The Determination of Coronary Flow Equivalent with Coincidence Counting Technic

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The measurement of organ blood flow in the intact animal and man is limited primarily to methods relying either on the Fick principle or on the dye-dilution method. Measurement of coronary flow in man has been accomplished by the uptake of an inert diffusing gas, nitrous oxide, by the heart muscle. This method requires that a state of equilibrium between the coronary circulation and the myocardium exists for the period of observation. The disadvantages are that only mean flow over a period of minutes can be determined, and sudden and transient flow changes are not recorded. In addition, some of the gas may traverse the coronary arterio-venous precapillary anastomosis. Finally, the procedure necessitates the intubation of the coronary sinus.

Radioisotopes have been employed in the measurement of coronary flow by a series of investigators. Based on the similarity in potassium and rubidium turnover rates, Love and Burch used myocardial rubidium-86 uptake as an indicator of coronary blood flow. They assumed that the percentage extraction of rubidium-86 by the heart was constant and that the myocardial uptake had a complementary exponential relationship with time. These authors also found that Pitressin and l-norepinephrine produced changes in rubidium-86 uptake that were in the same direction as their known effect on the rate of coronary flow.

Hansen and co-workers used krypton-85 in the measurement of coronary blood flow. Although this method has the technical advantage of ease of analytical determinations, the difficulties inherent in the nitrous oxide method are still present. Herd and associates injected krypton-85 into the coronary artery of dogs and externally monitored myocardial uptake of the isotope. They calculated coronary flow from the decline in precordial counting rate. A different approach to the measurement of coronary flow was chosen by others who recorded the passage of nondiffusible radioactive tracers through the coronary circulation. Flow was then calculated with the use of the dye-dilution formula of Stewart and Hamilton. This method has the disadvantage that the peak precordial counting rate, which is related to myocardial blood flow, is difficult to differentiate from other rapidly occurring events, such as those resulting from the passage of blood through the left side of the heart. Mena and his associates, using radioiodinated albumin, found that the presence of radioactivity in the coronary vascular bed was prolonged, accounting for the difference in the heart and arterial disappearance slopes. They concluded that a ratio of the two slopes might provide an index of coronary blood flow.

A principal disadvantage of methods employing rubidium-86 in the measurement of coronary flow has been the difficulty in determining the specific activity of the heart muscle alone, as separate from the structures surrounding that organ. Accurate assessment of the relationship between the coronary flow, the percentage extraction of rubidium by the heart, the heart rate, and the myocardial uptake of the isotope is lacking. It is the purpose of this communication to redefine these relationships and to evaluate the measurement of myocardial clearance by a coincidence.
counting method with rubidium-84, a positron (i.e., a positive electron) emitter.

Material and Methods

Principles of Coincidence Counting

Microequivalent concentrations of rubidium-84, although too dilute to interfere with potassium homeostasis, produce high detector counting rates. Rubidium-84 decays by positron (beta-plus) emissions 19 per cent of the time. The positron travels a few millimeters inside the body before annihilation with a negative electron, thereby producing two gamma photons of 0.51 million electron volts (Mev.) directed 180 degrees apart ("back-to-back"). A pair of scintillation detectors are utilized, also placed 180 degrees apart. Only events resulting from simultaneous (i.e., coincident in time) detection of the 0.51 (Mev.) gammas, one in each detector, are counted. This is in contrast to the so-called singles technic that is employed when rubidium-86 is used. This latter isotope decays by beta-negative (i.e., electron) emission; the electron, having a short range, goes undetected. However, 8.8 per cent of these decays also result in 1.08 Mev. gamma photons, which are detectable with a single scintillator. Use of this singles technic requires heavy lead collimation around two scintillation crystals to limit their field of view, because of the high penetrating power of gamma radiation. In contrast, the coincidence counting technic does not require lead collimators because the requirement of coincidence counts and the back-to-back production of the annihilation gammas automatically restrict detection to positron decays arising only within the cylinder defined by this coincidence pair of detectors.

The coincidence technic is to be preferred over the singles method for several reasons. From an engineering viewpoint, mechanical design is simplified because of the elimination of massive lead collimators. Background counting rates arising from natural radioactivity, cosmic ray activity, and the presence of radioactive contaminants in the room are essentially zero. In addition, certain factors, such as the transmission of gammas by the body, involved in the absolute calibration of the instrument with respect to a specific test subject, are more precisely determined. Also, for equal infused activities of rubidium-84 versus rubidium-86, the coincidence method gives approximately five times the counting rate of the singles method for a given field of view. Finally, the positron activity of emitting isotopes is measured in almost direct proportion to its tissue content and is not a function of the distance of the tissue from the counter as it is when a single detector is used. Each channel of the coincidence counting system uses a single-channel discriminator, which exclusively accepts the pulse corresponding to the energy of the annihilation gamma alone. Because of this fact, the signal-to-background noise ratio is so large that the statistical significance of each count is much greater than that of the singles counting method. The coincidence method provides means for distinguishing radioactivity of the heart muscle from that of the surrounding tissues. This is accomplished by monitoring the extracardiac tissue and the right side of the chest with an identical counting system, symmetrically placed over the right side of the chest. The differences in body transmission between the right and the left chest (due to the heart mass) are electronically corrected.

