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# The Use of Positron Emitter in the Determination of Coronary Blood Flow in Man

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The measurement of coronary blood flow in the intact animal and in man using radioisotopes and external counting technique has been attempted by several investigators (1-10). Different isotopes, such as Krypton-85, Rubidium-86, Potassium-42, radioiodinated serum albumin among others, have been used either by single bolus injection or by constant infusion (1-10). The recording of the precordial activity has been accomplished by using singles counting systems. These are systems which accept single pulses from detectors, in distinction to systems which require simultaneous detection of two or more events in coincidence. With these methods, the specific activity of the heart muscle cannot be separated from that of the surrounding structures. In addition, changes in the activity of the blood in the cardiac chambers or in the coronary arteries may interfere with counts recorded from the heart muscle alone.

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It was first shown in this laboratory that by the use of a positron emitter, Rubidium 84, and a coincidence counting system, a ratio between the myocardial uptake of $^{84}$Rb and the arterial counts could be obtained that was proportional to coronary blood flow (11). To emphasize the fact that this ratio could not be expressed in absolute units, it was given the term of clearance equivalent. Later, an objective method was developed in this laboratory in which coronary blood flow could be expressed in absolute units (ml/min) (12).

It is the purpose of this communication to discuss briefly the concepts underlying this method and to describe the results dealing with resting coronary blood flow in normal and arteriosclerotic patients and with the effect of nitroglycerin on the coronary circulation.

## MATERIAL AND METHODS

*Considerations concerning the coincidence counting technique:*

Rubidium-84 decays by the emission of positrons ($\beta+$) 19 per cent of the time; therefore, coincidence circuits can be used to detect the gamma rays resulting from positron annihilation.

The coincidence method has the following advantages over the singles methods: Background counting rates arising from natural radioactivity, cosmic radioactivity and the presence of background counting rates are essentially zero and the transmission of gamma photons by the body involved in the absolute calibration of the instrument with respect to a specific test subject is more precisely determined. In addition, for equal amounts of $^{84}$Rb versus $^{86}$Rb, the coincidence counting method gives approximately five times the counting rates of the singles method for a given field of view and the positron 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. However, coincidence counting while not describable by the inverse square law, is subject to tissue absorption of the gamma rays, making it sensitive to the relative position of the atom emitting the positron particle. Most important, the coincidence method provides means for distinguishing radioactivity of the heart muscle from that of the surrounding tissues, thereby simplifying the collimation.

If during a test, annihilation of different positrons from organs other than the heart strike the coincidence detectors during a very short time, a count will be registered. These accidental counts may interfere with the measurements of the absolute activity of the positrons in the heart muscle. According to Rossi, the number of accidental counts can be predicted by the following equation: (13)

1. $C\ (acid) = 2TC_1C_2$, where:

$C_1$ and $C_2$ are the singles counting rates in the upper and lower detectors of a coincidence pair and T is the resolving time of the circuit varying from instrument to instrument. If the resolving time is very small, the number of accidental counts will be proportionally reduced. In this laboratory two instruments are used; one has a resolving time of $1.12 \times 10^{-6}$ seconds, and the other of $0.1 \times 10^{-6}$ seconds. It was found that to overcome the influence of the accidental counts it was necessary to shield the pair of coincidence detectors with ½ inch lead. This shielding reduces the percentage of accidental counts to less than 7 per cent.

The coincidence apparatus has two pairs of detectors. Each scintillator consists of a 3-inch diameter by 2-inch thick sodium iodide crystal provided with a reflective coating of magnesium oxide, hermetically sealed and optically coupled to a photomultiplier. In addition, a well counter is incorporated which measures the radioactive material in the arterial blood. The well counter consists of a 1⅜ inches diameter by 2-inch sodium iodide crystal coated with magnesium oxide, hermetically sealed and optically coupled to a photomultiplier or equivalent. Each pair of the coincidence system as well as the well counter circuits are calibrated in such a way that only gamma photons with a peak energy of 0.51 MeV are recorded. This is accomplished by means of discriminators and by adjusting the voltage input to the photomultipliers.

