Myocardial Blood Flow in Man as Measured by a Coincidence Counting System and a Single Bolus of $^{84}$RbCl

By Suzanne B. Knoebel, M.D., Paul L. McHenry, M.D., Leon Stein, M.D., and Ahmet Sonel, M.D.

SUMMARY

Utilizing a coincidence counting system for the measurement of myocardial uptake of an 84-rubidium indicator, resting coronary blood flow (CBF) was measured in 33 normal subjects. The average CBF was $269 \pm 61 \text{ ml/min/total heart}$. This represented $5.2 \pm 1.6\%$ of the simultaneous cardiac output. Fourteen normal subjects had resting and exercising CBF measurements. The change in CBF with exercise was statistically significant ($0.005 > P > 0.001$). The characteristics of the method are discussed in relationship to possible clinical applications for the measurement of CBF.

Additional Indexing Words:
- Coronary blood flow
- Cardiac output
- Exercise
- Coronary sclerosis

If myocardial blood flow (CBF) is to be measured quantitatively in man by isotope techniques utilizing precordial counting, a first requisite is that the myocardium be isolated from other sources of radioactive emission seen by the counters. The development by Bing and associates of a coincidence counting system utilizing 84-rubidium ($^{84}$Rb), a positron-emitting isotope, has significantly enhanced this ability; and, therefore, it has become feasible to consider applying precordial counting techniques to the quantitative measurement of CBF in the human.

The purpose of this paper is (1) to report the values for CBF in milliliters per minute per total heart in resting and exercising supine normal humans as determined by coincidence counting and a single bolus injection of $^{84}$RbCl, (2) to relate CBF to the cardiac output (CO) in the same subjects and (3) to suggest clinical applications of the measurement.

Theoretical Discussion

The theoretical basis and experimental results in the intact dog of a method for measuring CBF in milliliters per minute per total heart utilizing $^{84}$RbCl and a coincidence counting system have been recently published. In the dog, the technique was shown to be reproducible and correlated well with concomitant Fick determinations. The technique is a modification of Sapirstein’s observations in rats and dogs that the fractional uptake of $^{86}$Rb or $^{42}$K by the heart equals the fraction of the CO received by the heart. Therefore,
CBF could be determined by the following proportion:

\[ \frac{\text{CBF}}{\text{CO}} = \frac{\text{Myocardial uptake}}{\text{Total body uptake}}. \]  

(1)

When the total body uptake and organ uptake cannot be determined by such direct means as utilized by Sapirstein, the quantity of isotope injected \( Q \) can be substituted for total body uptake and \( q \) can be substituted for organ uptake as monitored externally, provided myocardial isolation is possible. If a significant portion of the injected Rb or K indicator recirculates, however, the total body uptake during such recirculation must be less than \( Q \). Therefore, if CBF is estimated in an intact preparation by precordial counting of the myocardial uptake \( q \) and the quantity of recirculating isotope is appreciable, the proportion in (1) becomes

\[ \frac{\text{CBF}}{\text{CO}} = \frac{q(t)}{Q} \times f(t) \]  

(2)

where \( q(t) \), the myocardial uptake, is a function of time, \( t \), and \( f(t) \), the total body uptake divided by the injected quantity, is also a function of time. With increasing time, \( f(t) \) approaches unity.

The CO can be determined in the usual way by integrating the first arterial circulation curve of the isotope after exponential extrapolation of the downslope.

\[ \text{CO} = Q/ \int_0^\infty A_v(t) \, dt \]  

(3)

where \( A_v(t) \) represents the concentration of the isotope in arterial blood during the first circulation, determined by extrapolation after recirculation begins.

From equations 2 and 3

\[ \text{CBF} = \frac{q(t)}{\int_0^\infty A_v(t) \, dt} \times f(t). \]  

(4)

In the course of a few circulations, the indicator has nearly completely entered the tissues, \( f(t) \) is very close to unity, and \( q(t) \) has reached a relatively stable value which changes only slowly because of the large volume of distribution for the indicator in the myocardium. The formula for the calculation of CBF becomes

\[ \text{CBF} = \frac{q(t)}{\int_0^\infty A_v(t) \, dt}. \]  

(5)

The above relationships will be true only if the extraction ratio* for the heart after a series of recirculations is the same as for the total body. Sapirstein demonstrated in dogs that the fractional distribution of isotope in the heart remained constant in relation to the other organs for at least 100 seconds after the first arterial circulation of the isotope. Since there was significant recirculation of the isotope during this time, he reasoned that the lack of redistribution of the isotope reflected an extraction ratio for the heart equivalent to that for the total body; or, that the integrated concentration of isotope in the mixed venous blood \( \bar{V} \) was in effect equivalent to the integrated concentration in the coronary sinus blood \( \bar{V}_c \). This reasoning was later substantiated experimentally in dogs.4

In humans, it is also probable that little redistribution of isotope occurs as only small changes in myocardial activity are observed from 30 to 60 seconds and from 60 to 90 seconds following injection of isotope despite a marked change in blood activity.4,7 Direct measurements of \( \bar{V} \) and \( \bar{V}_c \) in two human subjects showed that the average body extraction of \(^{86}\text{Rb} \) for the first 90 seconds after injection exceeded myocardial extraction by an average of 6%,2 a difference which becomes insignificant in the final calculation.