Instrumental Methods Used in Man

Clearance of rubidium-84 in patients was measured by a specially designed instrument, exclusively devised for the external coincidence counting of rubidium-84 within the myocardium (fig. 1). The instrument consists of two pairs of coincidence detectors with use of 3-inch diameter by 2-inch thickness of sodium iodide crystals and a conventional well counter for continuously monitoring arterial specific activity. The counting rates of the precordial coincidence pair (H), the background (right chest) coincidence pair (B), the weighted difference of the two (H-B), and the well counter (A), are recorded on a four-channel strip-chart recorder with speeds of 0.5 or 1.0 inches per minute.

The myocardial scanning coincidence pair is directed over the left precordium with use of

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Cross section through the chest to illustrate the annihilation of beta-plus positrons in the heart muscle (coincidence pair I) and in the right side of chest (coincidence pair II). Only those gammas that strike a pair of sodium iodide crystals simultaneously are recorded.

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an aiming device. The position of the heart is ascertained by a roentgenogram of the chest in the test position. An identical counting pair is placed symmetrically over the right hemithorax above the area of projection of the liver to observe the uptake of rubidium in the chest exclusive of the heart and liver dome. Uptake of rubidium-84 by the heart muscle is then expressed as the weighted differences between the left and right side counting systems (H-B). Prior to the test, an Na$^{22}$ standard (2.0 μc.) source Lucite plug is placed successively under right and left coincidence counters (over the predetermined spot) as the patient lies on the table. The instrument is then electronically set to correct for the difference in mass between the two sides of the chest. Data collected from each channel of the instrument are sampled by the strip chart every 7.5 seconds; the count rate meter channel uses an integrating time constant of 7.2 seconds. The sensitivity of the coincidence counting system is relatively low as compared to the wall counter. In addition, the activity of blood in cardiac chambers can be assumed to be constant. Consequently, counting rates originating from blood in the cardiac chamber can be neglected. One hundred microcuries of rubidium-84 in 30 ml. of saline are continuously infused intravenously by means of a special motor-driven syringe at a speed of 2 ml./minute. Simultaneously, arterial blood is drawn from a vinyl catheter inserted into a brachial artery. The arterial blood is drawn at a constant speed (7 ml./min.) through a radicoll inserted into the wall counter.

**Experiments on the Isolated Heart**

A modified Langendorff technic was used to explore the relationship between coronary flow, heart rate, and the percentage extraction of rubidium-84 by the myocardium. Dogs were anesthetized with Nembutal (30 mg./Kg. weight). Without interruption of the coronary circulation, the heart was then excised and perfused with 800 ml. of fresh oxygenated heparinized dog blood; perfusion pressure and blood flow could be altered by means of a Sigma motor pump. A total of 10 different flow rates was utilized in experiments on six dog hearts. In two additional experiments, heart rate was altered from 90 to 120 beats per minute by a pacemaker. Three to 6 μc. of rubidium-84 were added to the perfusion reservoir containing approximately 800 ml. of dog blood. The isotope was added 10 minutes after perfusion of the heart had commenced. Experiments were terminated after 35 minutes. Simultaneously, inflow and outflow samples (coronary arterial input and total venous efflux) were obtained at intervals of 1 minute. Sampling time was 10 seconds. The extraction ratios were then plotted against time and the regression line was calculated separately for two separate flow periods. The same procedure was followed when the heart rate was altered.

**Concept of Clearance Equivalent**

The term "equivalent" is used because the values obtained by this method cannot be expressed in absolute units and because the limited area of the crystals permits detection of activity from a restricted portion of the myocardium only. Clearance is defined as the quantity of a specific substance cleared from the blood in a unit of time. Myocardial clearance of rubidium-84 is defined by the equation

\[ \text{Clearance} = \frac{dK/dt}{A} \]  

(1)

where \( dK/dt \) is the rate of uptake of radioactivity of the organ (first derivative of the myocardial uptake disintegrations/min.$^2$). \( A \) is the concentration of radioactivity in the arterial blood (disintegration/min. × ml.$^3$). In order to calculate coronary flow with the Fick principle, the uptake of a substance by the heart and the concentration of this substance in arterial and coronary venous blood must be known. In applying this to a tracer that has no carrier, the coronary flow may be determined as follows:

\[ \text{Coronary flow} = \frac{dK/dt}{A - V} \]  

(2)

where \( V \) is the concentration of radioactivity in the venous blood.

