Measurement of Coronary Blood Flow Using Radioactive Iodine Compared with Nitrous Oxide

By Ivan E. Forte, A.B., M.S., Jerry E. Schmitthenner, M.D., and Hunter S. Neal, M.D.

With the technical assistance of A. Jane Williams, Harry Woske, Robert Richards, and Joseph H. Hafkenschiel

Quantitative measurement of coronary blood flow by indicator-dilution methods has been attempted by various groups within the past five years. The theory upon which these studies have been based is that after injection into either the pulmonary artery or left ventricle, the first activated blood to reach the right ventricle on recirculation returns by way of the coronary vessels. Henly and co-workers rapidly injected a bolus of I$^{131}$ human serum albumin into the distal pulmonary artery and monitored the curves in the right side of the heart. The resulting calculations gave coronary-flow values averaging less than 5 per cent of the cardiac output. No standard was used for comparison. Pre-cordial counting to approximate coronary blood flow has been investigated by Love and Burch and compared with a direct method of measuring the blood emptying from the coronary sinus, using an infusion of the radioactive tracer. Two questions have been raised: (a) Is it possible, by injecting a radioactive bolus into the left side of the heart, to record an isotope-dilution curve in the blood of the coronary sinus draining the left ventricle, and if so, is this dilution reflected in the proximal pulmonary arterial circulation curve or in a precordial curve? (b) If such curves following bolus injection into the left side of the heart are meaningful, how does the quantitative estimate of the myocardial blood flow and of its ratio to the cardiac output, similarly derived, compare with a blood-flow value recorded almost simultaneously by the nitrous-oxide desaturation method, and what fraction of the Fick cardiac output is this value?

Injections were made into the distal pulmonary artery, aortic root, left ventricle, or coronary artery. As to question (b), our familiarity with the application and use of the formulas for the nitrous-oxide technique and Fick cardiac output during the past few years afforded the opportunity to compare calculated isotope-dilution formula values. It was in this way that the indirect nitrous-oxide method was calibrated against direct measurement of coronary blood flow by means of a bubble flowmeter. However, no formulas have been found which, when applied to our data, have yielded acceptable fractions of the cardiac output. Therefore, the present report deals with our interpretation of question (a) above.

Methods

The animals for this study were anesthetized under morphine-Dial-urethane-pentobarbital as recommended by Foltz, with some modification. The animal preparation was completed as described originally by Eckenhoff et al. The femoral or carotid artery was catheterized, using the Odman-Ledin method of positioning the catheter in either the left ventricle or the aortic root.
The coronary blood flow and cardiac output were determined by the methods mentioned above. The values resulting from these standardized procedures were to be compared with values derived by using the isotope-dilution technique. Two 50-ml. oiled and heparinized syringes were used to withdraw arterial and venous blood through the glass helix described by Conn and Robertson, placed in a deep-well scintillation counter. These counters were attached to amplifiers of linear count rate meters, the resulting curves being recorded on a two-channel instrument. The speed of withdrawal through the monitoring system varied from 0.5 to 1.0 ml/sec. on the arterial side and 0.25 to 1.0 ml/sec. on the venous side. This continuous withdrawal for a period of 40 to 50 seconds was maintained at 1.0 ml/sec. if at all possible, even though slower speeds gave satisfactory curves. Occasionally, it was not possible to secure adequate flow through the catheter in the coronary sinus, and a proximal pulmonary artery catheter was substituted.

The Rectiriter speed was set at its maximum of 12 inches per minute, and the fastest rate meter response of 0.5 second was necessary since the dilution curves were completed in a few seconds. Radioactive sodium iodide was tried and abandoned since blocking doses of Lugol's solution for the thyroid gland were needed. Albonotope with I$^{131}$ was tried, and was the substance of choice. Also used was either Diodrast I$^{131}$ or Renografin I$^{131}$ because of a shorter biological half-life and the availability of data on the rate of excretion. The latter was of importance since it was expedient to have most of the radioactivity eliminated in the urine during the day of the experiment.