**Method**

Thirty-three subjects were studied. There were 22 males and 11 females. The age range was from 17 to 61 years with an average age of 35

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*The extraction ratio of a perfused region is, for a particular substance, the ratio between the integrated arteriovenous concentration difference across the region and the integrated arterial concentration from the time of isotope injection to the time under consideration.
Frequency distribution of the ages of 33 normal subjects studied.

The age distribution is shown in Figure 1. Only two of these subjects had any personal or family history of heart disease, diabetes, or hypertension. Both had family histories of hypertension and diabetes, but they had neither disease themselves. Two histories were taken and two physical examinations were done on each subject by different physicians and recorded independently. These records were checked for agreement only when the data were gathered for evaluation. All subjects were normal on cardiovascular examination and all had normal resting electrocardiograms. In 10 of the subjects, the resting CBF was determined on two occasions. In 14, the resting and the exercising CBFs were determined. In nine, a single resting CBF only was determined. The CO was determined simultaneously with all CBF determinations; however, some were inadequate because of various technical difficulties.

The myocardial uptake of $^{82}$Rb was measured by the use of the Co-Insitron (American Science and Engineering). The instrument consists of two pairs of coincidence detectors, one 4 inches in diameter and one 2 inches in diameter, and a conventional well counter for continuously monitoring arterial specific activity. The myocardial scanning pair (4-inch) was directed over the center of the cardiac silhouette by an aiming device, the location having been previously determined during fluoroscopic examination of the patient in the test position. In all cases, the 4-inch crystal covered the silhouette as outlined on the thorax. A plotting of the cardiac silhouettes, determined fluoroscopically, of nine normal subjects with a superimposed circle of 4-inch diameter is shown in Figure 2. The second counting pair (2-inch) is positioned over the right hemithorax cephalad to the dome of the liver to count the uptake of rubidium by the chest walls exclusive of the heart. Uptake of the myocardium was then expressed as the difference between the left and right side counting pairs, after correction for the efficiencies of the two crystal pairs. Prior to the examination, readings were taken with standard source dishes under the upper crystal of each pair so that the body absorption could be determined. The well counter was standardized with a known volume radiooil and the relative efficiencies of the well counter and coincidence pairs were determined. The efficiency factor procedures incorporated geometrical factors (solid angle, detector area, and source shape), scintillator crystal stopping powers, the nuclear properties of the isotope, table top transmission, and electronic logic discriminator threshold settings into their definition; and, their determination was inherent in the operation of the Co-Insitron. Counts from each counting system were totalized on a scaler at 2-second intervals and recorded by a digital printer which in turn resets and restarts the scaler unit (Atec, Inc.).

For the resting CBF, every attempt was made to reassure the subjects and to avoid excitement. All procedures were carefully explained prior to their participation. The laboratory was quiet, and no indication was given the subject as to when a determination was to be done. The indicator, 0.3 μC of $^{82}$RbCl/kg, was injected into an antecubital vein through an 18-gauge needle attached to a three-way stopcock and followed by a 10-ml saline flush. Simultaneously arterial blood
Table 1
Comparison of Cardiac Output in Dogs Determined with Indocyanine Green (Cardio-Green) and $^{84}$Rb

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Dog no.</th>
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<th>$^{84}$Rb</th>
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<td>2213</td>
<td>2390</td>
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<tr>
<td>2</td>
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Av 1583 1560
SD ±454 ±406

Figure 3
Comparison of cardiac output (CO) as determined by $^{84}$Rb and indocyanine green (Cardio-Green).

Figure 4
Relationship of the measurement of cardiac output in ml/min by $^{84}$Rb (ordinate) and indocyanine green (abscissa).

Figure 5
Coronary blood flow in ml/min/total heart in 33 normal subjects.

was withdrawn at a constant speed (40 ml/min) from a 17-gauge Cournand needle which had been inserted several minutes before into a bra-
Comparison of two determinations of coronary blood flow in 10 normal subjects at rest. The second determination is on the left, the first on the right.

- The arterial blood was passed through a radicoil inserted into the well counter. The precordium was counted for 3 minutes. The arterial withdrawal was stopped when, by observing the recorder, it was apparent that the primary arterial curve had been recorded and recirculation had begun.