The relationship between clearance and flow is obtained as follows: By dividing both numerator and denominator by \( A \), one obtains

\[ \text{Flow} = \frac{\frac{dK/dt}{A}}{\frac{A - V}{A}} \]  

(3)

where \( \frac{A - V}{A} \) represents the extraction ratio of rubidium-84 by the heart. Therefore,

\[ \text{Flow} = \frac{\text{clearance}}{\text{extraction ratio}} \]  

(4)

Thus, flow and clearance are functionally related. Furthermore, if the extraction ratio is a constant, flow is proportional to the clearance. A more general consequence of equation 4 is that if the flow does not change with time, then clearance and the extraction ratio exhibit the same time behavior.

**Treatment of Data**

Figure 2 is a replica of the print-out of the recorded data obtained during infusion of ru-
Illustrates a print-out of the recorded data. A, disintegration in arterial blood; B, disintegration from the right side of chest; H, disintegration from the left side of chest.

Bidium-84. The data were obtained during the period when the number of disintegrations in the arterial blood (A) after its initial rise had become relatively constant. It may be seen at that time that the uptake of bidium-84 over both sides of the chest and also the difference between the right and left side (H-B) is rising.

From the work of Conn and Robertson, using K in the kinetics of potassium transfer in dog hearts, it is apparent that provided the level of the isotope in arterial blood remains approximately constant, the myocardium may be considered as a two-compartment system. Accordingly, one has to make the assumption that rubidium exchange between the capillaries and the interstitial fluid of the myocardium is rapid. On this basis, effective exchange between plasma and interstitial fluid is blood-flow limited. The exchange of rubidium between interstitial and intercellular fluid follows that of potassium and is determined by a variety of factors, foremost an active metabolic process, regulating transfer of this ion across the membrane. Such elements as heart rate may also influence rubidium uptake.

By inspection of the raw data of the myocardial uptake of bidium-84, it was not possible to decide whether the raw data for H-B were a straight line or an exponential curve. After plotting the data on semilogarithmic paper with time as the abscissa and myocardial uptake as the ordinate, a straight line was obtained (fig. 3), illustrating this to be an exponential function. When one treats the raw data of H-B as a straight line, with equation \( y = a + bx \) (b = slope, a = y intercept), the results are almost identical.

**Calculation of the Myocardial Uptake of Bidium and Its Clearance Equivalent**

To avoid bias based on subjective treatment of the data, calculations were entirely performed by computer analysis. Points used for calculations included those beginning with the sixth minute following onset of infusion of bidium-84 and terminating with the fifteenth to eighteenth minute.

In the tests in which nitroglycerin was employed, two separate but identical calculations were performed; in the first, the raw data for the 4-minute period preceding administration of nitroglycerin, and 1 minute immediately following were used; in the second, the remaining (subsequent) minutes (5 to 8) were used. The horizontal distance between two points is set by the strip chart recorder as 0.133 inches (7.5 points/minute). One minute is represented by one inch of distance on the strip chart.

The vertical distance between the zero line and each point of the H-B curve and the A curve is also determined in inches (fig. 2). In practice, since a digital computer is employed, the points are read from the strip chart in

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**Figure 2**

Illustrates a print-out of the recorded data. A, disintegration in arterial blood; B, disintegration from the right side of chest; H, disintegration from the left side of chest.

**Figure 3**

The relationship of the difference in disintegration between the two sides of the chest (H-B), plotted against time on semilogarithmic paper. A straight line is obtained. The solid line is the regression line; the interrupted lines are the standard deviations.
These are the only measurements performed prior to the use of the computer. The data are converted into inches and then programmed for statistical analysis. Programming is carried out in such a manner that the following information can be obtained: the first derivative of the myocardial uptake of rubidium (H-B), and the clearance equivalent of rubidium \( \frac{dK}{dt} \). The detailed calculations are contained in the Appendix.

**Errors and Limitations of Method**

The various errors that enter into determining the precision of a measurement can be grouped into three classes: (1) accidental, (2) statistical, and (3) systematic. Accidental errors include those arising from drifts in instrumental properties and human judgment in scale interpretation. Statistical errors arise because of the nature of the quantities that must be directly observed (i.e., the quantities that furnish the raw data) in order to enable calculation of the desired quantity. These errors arise here because the raw data recorded by the instrument represent nuclear disintegration, and radioactive decay is intrinsically a statistical process. This source of error is thus unavoidable. Since the raw data obtained by the instrument arise from nuclear disintegration, the frequency distribution of the number of nuclear decays that occur in a fixed time interval, and likewise that of recorded counts in the same interval, is not the normal Gaussian distribution, but the Poisson distribution. The radioactive processes of disintegration are mutually independent and randomly distributed in time. The Poisson distribution is characterized by a single independent parameter, the mean value alone.\(^{13}\)

Equations 11 to 14 (see Appendix) dealing with standard deviations are based on the Poisson statistics.\(^{13}\) Equations 8, 9, and 10 (see Appendix) are obtained from the method of least square, assuming that all portions of the data are weighed equally.

Systematic errors can include those arising from technics of absolute instrument calibration, experimental technics employed, and similar errors, each of which, in different experiments, contributes an error always of the same sign. These are not susceptible to mathematical analysis.

