronary arterial injection.

Coronary thrombus formation in either of the major left coronary branches was reflected in substantial flow reductions when isotope was delivered via the artery distal to the thrombus. A similar flow decrement was observed when the gas was delivered via the corresponding venous site, while normal blood flow levels were derived from the nonischemic area. Application of the method to detection of coronary arterial obstruction in man is discussed.

ADDITIONAL KEY WORDS

regional blood flow coronary vein injection of Kr\textsuperscript{85} myocardial ischemia coronary artery thrombosis coronary sinus great cardiac vein anesthetized dogs

The rate of exchange of inert gases between tissue and blood has been established as a measure of organ blood flow.\textsuperscript{1} In the intact animal and in man, the use of nitrous oxide gas for measurement of the mean rate of blood flow through the left ventricle is well accepted.\textsuperscript{2} More expeditious determination of coronary blood flow has been obtained by precordial monitoring of radioactive decay following the injection of Kr\textsuperscript{85} dissolved in saline into a coronary artery; this method has been validated in the experimental animal by comparison with direct flow measurements.\textsuperscript{3, 4}

Selective injection into either the anterior descending or circumflex branch of the left coronary artery makes possible the measurement of nutrient flow to the anatomic area of the left ventricle perfused by the injected branch.\textsuperscript{5} In the presence of branch obstruction distal to the site of injection, proximal delivery of injected isotope would be expected to be largely to nonobstructed coronary arterial branches, and the radioactive decay curve would predominantly reflect clearance of isotope from nonischemic tissue. In preliminary studies using injection proximal to the arterial obstruction, blood flows in the normal range were frequently encountered.

The present investigation was undertaken to determine if regional, rather than generalized, alterations of coronary blood flow might be accurately localized by selective retrograde delivery of the radioactive inert gas to ventricular tissue by way of the coronary venous system. The transient reversal of the coronary venous pressure gradients created by rapid
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injection into the coronary venous system would presumably permit delivery of Kr\textsuperscript{85} to the capillary bed and left ventricular tissue.

By selective placement of a coronary sinus catheter, regional flow alterations might be accurately delineated, since the blood flow of the left anterior descending branch of the left coronary artery enters the coronary venous system via the great cardiac vein, while the circumflex effluent flows into the coronary sinus.\textsuperscript{8} Indicator dilution curves in the coronary venous system have indicated the ready separation of the left ventricular venous drainage in vivo.\textsuperscript{8} Thus, if these assumptions are correct, a measure of blood flow to the area of left ventricle perfused by either of the two major branches of the left coronary artery would be feasible by delivery of isotope from the venous side, and would obviate the difficulty of isotope delivery in the presence of arterial obstruction.

Methods

Fifty-eight intact mongrel dogs, weighing 15 to 25 kg, were anesthetized with 25 mg/kg of Nembutal iv. After endotracheal intubation, ventilation was regulated by a Harvard pump respirator. To ascertain whether Kr\textsuperscript{85} dissolved in saline was delivered to left ventricular tissue when injected into the coronary venous system, a No. 8 Goodale-Lubin catheter (o.d. 2.54 mm) was positioned at various levels in the coronary venous system of the left ventricle in 8 animals. During injection of angiographic dye, no evidence of venous obstruction was found even at the level of the junction of the great cardiac vein and coronary sinus, where the venous diameter was approximately twice that of the catheter. Forty-five seconds after a single coronary venous injection of approximately 200 \( \mu \)C of Kr\textsuperscript{85} in 0.5 ml of saline, the chest was opened and the heart was arrested within 5 to 10 sec by iced saline in the pericardial sac. Evans blue dye was injected to identify the coronary venous segment and the heart was excised and subdivided into sections of whole wall thickness. Since this period is greater than the longest transit time in the canine ventricle,\textsuperscript{9} gas that failed to traverse the vascular wall would have left via the right atrium and would not be included in radioactive counts of tissue taken 45 to 60 sec after injection. In 2 animals, Kr\textsuperscript{85} in saline was injected into the left anterior descending artery and tissue was taken as described above. The tissue sections were immediately placed into sealed plastic tubes and subsequently counted in a 2-inch crystal well-counter with a single-channel spectrometer, using a 5-volt window at the Kr\textsuperscript{85} peak. After counting, the tissue was weighed to the nearest milligram on an analytical balance.