In the subjects doing exercise, the second injection of isotope was given while exercise continued so that the arterial curve was inscribed during exercise. Then the exercise was stopped while the 3-minute precordial counting was done. The aiming device was rechecked to assure that the subjects had not changed position with exercise. Exercise consisted of raising and lowering one leg until the subject stated he could not continue or the heart rate as determined by electrocardiographic monitoring accel-
Comparison of Two Measurements of Resting Coronary Blood Flow

<table>
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<tr>
<th>Subject</th>
<th>Study 1 CBF (ml/min)</th>
<th>CO (L/min)</th>
<th>Study 2 CBF (ml/min)</th>
<th>CO (L/min)</th>
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Av
sd

Results

The average resting CBF for 33 subjects was 269 ± 61 ml/min, which represented 5.2 ± 1.6% of the simultaneous CO (table 2, fig. 5). In 10 subjects two determinations of resting CBF were made in order to study the reproducibility of the determination. Despite some change in CO between the two determinations, as measured in five subjects,

\[ P = < 0.005 \text{ when analyzed as paired data.} \]
## Table 4

<table>
<thead>
<tr>
<th>Subject</th>
<th>Rest CO (L/min)</th>
<th>Rest CBF MI/min</th>
<th>Rest CO (%)</th>
<th>Exercise CO (L/min)</th>
<th>Exercise CBF MI/min</th>
<th>Exercise CO (%)</th>
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</table>

\[ t = 4.00 \ (0.005 > P > 0.001) \] when analyzed as paired data, each subject serving as his own control.

The average for the group was not statistically different. The standard deviation of the individual readings, when analyzed as paired data, was 32 ml/min (table 3, fig. 6).

For the exercising subjects, the average resting CBF was 288±63 ml/min. The average CO during rest was 4.9±1.1 L/min. The CBF represented 5.9±1.1% of the CO. The exercising CO rose in all subjects. The average rise was 6.4±1.0 L/min (table 4). This represents minimal exercise for the entire group. In 12 subjects the CBF rose with exercise and an increase in CO. The change in CBF with exercise was statistically significant (0.005 > P > 0.001) when analyzed with each subject serving as his own control (fig. 7). In two subjects an increase in CBF was not concomitant with increased CO.

### Radiation Dosimetry

The subjects having two injections of $^{84}$Rb Cl, 0.3 $\mu$C/kg, received an average of 50 $\mu$C of isotope. Because of the presence of $^{86}$Rb and $^{83}$Rb in the solution and the varying biological half-lives, the absorbed dose is difficult to calculate absolutely. Assuming the highest possible dosage, the subjects received a total body dose of the order of 1.75 rads. Subsequent subjects have received 0.2 $\mu$C/kg, thus reducing the radiation exposure.
Discussion

The data presented here on CBF in humans were not correlated directly with those determined by any other established technique as it is not obvious how this could be accomplished. Previous determinations of coronary blood flow in the human have been necessarily expressed in terms of milliliters per minute per 100 g of myocardium (or left ventricle). Comparison of flows determined by the nitrous oxide inhalation technique, which has furnished almost all of the information available regarding coronary blood flow in humans, with the data here can, thus, only be approximated. Using the nitrous oxide technique, Bing\(^8\) found the average CBF in a series of normal subjects to be 77 ml/min/100 g of left ventricle. Rowe,\(^9\) in 1959, reported on a total of 84 subjects of both sexes and an average age of 31 years. The mean CBF in this group was 80.6 ml/min/100 g. Similar values have been reported per 100 g of myocardium as derived by other techniques. If the average weight of the heart may be taken as 300 g and if it is assumed that flow per unit weight is uniform, the extrapolated average CBF would be approximately 230 to 330 ml/min for the nitrous oxide technique. It is presumed that it is from such extrapolation that values for total myocardial blood flow and the percentage of cardiac output which is CBF have been derived and reported.\(^10\) Direct flow-metering techniques in animals give results per artery which is being monitored, and it is thus not possible to compare direct flow values with those obtained with the coincidence counting technique unless both the right and left coronary arteries were monitored. It is also possible that there is an actual difference between flow through the large arteries and nutrient flow.

\[
\text{CBF} = \frac{q(t)}{\left(\int_0^\infty A_\omega(t)\,dt + \int_0^t a_R(t)\,dt - \int_0^t Vc(t)\,dt\right)}
\]

The question of the accuracy of coronary blood flow rates determined by techniques dependent on plasma clearance of a tracer has been raised on numerous occasions and investigations have been designed to answer the question. Moir\(^11\) concluded by a comparison of flows measured by a rotameter and \(^{86}\)Rb clearance that the \(^{86}\)Rb method gave accurate estimates of directional changes in CBF but that a systematic understatement of flow was observed particularly at high flow rates. Whether the assumption that at high flow rates exchange is time limited or whether the discrepancy is due to a redistribution of the blood to non-nutrient vessels has not been adequately demonstrated. The method discussed here has largely obviated this difficulty; for, it has converted a model-dependent measurement (extraction) into a model-independent system as related to the mechanisms responsible for actual uptake. The only requisite is that the heart and the total body be extracting proportionally. The model nonspecificity may be seen from the following considerations.