The first two experiments were performed in an attempt to obtain isotope-dilution curves while continuously injecting a radioactive sodium iodide solution and sampling serially. Continuous infusion was not as satisfactory as giving the radioactive isotope rapidly as a bolus. Also, less radioactivity was needed with a single injection than with continuous administration.

The next four experiments involved rapid injection of boluses through the catheter in the distal pulmonary artery. In the next 11 experiments, the resulting curves were compared with those obtained by use of a catheter in the aortic root or left ventricle as the site of injection. The dose of Renografin given in the left ventricle for femoral-artery curves was about 20 μc. in dogs averaging 27 Kg.

An external counting device was projected over the anterior thorax, usually a little to the left of the midline between the third and fifth interspaces. When the external counter with its flat field collimator was placed on the surface of the thorax to monitor the area of the pulmonary cone, the injected bolus of about 5 μc. gave a satisfactory curve in the range of 1,000 counts per second.

For standardization, the same amount of isotope as used in a given experiment was diluted in a liter of human blood and pulled through the tubing into the helix in the deep well at comparable flows. The formulas of Conn$^{10}$ and Henly$^{5}$ were applied to the data secured in these experiments, on the assumption that the area under the peak of the curve was inversely proportional to the rate of blood flow through the coronary vasculature.

**Results**

A total of seventeen experiments was performed. It was not technically possible to record all of the curves at one time that one would expect to obtain in an "ideal experiment." Table 1 tabulates the types of information desired in an ideal experiment. Eight

---

**Figure 1**

Experiment 17, 2/16/60, dog Tau. Bolus 2 was injected into the coronary artery. The activity is in counts per second and time is marked in seconds, with simultaneously recorded coronary-sinus and femoral-artery curves. See text.

---

*The instruments used were the Dual 'Rectiriter' manufactured by the Texas Instrument Company, and the model FAX12S Count Rate Meter made by the Reed Curtis Division of the American Electronics Corporation.*
Comparison of Coronary Flow Measured by N\textsubscript{2}O Desaturation and Isotope Dilution After Injection of Isotope into Left Side of Heart

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>Bolus injected</th>
<th>Ratio of coron. flow (N\textsubscript{2}O) to card. output (Pick)</th>
<th>Satisfactory isotope-dilution curves</th>
<th>Satisfactory agreement with ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Aortic root</td>
<td>3.4%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Aortic root &amp; left vent.</td>
<td>1.8%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Left vent.</td>
<td>2.5%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>Left vent.</td>
<td>--</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Left vent.</td>
<td>--</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Left vent.</td>
<td>--</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Left vent.</td>
<td>--</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Coronary artery &amp; aortic root</td>
<td>--</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

In our experiments, an isotope-dilution pattern was obtainable in only three of eight dogs tested. Figure 1 shows the curves resulting when a bolus was introduced directly into a coronary artery (bolus 2, experiment 17). The arrow at the bottom indicates that at zero time the bolus was injected and the blood was pulled through the system at 1 ml/sec. for three seconds before the radioactivity appeared. In this figure, the times of rise for the coronary-sinus and femoral-artery curves almost coincide. Formulas presently available could not be used because the fraction of the bolus going into the coronary vessels is unknown, for some went into the aorta to produce the femoral arterial dilution.

Two curves from experiment 13 are shown in figure 2, indicating the effects of dilution in the pulmonary vascular bed on the response of the pulmonary-artery curve as compared with the coronary-sinus curve.

Discussion

At the time this study was undertaken, it was thought possible to design a method using isotope dilution to measure coronary blood flow at rest and a few minutes later during exercise. We expected that such a method, using a bolus, would have advantages over both the nitrous-oxide flow method and the exercise electrocardiogram. The work summarized here indicates that there are several practical obstacles yet to be overcome before such a method is feasible in the dog, with present instrumentation, not to speak of some theoretical limitations.

From the point of view of flow calculations using the classical dye-dilution formula,\textsuperscript{*} the values for the numerator, the injectate (I), have to be approximated. This is necessary because the precise amount of the bolus going into the coronary arteriolar bed is not known even when the catheter is in one of the coronary arteries (see fig. 1), since some of the isotope gets into the aorta and the systemic arterial circulation.