The error arising from scatter (due to Poisson distribution) has been experimentally defined by measuring under a pair of coincidence counters the disintegration from a source of radioactivity. Two excised, non-beating hearts of dogs injected with 14 and 28 μc. of rubidium-84 were employed as source. The standard deviation of the calculated mean values of the points of disintegration with time \((\pm \sigma)\) was calculated and found to average 4 per cent.

**Selection of Patients**

The tests were performed on a total of 31 patients, ranging in age from 15 to 58 years. Nitroglycerin was administered in 20 individuals. In nine of these coronary artery disease was present. The patients usually received two tablets of nitroglycerin (each 1/150 grain), sublingually. Coronary artery disease was assumed to be present if one or a combination of the following three criteria was met (table 4): (1) coronary arteriography revealed narrowing and beading of the coronary arteries; (2) history of recent infarct was present as substantiated by electrocardiographic and enzymatic studies; (3) a previous infarct was suspected on the basis of history and of electrocardiographic findings.

**Results**

**Results on the Isolated Heart**

The data on the isolated perfused heart are

![Figure 4](http://circ.ahajournals.org/)

*Figure 4*

Results obtained on the isolated heart. Changes in rate of perfusion fail to alter the relationship between percentage of the extraction of rubidium-84 (ordinate) and time (abscissa).
Table 1

Data on the Isolated Perfused Heart

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Flow (ml. min.)</th>
<th>Heart rate</th>
<th>Regression line</th>
<th>σ of the regression line</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>Constant</td>
<td>-1.160</td>
<td>±0.230</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>Constant</td>
<td>-1.430</td>
<td>±0.360</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>Constant</td>
<td>-0.817</td>
<td>±0.243</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>Constant</td>
<td>-0.891</td>
<td>±0.353</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>Constant</td>
<td>-1.120</td>
<td>±0.177</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>Constant</td>
<td>-0.500</td>
<td>±0.208</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>Constant</td>
<td>-0.870</td>
<td>±0.268</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>Constant</td>
<td>-0.438</td>
<td>±0.234</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>Constant</td>
<td>-0.948</td>
<td>±0.102</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>Constant</td>
<td>-0.607</td>
<td>±0.411</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>120 BPM</td>
<td>-1.050</td>
<td>±0.150</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>92 BPM</td>
<td>-0.962</td>
<td>±0.100</td>
</tr>
</tbody>
</table>

Figure 5

Clearance equivalents calculated for the fifth to tenth minute (black column) and the eleventh to fifteenth minute (white column). The patients had no coronary artery disease, and nitroglycerin was not administered. Figure on top of column: mean values with standard deviation (interrupted line).

illustrated in table 1 and figure 4. Changes in rate of perfusion of about 25 to 50 per cent failed to influence the myocardial extraction ratio of rubidium-84 to any measurable extent. Alterations in heart rate also were without effect on the extraction ratio.

Results in Man

The results on normal individuals who did not receive nitroglycerin are illustrated in table 2 and figure 5. In all but one patient (no. 66) effective clearance was lower for the latter 5- to 8-minute interval. This is due,
of course, to the fact that extraction monotonically decreases with time under conditions of constant coronary flow and the fact that the clearances are averages over 5- to 8-minute intervals. Results of a typical test are illustrated in figure 6 and of other tests in table 2.

Data on the effect of nitroglycerin on individuals without coronary artery disease are shown in table 3 and figures 7 and 8. Table 3 illustrates that nitroglycerin produced a significant rise in clearance equivalent. This effect was statistically highly significant (0.005 > p > 0.001). The action of nitroglycerin is also

<table>
<thead>
<tr>
<th>Patient number &amp; initials</th>
<th>Age and sex</th>
<th>d (H-B)</th>
<th>Clearance equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>dt</td>
<td></td>
</tr>
<tr>
<td>50, J.W.</td>
<td>26 M</td>
<td>Before</td>
<td>7.44 ± 0.13*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.94 ± 0.15*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-6.70 ± 0.30†</td>
</tr>
<tr>
<td>64, H.J.</td>
<td>44 M</td>
<td>Before</td>
<td>11.53 ± 0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>8.95 ± 0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-25.80 ± 1.20</td>
</tr>
<tr>
<td>H7, W.C.</td>
<td>40 M</td>
<td>Before</td>
<td>3.90 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>3.30 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-18.00 ± 1.40</td>
</tr>
<tr>
<td>67, E.S.</td>
<td>38 M</td>
<td>Before</td>
<td>8.30 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>8.20 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>1.00 ± 0.10</td>
</tr>
<tr>
<td>68, G.S.</td>
<td>39 M</td>
<td>Before</td>
<td>10.70 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>7.90 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-26.20 ± 1.30</td>
</tr>
<tr>
<td>66, B.C.</td>
<td>28 F</td>
<td>Before</td>
<td>8.10 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>11.30 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>39.50 ± 2.00</td>
</tr>
<tr>
<td>H8, A.S.</td>
<td>28 F</td>
<td>Before</td>
<td>4.70 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>4.10 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>12.80 ± 0.80</td>
</tr>
<tr>
<td>71, W.N.</td>
<td>49 M</td>
<td>Before</td>
<td>5.90 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.20 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>3.05 ± 0.10</td>
</tr>
<tr>
<td>73, O.W.</td>
<td>47 M</td>
<td>Before</td>
<td>4.77 ± 0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>5.11 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>7.00 ± 1.30</td>
</tr>
<tr>
<td>74, J.G.</td>
<td>39 F</td>
<td>Before</td>
<td>6.53 ± 0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>5.22 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-20.00 ± 3.00</td>
</tr>
<tr>
<td>75, L.S.</td>
<td>58 M</td>
<td>Before</td>
<td>8.30 ± 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.88 ± 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-17.00 ± 2.40</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>% Change</td>
<td>-7.41 ± 1.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &lt; 0.300)</td>
<td></td>
</tr>
</tbody>
</table>