From the Fick principle, CBF can be calculated as

\[
\text{CBF} = \frac{q(t)}{\left(\int_0^t a(t)\,dt - \int_0^t Vc(t)\,dt\right)}
\]

where \(\int_0^t a(t)\,dt\) is the integrated arterial concentrations from the moment of injection to any time \(t\), and \(\int_0^t Vc(t)\,dt\) is the integrated coronary sinus concentration for the same time interval.

Since

\[
\int_0^t a(t)\,dt = \int_0^\infty A_\omega(t)\,dt + \int_0^t a_R(t)\,dt
\]

where \(a_R(t)\) represents the arterial concentration due to recirculation, the equation may also be written as

\[
\int_0^t a(t)\,dt = \int_0^\infty A_\omega(t)\,dt + \int_0^t a_R(t)\,dt - \int_0^t Vc(t)\,dt
\]

Because the pulmonary extraction of Rb or K is minimal, the arterial recirculation concentrations, \(a_R(t)\), at any time, \(t\), is the
same as the mixed venous concentrations, V(t), a few seconds earlier. With increasing t, the integrated arterial recirculation concentration approaches the integrated mixed venous concentrations.

If the extraction ratio (ER) for the heart is equivalent to the ER for the total body, then
\[ \int_0^t V_c(t) \, dt \text{ is equivalent to } \int_0^t V(t) \, dt. \]

Accordingly, with increasing t, \( \int_0^t a_R(t) \, dt \) approaches \( \int_0^t V_c(t) \, dt \) and (9) becomes
\[ CBF = q(t) / \int_0^\infty A_o(t) \, dt. \]  

(11)

For an indicator such as Rb or K, where tissue uptake is rapid and almost complete within a few circulations, it is also possible to state that with increasing t, the ratio
\[ R = \frac{\int_0^t a_R(t) \, dt - \int_0^t V_c(t) \, dt}{\int_0^\infty A_o(t) \, dt} \]

becomes much smaller than 1 and may be neglected in (9) which then also becomes
\[ CBF = q(t) / \int_0^\infty A_o(t) \, dt. \]  

(13)

It may be seen that equations (5), (11) and (13) are identical.

If this technique can be accepted to give an approximate measure of nutrient CBF per total heart, the pertinent question is the value of such a measurement. The work of Cohen and associates suggests that CBF determinations will not distinguish patients with coronary artery disease from normal subjects either at rest or during an applied stress such as exercise or isoproterenol infusion. These flow studies were done by a 85-krypton clearance technique. It is possible that ischemic areas do not take up the krypton indicator and, thus, do not contribute to a delayed clearance curve. As a result only the flow through normal vessels is measured. The coincidence technique depends on an average myocardial uptake of indicator. Unperfused areas then contribute to the CBF value by adding a zero value to the obtained average. Preliminary studies in this laboratory in patients with proved coronary heart disease indicate that when total CBF is measured in response to exercise, an appropriate increase in CBF is not demonstrated. It is necessary, however, to evaluate further in these patients the variable relationship between CO and CBF; for, there are different energy requirements for ejection of equal increments of output against high or low blood pressures.

Another possibility to be considered when assessing CBF in patients with coronary heart disease is that those who survive myocardial infarction or who have angina without infarction may be those who have developed coronary artery collaterals and, thus, may respond normally to applied stress.

Because of the unique feature of the coincidence counting method that the flow measured represents flow through true capillaries, it is possible that serial measurements in response to stress could reveal such development of nutrient collaterals in the course of recovery from myocardial infarction, treated and untreated. The two subjects studied who had an increased CO and decreased CBF may demonstrate a diversion of flow from true capillaries as a response to exercise although an absolute decrease in the energy requirements of the myocardium in these subjects cannot be ruled out.

References


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**Mystic Insight**

Then said a teacher, Speak to us of Teaching.

And he said:

No man can reveal to you aught but that which already lies half asleep in the dawn of your knowledge.

The teacher who walks in the shadow of the temple, among his followers, gives not of his wisdom but rather of his faith and his lovingness.

If he is indeed wise he does not bid you enter the house of his wisdom, but rather leads you to the threshold of your own mind.

The astronomer may speak to you of his understanding of space, but he cannot give you his understanding.

The musician may sing to you of the rhythm which is in all space, but he cannot give you the ear which arrests the rhythm nor the voice that echoes it.

And he who is versed in the science of numbers can tell of the regions of weight and measure, but he cannot conduct you thither.

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