The denominator, which is obtained by integration of the area under the peak of the curve, has variables which we have not been able to control satisfactorily, assuming that the blood being monitored is the venous drainage of the organ in which the blood flow is to be measured. In this instance, we sampled blood from the coronary sinus, assumed to represent the major pathway by which blood draining from the left ventricle returns to the right heart. The rate of blood flow out of the coronary sinus is approximately 1.0 ml/sec.

When a Goodale-Lubin catheter of the largest size that can be introduced into the right heart of a large dog is used in the coronary sinus,

\[ F = \frac{1}{A \times t} \]

\( F \) = coronary flow, \( A \) = average concentration multiplied by time, and \( t \) is a calibration factor relating counts to concentration.
Figure 2

Experiment 13, 10/20/59, dog Nu. Bolus 3 was injected into the left ventricle. The counts per second indicate the activity of the radioactive isotope in the blood, and time is indicated in seconds for the recorded curves. The pulmonary-artery and coronary-sinus curves were superimposed to reveal the effect of flow and dilution on the size of the peaks. See text.

one is fortunate if the blood can be withdrawn either by hand or mechanically at this speed, the usual difficulty being irregular return of blood. Even though we kept the catheter as short as possible and matched the volume of the arterial sampling pathway, an unmeasurable error was introduced as a catheter artifact. Also, some of the isotope could leave the circulation and go into the interstitial space. As the blood is drawn from the catheter through the helix there is a lag in response of the scintillation counter and the amplifiers.

This is compounded with the randomness of the sampling of the radioactive bombardments in linear count rate meters. The inertia of the direct-writer pen arm and the paper speed limitations add another unknown time factor. Calibration of both channels so that the ordinates are the same further complicates the procedure. It is not surprising, then, that we are unable regularly to obtain curves from coronary-sinus blood when the bolus is introduced into the coronary artery. Having such a curve, we recognize now that without knowing the amount of injectate (I), the curve obtained cannot be calculated. Conn, in reviewing the field, has stated, "At present this author's opinion is that the future of these techniques is unknown but dubious. The probably uncertain and varying accuracy and the numerous technical difficulties involved are likely to prevent widespread use of these methods." This states simply our present opinion.

In the effort to find a more accurate quantitative measure of coronary blood flow, we have attempted to use radioactive material and correlate its appearance in either a precordial counter, or a catheter which sampled coronary-sinus blood withdrawn into a helix set in a scintillation counter. In theory, this seems as sound now as when we started, but because of the great number of variables and possibly some inherent flaws in our equipment, we were unable to secure readily reproducible curves. Furthermore, having an acceptable curve (see fig. 1), one needs a formula which would give reasonable values for coronary blood flow in dogs. We conclude that further studies with application of this approach to the patient with coronary disease are not warranted.

Summary

The short time required for arterial blood to pass from the heart through the coronary sinus requires fast recording. Curves recorded simultaneously from the precordium and from either the proximal pulmonary artery or the coronary sinus afforded no means for approximating coronary blood flow. These results are interpreted as indicating that the radioisotope-dilution method for the determination of coronary blood flow is impracticable in the dog, with our present instrumentation. This is because of the inherent uncertainty and the numerous technical difficulties involved in putting a bolus into a coronary artery and recording from coronary-sinus blood, when using as standards of reference a nitrous-oxide flow and the Fick cardiac-output measurements.

Acknowledgment

We are grateful to Cecil Riegel, Larry Curtis, Leonard Stanton, Hadley Conn, Donald Heiman, Kaare Rodahl, and William Keim for supplying...
MYOCARDIAL BLOOD FLOW

radioactive standards, helping to assemble and calibrate the monitoring equipment, and interpreting the recorded data.

References
Measurement of Coronary Blood Flow Using Radioactive Iodine Compared with Nitrous Oxide

IVAN E. FORTE, JERRY E. SCHMITTHENNER and HUNTER S. NEAL
With the technical assistance of A. Jane Williams, Harry Woske, Robert Richards, and Joseph H. Hafkenschiel

_Circ Res._ 1961;9:547-551
doi: 10.1161/01.RES.9.3.547

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/3/547