* Standard deviation of a growth rate.
† Per cent of error associated with a change in growth rate.

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shown in figure 8 where the standard deviations of the clearance equivalent ($\pm \sigma$) are plotted together with the mean, prior to and following the administration of nitroglycerin.

Table 4 and figures 9 and 10 demonstrate that in eight of nine patients with coronary heart disease nitroglycerin failed to increase either the slope or the clearance equivalent. A typical test is illustrated in figure 10.

Table 3

<table>
<thead>
<tr>
<th>Patient number &amp; initials</th>
<th>Age and sex</th>
<th>$d \frac{(H-B)}{dt}$</th>
<th>Clearance equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>37, H.M. 49 M</td>
<td>Before</td>
<td>5.76 ± 0.14*</td>
<td>0.0302 ± 0.0012</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>6.32 ± 0.09*</td>
<td>0.0303 ± 0.0012</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>9.70 ± 0.30+</td>
<td>0.25 ± 0.10</td>
</tr>
<tr>
<td>38, W.W. 25 M</td>
<td>Before</td>
<td>4.67 ± 0.16</td>
<td>0.0283 ± 0.0014</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>7.02 ± 0.10</td>
<td>0.0367 ± 0.0015</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>50.30 ± 3.20</td>
<td>29.68 ± 2.00</td>
</tr>
<tr>
<td>40, R.U. 23 M</td>
<td>Before</td>
<td>6.86 ± 0.13</td>
<td>0.0345 ± 0.0017</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>10.61 ± 0.09</td>
<td>0.0478 ± 0.0019</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>54.60 ± 3.50</td>
<td>38.50 ± 2.50</td>
</tr>
<tr>
<td>41, J.D. 33 M</td>
<td>Before</td>
<td>6.92 ± 0.12</td>
<td>0.0376 ± 0.0015</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>8.26 ± 0.08</td>
<td>0.0402 ± 0.0016</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>19.40 ± 0.70</td>
<td>6.91 ± 0.27</td>
</tr>
<tr>
<td>45, F.G. 49 M</td>
<td>Before</td>
<td>9.42 ± 0.13</td>
<td>0.0410 ± 0.0012</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>12.11 ± 0.07</td>
<td>0.0477 ± 0.0014</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>28.60 ± 0.30</td>
<td>16.34 ± 0.48</td>
</tr>
<tr>
<td>47, W.S. 54 M</td>
<td>Before</td>
<td>10.91 ± 0.12</td>
<td>0.0420 ± 0.0013</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>12.63 ± 0.06</td>
<td>0.0481 ± 0.0019</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>15.70 ± 0.80</td>
<td>14.52 ± 0.70</td>
</tr>
<tr>
<td>51, J.C. 42 M</td>
<td>Before</td>
<td>8.34 ± 0.13</td>
<td>0.0263 ± 0.0008</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>13.37 ± 0.11</td>
<td>0.0374 ± 0.0011</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>60.30 ± 1.80</td>
<td>42.20 ± 1.20</td>
</tr>
<tr>
<td>53, B.J. 58 M</td>
<td>Before</td>
<td>8.43 ± 0.10</td>
<td>0.0374 ± 0.0011</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>12.36 ± 0.13</td>
<td>0.0504 ± 0.0015</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>46.60 ± 1.30</td>
<td>34.76 ± 1.00</td>
</tr>
<tr>
<td>55, J.G. 15 M</td>
<td>Before</td>
<td>10.30 ± 0.16</td>
<td>0.0459 ± 0.0014</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>11.19 ± 0.09</td>
<td>0.0412 ± 0.0012</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>8.60 ± 0.25</td>
<td>-10.20 ± 0.30</td>
</tr>
<tr>
<td>62, E.W. 34 M</td>
<td>Before</td>
<td>5.47 ± 0.22</td>
<td>0.0332 ± 0.0017</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>8.35 ± 0.19</td>
<td>0.0435 ± 0.0017</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>52.70 ± 2.60</td>
<td>31.02 ± 2.00</td>
</tr>
<tr>
<td>H3, L.J. 41 F</td>
<td>Before</td>
<td>5.45 ± 0.12</td>
<td>0.0157 ± 0.0005</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>7.65 ± 0.08</td>
<td>0.0187 ± 0.0006</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>40.40 ± 1.20</td>
<td>19.10 ± 0.50</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>+35.17 ± 1.40 (p &lt; 0.001)</td>
<td>+20.28 ± 1.00 (p &lt; 0.005)</td>
</tr>
</tbody>
</table>

* Standard deviation of a growth rate.
† Per cent of error associated with a change in growth rate.