The pressure generated from rapid injection of Kr\textsuperscript{85} into the coronary venous system of 3 animals was measured by placing three small catheters in the coronary venous system. While injecting into one catheter, pressures were recorded from the coronary sinus and great cardiac vein. Effects of coronary venous injection on coronary inflow were also determined in a separate group of 5 animals by the placement of an S series flow sensor of appropriate size on a branch of the left coronary artery, utilizing a 400-cycle/sec gated sine wave flowmeter (Statham).

Since accurate coronary blood flow measurements have been obtained after intra-arterial delivery of isotope,\textsuperscript{3,4} decay curves after coronary arterial injection of Kr\textsuperscript{85} were compared with those after venous injection. In 19 closed-chest animals, catheters were placed in either the circumflex branch of the left coronary artery and the coronary sinus, or in the descending branch of the left coronary artery and the great cardiac vein. The o.d. of the Sones catheter was 1.87 mm, and in some animals its placement in the anterior descending artery resulted in blood flow reduction. This was usually transient and blood flow returned to a stable level in the normal range as did the ECC prior to the comparative flow studies. Position of the venous catheter was verified by angiography or after opening the chest at the end of the experiment.

During paired arterial and venous injections of Kr\textsuperscript{85} in saline, repeat injections were performed when the radioactivity from the previous blood flow measurement had diminished to background levels, about 6 min in the normal animal. In animals with marked blood flow reduction, the interval was 10 to 15 min. If previous background levels were not achieved after disappearance of the exponential slope, then the residual plateau radioactivity was subtracted in the customary manner from the subsequent Kr\textsuperscript{85} curve.\textsuperscript{8} The reproducibility of the method was demonstrated in 3 animals in which the major determinants of coronary blood flow, heart rate, and arterial pressure\textsuperscript{7} were relatively constant for 2 hours. Flow measurements derived from arterial and venous injections in sequence showed minimal variation (Table 1). Comparison of paired determinations during the correlation studies were performed only when the variation of these hemodynamic parameters was less than 10%.

With the animal in the left oblique position, radioactivity was continuously monitored from the precordial area above the left ventricle by a
Thrombus formation was gradual over a period of 30 sec were discarded on the assumption that an exponential washout of radioactivity. This occurred 30 sec after coronary sinus injection. The myocardiil tissue to provide the characteristic ex-

insufficient quantity of the gas had entered the myocardial tissue to provide the characteristic ex-

periments and epicardial ECG changes obtained from the saline-filled coronary sinus catheter, thrombus formation was gradual over a period of 30 to 75 min. To obtain comparable peak activities after venous injections, it was necessary to inject approximately twice the arterial dose of Kr85, 150 to 200 μC, followed by a 5 to 10-ml saline flush. All curves which demonstrated greater than 67% dissipation of the initial injected dose at 30 sec were discarded on the assumption that an insufficient quantity of the gas had entered the myocardial tissue to provide the characteristic exponential washout of radioactivity. This occurred most characteristically when an end-hole cathetet was placed near the orifice of the coronary sinus, presumably because of rapid washout of Kr85 in the coronary sinus blood. The acceptable decay curves in the normal animals (Fig. 1) and in those with arterial obstruction were monoe-

pression, as previously reported for arterial injections. Statistical variations are expressed as standard error of the mean.

Results

In studies of Kr85 distribution, tissue radioactivity following coronary artery injection was quantitatively greater than that following venous injection, presumably due to initial washout of a portion of the isotope immediately after coronary sinus injection. The myocardial distribution of Kr85 appeared to be similar during injections into the anterior descending branch of the left coronary artery and into the great cardiac vein. In 4 arrested hearts, simultaneous injection of Evans blue dye into the anterior descending branch of the left coronary artery and Congo Red into the great cardiac vein revealed a similar distribution of these dyes. The highest tissue concentrations of radioactivity were localized to the specific area injected (Fig. 2); half of the group of 8 received isotope in the great cardiac vein and the remainder in the coronary sinus. The mean (±sd) value of the injected areas was 6,575 ± 412 count/min per gram of tissue, contrasted with the relatively low value

 TABLE 1
Reproducibility of Coronary Blood Flow Derived from Successive Arterial and Venous Injections of Kr85 (ml/100 g/min)

<table>
<thead>
<tr>
<th>Dog 1</th>
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<tr>
<td>LAD</td>
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<td>LAD</td>
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<td>76</td>
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Kr85 was injected alternately in the arterial and venous systems at 10-min intervals.