Discussion

The method used in this study differs in several ways from those previously employed to estimate coronary blood flow in man. As
compared to procedures in which coronary flow is measured after intubation of the coronary sinus, either with nitrous oxide or krypton-85, the procedure is much easier to carry out.\textsuperscript{4,6} Like the nitrous oxide method, our current technic does not permit observation of instantaneous alterations in flow, since

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{Figure 6}
The result of a typical control experiment (no arteriosclerotic heart disease, no nitroglycerin was administered). The solid lines represent the clearance equivalent with its standard deviation. The interrupted lines are the means for fifth to tenth minute and the eleventh to fifteenth minute, respectively.
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8}
\caption{Figure 8}
The effect of nitroglycerin on clearance equivalent of rubidium-84 on a patient without coronary artery disease. The solid lines are the clearance equivalent with its standard deviation. The interrupted lines are the means for the fifth to tenth minute and the eleventh to fifteenth minute, respectively. Arrow denotes the administration of nitroglycerin.
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7}
\caption{Figure 7}
Clearance equivalents calculated for the fifth to tenth minute (black column) and the eleventh to fifteenth minute (white column). Nitroglycerin was administered to individuals without coronary heart disease after the tenth minute. Figure on top of columns: mean values with standard deviation (interrupted line).
\end{figure}
the effective clearance is calculated from the first derivative of the myocardial uptake of rubidium-84, computed for a total of 5 to 8 minutes. Furthermore, in both methods, the flow or its equivalent is measured through that portion of the myocardium only which is seen by the pair of coincidence crystals. Finally, clearance equivalents obtained are not expressed in absolute units (ml./min.).

As compared to methods employing the recording of rapid circulation of non-diffusible radioactive tracers through heart muscle and calculating flow with the dye-dilution method, the method described here has the advantage of objective computation. In the method of Sevelius and Johnson, the peak of precordial activity is difficult to differentiate from other rapid events. In addition, the method of calculation is subjective.

Radioisotopes have also been employed in the measurement of coronary flow in dogs by direct injection into a coronary artery. Coronary flow was then calculated from the decline of precordial radioactivity. This method largely eliminates the errors inherent in the procedure of Sevelius and Johnson, but it is

Table 4
Effect of Nitroglycerin in Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patient number &amp; initials</th>
<th>Age and sex</th>
<th>Diagnostic criteria</th>
<th>d (H-B) dt</th>
<th>Clearance equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>32, E.G.</td>
<td>46 M 3</td>
<td>Before</td>
<td>6.82 ± 0.16*</td>
<td>0.0486 ± 0.0024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.67 ± 0.19*</td>
<td>0.0412 ± 0.0025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-2.20 ± 0.18†</td>
<td>15.02 ± 1.20</td>
</tr>
<tr>
<td>33, K.S.</td>
<td>51 M 1</td>
<td>Before</td>
<td>10.13 ± 0.08</td>
<td>0.0337 ± 0.0010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>9.57 ± 0.06</td>
<td>0.0282 ± 0.0009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-5.50 ± 0.20</td>
<td>-16.32 ± 0.50</td>
</tr>
<tr>
<td>46, M.S.</td>
<td>59 M 2</td>
<td>Before</td>
<td>7.03 ± 0.14</td>
<td>0.0313 ± 0.0013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>3.17 ± 0.09</td>
<td>0.0123 ± 0.0006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-54.90 ± 3.50</td>
<td>-60.70 ± 3.80</td>
</tr>
<tr>
<td>70, S.F.</td>
<td>38 M 3</td>
<td>Before</td>
<td>7.40 ± 0.20</td>
<td>0.0385 ± 0.0015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>7.30 ± 0.10</td>
<td>0.0323 ± 0.0010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-0.70 ± 0.10</td>
<td>-16.00 ± 0.80</td>
</tr>
<tr>
<td>52, L.B.</td>
<td>54 F 2</td>
<td>Before</td>
<td>6.86 ± 0.15</td>
<td>0.0215 ± 0.0009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.47 ± 0.09</td>
<td>0.0179 ± 0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-5.70 ± 0.30</td>
<td>-16.74 ± 1.00</td>
</tr>
<tr>
<td>56, J.M.</td>
<td>42 M 2</td>
<td>Before</td>
<td>10.63 ± 0.14</td>
<td>0.0308 ± 0.0009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>9.25 ± 0.07</td>
<td>0.0240 ± 0.0007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>-12.90 ± 0.40</td>
<td>-22.07 ± 1.00</td>
</tr>
<tr>
<td>60, R.H.</td>
<td>39 M 2</td>
<td>Before</td>
<td>9.82 ± 0.12</td>
<td>0.0496 ± 0.0020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>12.28 ± 0.07</td>
<td>0.0520 ± 0.0015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>25.10 ± 1.20</td>
<td>4.84 ± 0.24</td>
</tr>
<tr>
<td>65, L.C.</td>
<td>39 M 1</td>
<td>Before</td>
<td>6.16 ± 0.16</td>
<td>0.0474 ± 0.0024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>6.49 ± 0.11</td>
<td>0.0402 ± 0.0016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>5.40 ± 0.30</td>
<td>-15.19 ± 1.00</td>
</tr>
<tr>
<td>H10, L.H.</td>
<td>55 F 3</td>
<td>Before</td>
<td>2.01 ± 0.15</td>
<td>0.0060 ± 0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>4.07 ± 0.12</td>
<td>0.0110 ± 0.0004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>100.20 ± 18.00</td>
<td>83.00 ± 7.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>+5.42 ± 2.68</td>
<td>-8.42 ± 1.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Change</td>
<td>(p &lt; 0.80)</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

* Standard deviation of a growth rate.
† Per cent of error associated with a change in growth rate.

Circulation, Volume XXIX, June 1964
Clearance equivalent calculated for fifth to tenth minute (shaded column) and the eleventh to fifteenth minute (white column). Nitroglycerin was given to patients with coronary artery disease after the tenth minute. Figure on top of columns: mean values with their standard deviations (interrupted lines).

 unlikely that it can be used as a clinical test. It also permits calculation of flow through only a restricted area of the myocardium, and since it employs a singles counting technic, necessitates careful and difficult collimation.

This is also the case when rubidium-86 is employed. This isotope requires heavy lead collimation around the crystal to limit its field of view. There are other disadvantages of the singles technic, such as interference by room background counting, low counting rates, and the difficulty in separating activity of the heart from surrounding structures.

The method employed in this study utilizes a positron emitter. The physical principles of this system have been described in detail in a previous paragraph. The advantages of the coincidence over the singles method are simplified mechanical design because of elimination of lead collimation, elimination of background noise, and higher counting rate. In addition, counting rate does not obey the rules of inverse square and the activity of gamma-emitting isotopes is measured in direct proportion to its tissue content. Counting rates from structures surrounding the heart do not inter-
here and the efficiency is about five times greater for rubidium-84 as compared to rubidium-86. In the system employed here a double-coincidence method is employed, with coincidence pairs being placed in front and back of the right and left side of the chest, respectively; this permits continuous correction for disintegration emanating from the left side of the chest alone.

Although the coincidence counting procedure eliminates many disadvantages of procedures employing singles, one of the faults of external counting remains that of measuring the radioactivity of a limited area of the myocardium only.

In using the clearance of rubidium-84 as a measure of myocardial blood flow, it is essential that the relationship between the myocardial extraction and flow be known. In previous studies on the isolated perfused rabbit heart, an exponential relationship between the myocardial extraction and rate of coronary flow was found. Thus, as coronary flow increased, the percentage myocardial extraction of rubidium-86 diminished in an exponential fashion. Donato and co-workers, using potassium-42 and rubidium-86, in the measurement of coronary flow, believe that the myocardial clearance of these isotopes reflects coronary flow not because the instantaneous myocardial extraction ratio is unity, but because they found that the amount of isotope in the myocardium changed very little for some time after the first circulation. Sapirstein also demonstrated that the organ uptake of rubidium-86 and potassium-42 immediately after single intravenous injection reflects the fractional organ blood flow. The experimental conditions of Donato and Sapirstein differ from those used here because only single injections were used by these investigators.

Conn and Robertson thoroughly examined the relationship between the activity of potassium-42 in arterial and coronary venous blood at varying arterial activities of the isotopes. They found that the arteriovenous differences for potassium display exponential characteristics with respect to time. This was confirmed later in this laboratory.

The experiments on the isolated heart reported here (fig. 4) show that changes in coronary flow do not alter the myocardial extraction of rubidium to a measurable extent. This is in contrast to data previously published from this laboratory. The independence of the extraction ratio of rubidium-84 with changing coronary flows is the basis for the concept, expressed in this report, that myocardial clearance of coronary flows is the basis for the concept, expressed in this report, that myocardial clearance of rubidium-84 is a direct function of flow. Expressed more precisely, this fractional change in coronary blood flow is given exactly within the limits of experimental accuracy by the fractional change in myocardial clearance.

The results reported here demonstrate a marked difference in the physiologic response to nitroglycerin between normal individuals and patients with coronary artery disease (tables 3 and 4, figs. 7-10). In the former, the drug resulted in all but one individual studied in a statistically significant increase in the effective clearance of rubidium-84. The average increases were 20.3 per cent (effective clearance); the probability value for the clearance is $0.005 > p > 0.001$.