LAD = anterior descending branch of left coronary artery; GCV = great cardiac vein; Circ = circumflex branch of left coronary artery; CS = coronary sinus.

gamma scintillation probe with a 1-inch crystal and 20-degree flat field collimator. The probe was powered by a rate meter (Nuclear-Chicago 1620A) operated at a 1-sec time constant. The output of the rate meter was fed into a Model G22 Varian potentiometric recorder with a paper speed of 1 inch/min.

To determine if branch obstruction was detectable by coronary venous injection, a thrombus was formed in the anterior descending or circum-

flex branch of the left coronary artery of 18 closed-chest dogs by modification of a previous method. This consisted of placement of an insu-

lated stainless steel wire in the proximal side holes of a No. 8F Sones catheter, thus allowing injection of Kr85 beyond the partially occluded artery during thrombus formation. Flows obtained by injections at various levels of the coronary venous system were compared with flows through the obstructed artery by injecting Kr85 distal to the forming thrombus. The mean systemic arterial pressure, recorded on an Electronics for Medicine recorder, was 108 ± 12 mm Hg during the experimental observations in the animals reported below. As judged by blood flow measurements and epicardial ECG changes obtained from the saline-filled coronary sinus catheter, thrombus formation was gradual over a period of 30 to 75 min. To obtain comparable peak activities after venous injections, it was necessary to inject approximately twice the arterial dose of Kr85, 150 to 200 μC, followed by a 5 to 10-ml saline flush. All curves which demonstrated greater than 67% dissipation of the initial injected dose at 30 sec were discarded on the assumption that an insufficient quantity of the gas had entered the myocardial tissue to provide the characteristic exponential washout of radioactivity. This occurred most characteristically when an end-hole catheter was placed near the orifice of the coronary sinus,
of 182 ± 43 count/min per gram in the tissue area draining into the noninjected vein.

The hemodynamic basis for tissue delivery of isotope during injection into the coronary venous system appeared to be at least partly due to the rapid pressure rise distal to the catheter tip, which presumably effected a transient reversal of the normal capillary-venous pressure gradient. During injection into the great cardiac vein, the pressure in this venous segment was acutely increased by 20 to 40 mm Hg, while minimal changes occurred in the coronary sinus. During injection into the coronary sinus, the pressure rose by 15 to 30 mm Hg in the coronary sinus and great cardiac vein. The longer diffusion distance to the great cardiac vein and its capillary bed appeared to be the major factor favoring localization of gas to the coronary sinus area, as depicted in Figure 2. This relationship has also been observed when using hydrogen gas and platinum electrodes in the appropriate myocardial sites in open-chest dogs (unpublished studies).

In normal animals, analysis of 55 pairs of curves obtained following sequential injection of Kr$^{85}$ into a left coronary artery branch and its corresponding venous injection showed good correlation ($r = 0.88$) over a broad range of values (Fig. 3), in support of the data in Table 1. The venous injection itself elicited no evidence of injury on the epicardial ECG and had no significant effect on heart rate or arterial pressure. With electromagnetic flowmeters on the anterior descending (2 dogs) or circumflex artery (3 dogs), the transient pressure increase within the great cardiac vein or the coronary sinus, respectively, had no immediate or late effects on coronary arterial inflow.