In contrast, in all but two patients with arteriosclerotic heart disease, nitroglycerin failed to raise the effective clearance of rubidium-84 (table 4, figs. 9 and 10). The average change was $+5.42$ per cent for the effective clearance of rubidium. This was statistically significant ($0.05 > p > 0.025$). These findings are in agreement with those reported by others using the nitrous oxide method.

It is not claimed that the method used in this report represents a procedure for quantitative measurement of coronary blood flow. Neither does it permit conclusions on the dynamics of rubidium exchange between various compartments of the heart muscle. It is likely that at the present time because of the accuracy in the recognition of arteriosclerotic heart disease, the future of the method lies primarily in its clinical application. Another advantage that makes this procedure of clini-
rical value is that the coincidence counting system has a relatively high degree of accuracy and simplicity as compared to other procedures. It is hoped that later refinements in technic will make possible quantitative studies of coronary flow in man.

**Summary**

The coincidence counting technic was used to measure the coincidence equivalent of rubidium-84 as a function of coronary flow by the human heart in vivo. This technic makes possible a distinction of radioactivity of the heart muscle from the surrounding tissue, eliminates lead collimation, and is more sensitive than the singles technic.

In experiments on isolated dog heart it was found that changes in rate of perfusion of the coronary arteries failed to influence the myocardial extraction ratio of rubidium-84. Alterations in heart rate were also without effect.

Nitroglycerin increased the coincidence equivalent of rubidium-84 in patients without coronary heart disease. In patients with coronary artery disease the drug led to fall in coincidence equivalent.

The method has been helpful in distinguishing between normal individuals and those with coronary artery disease.

**Acknowledgment**

We appreciate the assistance of Mr. Zoltan Varga in the aid he has given us in the statistical analysis of the data. We particularly want to express our appreciation to Dr. Frank Paolini from the American Science and Engineering, Inc., who has been instrumental in the development of this technic and in carrying it out. We are most grateful to Dr. Kenneth Krabbenhoft, in the Department of Radiology, Harper Hospital, for his help.

**Appendix**

For the following equations are used: \[ y = ab^x \] \[ \ln y = \ln a + x \ln b \] \[ \frac{dy}{y} = \ln b \, dx \] \[ \frac{dy}{dx} = \ln by \]

where dy represents a change in vertical distance between subsequent points with time; dx represents a change in horizontal distance; \[ \frac{dy}{dx} \] is the rate of myocardial uptake of rubidium (its first derivative); \[ \ln b \] is the specific growth rate obtained from the following equation: \[ \ln b = \frac{N \Sigma x \ln y - \Sigma x \ln y}{N \Sigma x^2 - (\Sigma x)^2} \] (8)

where \( x \) is the horizontal distance of each subsequent point \( y \) is the vertical distance of each subsequent point \( N \) is the number of observed points.

The clearance equivalent \[ \frac{dK}{dt} \text{ (equation 2)} \]

is then determined for each individual point of raw data on the strip chart by dividing each A point into the value obtained for the first derivative as obtained by equation 3. Consequently, for each test, 75 to 98 clearance equivalents are obtained.

The data are subjected to statistical analysis based on the Poisson distribution curve. The standard deviation \( \sigma \) of the first derivative of H-B is by using the equation: \[ \sigma = \sqrt{\left( \frac{\ln y - \ln a - \ln bx^2}{\ln b} \right)^2} \] (9)

The symbols in this equation with the exception of \( \ln a \) have already been defined under equation 7. \( \ln a \) is calculated as follows: \[ \ln a = \frac{\Sigma x \ln y - \Sigma x \ln y}{N \Sigma x^2 - (\Sigma x)^2} \] (10)

where \( \ln a \) is the value \( \ln y \), when \( x \) equals zero.

\( \sigma \) of \( \bar{A} \) is calculated for each individual point of \( A \), as recorded directly on the strip chart; the formulas commonly used for the calculation of the standard deviation are: \[ \bar{A} = \frac{N}{\Sigma i=1} \] \[ \sigma = \sqrt{\frac{\bar{A}}{T}} \] (11) (12)

where \( A \) is the vertical distance between each subsequent point (7.5 points/min.) \( T \) is the total number of minutes used for the equation, as defined above.

The standard deviation of the clearance is obtained by the following equation: \[ \sigma \text{ of clearance equivalent} = \frac{(\sigma \text{ of } dK/dt)^2}{(\text{of } dK/dt)^2} + \]
The mean clearance for each period of observation is then obtained, as follows:

\[
\text{Mean clearance} = \frac{\sum_{i=1}^{N} \text{Clearance}_i}{N}
\]  

\[(14')\]

References


2. Stewart, G. N.: Researches on the circulation time and on the influences which affect it. IV. The output of the heart. J. Physiol. 22: 11, 1897.


The Determination of Coronary Flow Equivalent with Coincidence Counting Technic

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