The ability of the venous injection method to detect alterations in regional flow was evaluated during the gradual occlusion of a branch of the left coronary artery. Figure 4 demonstrates the time course of the coronary flow changes in a single animal with a thrombus of the anterior descending artery as measured sequentially by coronary arterial and venous injection. From control values

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at the upper range depicted in Figure 3, there was a progressive decline in flow during thrombus formation. Reduced flow values derived from Kr\textsuperscript{86} injections into the great cardiac vein paralleled those from the left anterior descending coronary artery, while blood flow in the circumflex artery and in its outflow channels into the coronary sinus was found to be in the normal range. Comparison of 73 pairs of curves obtained in this group of animals demonstrated good correlation ($r = 0.90$) between the flow value derived from arterial injection and the subsequent venous injection (Fig. 5).

During the thrombus study, the coronary venous catheter was repositioned to the drainage area of the unaffected coronary branch (Fig 6). Flows obtained from these venous injection sites were clearly higher than those from the obstructed area. Values from the nonischemic area were not significantly different from the control flows obtained prior to thrombus formation, provided arterial pressure and heart rate remained essentially unchanged. The fact that flow to the normal area was not increased 15 to 20%, as found immediately after sudden occlusion\textsuperscript{9}, may be related to the later time in which these measurements were made (Fig. 5), or to the insensitivity of this method for detecting small flow changes.

**Discussion**

Retrograde delivery of Kr\textsuperscript{86} to myocardial tissue by coronary venous injection establishes a precondition for coronary blood flow measurement by the clearance principle, as employed during arterial injections.\textsuperscript{1} This is presumably accomplished by transient reversal of the normal venous pressure gradient. The brief coronary venous hypertension had no discernible effect on coronary artery inflow, and even sustained venous pressure elevation has been found to produce only slight effects on inflow.\textsuperscript{10}

The degree of rise in capillary pressure during an acute venous pressure increment has been found in other vascular beds to average at least 60% of the venous pressure elevation.\textsuperscript{11} Attenuation of the effect on capillary pressure has been related to postcapillary dilation, predominantly in the larger venous vessels. With the retrograde delivery of Kr\textsuperscript{86} from the great cardiac vein, this problem does not prevent tissue delivery of gas to sites several centimeters distal to the point of injection at the peripheral branches of this vein (Fig. 2). However, during coronary sinus injection the transient pressure elevation in the great cardiac vein may be largely due to

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**Figure 5**

Coronary blood flow during thrombus formation in either left anterior descending artery or circumflex artery. Values after injection of Kr\textsuperscript{86} in saline into coronary sinus or great cardiac vein correlate well with values after arterial injection distal to the thrombus.

**Figure 6**

Regional flows obtained from injections of Kr\textsuperscript{86} in saline into coronary venous system. Values derived by injection into nonischemic area are substantially higher than those of the area perfused by the obstructed coronary artery. The wide range of standard errors reflects the broad range of control values shown in Figure 3.
the obstructive effect of the injection without significant retrograde blood flow or gas diffusion to the more distant capillary bed, since accumulation of gas is confined to tissue supplied by the circumflex artery.

Coronary blood flow reductions due to atherosclerosis significant enough to produce clinical effects are probably regional rather than diffuse in character, so that mean flow values frequently fail to demonstrate significant reduction despite the presence of anatomic and functional impairment. Use of the described technique permits measurement of regional as well as mean flow in the closed-chest preparation. While precise quantification requires weighing ventricular tissue, it is clear that an area of substantially reduced flow can be discriminated from a normally perfused area in vivo if delivery of isotope is largely confined to discrete vascular drainage sites.

Although, in man, major branch obstruction is probably of greater frequency and significance, the detection of small branch obstruction when present may be difficult unless more precise means of localization of the venous injection are developed. Further, the altered chemical composition of muscle occurring at various stages in the postmyocardial infarction period may substantially hinder the valid detection of coronary flow reduction in this situation. Enhanced lipid concentration of the myocardium may alter the partition coefficient for $\text{Kr}^{85}$, while a sizable area of connective tissue present in the healing phase may also indicate a relatively low clearance of gas that may be erroneously attributed to low muscle blood flow.

An additional problem may be encountered if the normal flow area is perfused at a hypotensive pressure level, or if marked bradycardia is present. The attendant reduction in coronary flow would make discrimination between normal and ischemic tissue more difficult, particularly if sequential flow measurements are used. Simultaneous injection of two gases having different gamma energies into various levels of the coronary venous system might obviate this difficulty.

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References

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