One pair of coincidence detectors is positioned over the precordial area (H) and the other is symmetrically placed over the right side of the chest (B) (Fig. 1). In addition, the activity of the arterial blood is counted in the well counter (Aw). The apparatus electronically subtracts the precordial counts (H) from the chest background (B) and this difference expresses the myocardial uptake of $^{84}$Rb (H-B). The activities of H, B, H-B and Aw are registered separately every eight seconds on a strip chart of a four channel recorder with speeds of 0.5 and 1.0 inches per minute. The difference in transmission between both sides

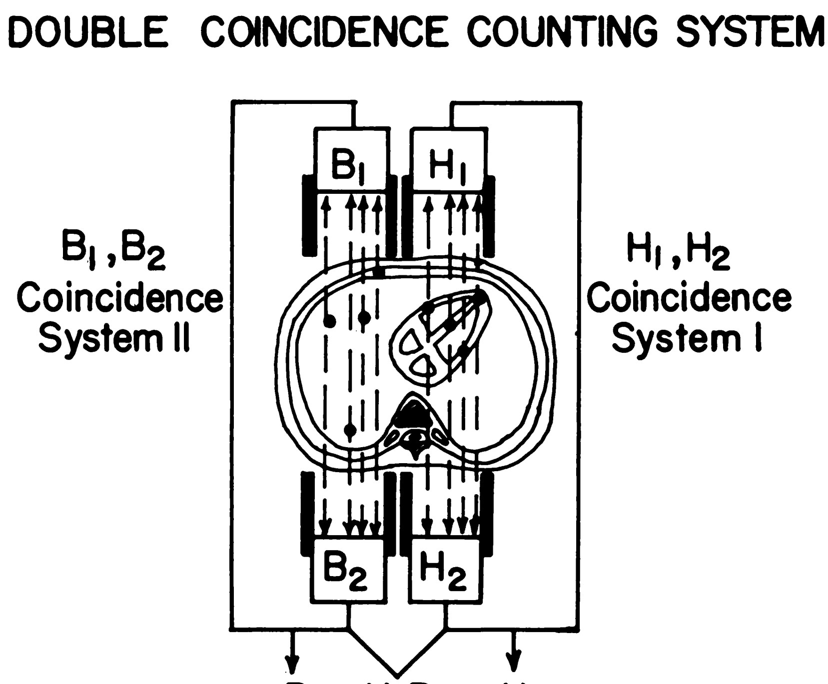


**Fig. 1. Schematic representation of the double coincidence counting system. One pair of detectors ($H_1$ and $H_2$) is located in front and back of the left side of the chest. The other pair ($B_1$ and $B_2$) is located over the right side of the chest. All detectors are shielded with half inch lead. The apparatus substracts electronically the precordial counts (H) from the chest background (B) and this difference expresses the myocardial uptake of $^{84}$Rb (H-B).**

of the chest is corrected for by counting the emmissions of a known dilution of $^{84}$Rb in saline placed in succession on both sides of the chest; the rubidium is placed in a three-inch diameter stainless steel container with a volume of 20 ml. Thus, the isotope in the container acts as an extended source. Once the projections of the heart and liver dome are determined on the chest wall by fluoroscopy or roentgenography, each pair of detectors is aligned in such a fashion that the upper shields touch the chest while the pair of lower detectors are separated from it by the table.

Experiments have shown that in normal hearts, scintillators on the left side of the chest pick up all the radiation from the myocardium. It was shown, however, that in hearts weighing 400 gms, only 90 percent of myocardium radiation can be detected.

Rubidium-84 (0.4 $\mu$C/lb of body weight) is diluted in 30 ml of normal saline and infused by means of a special motor driven syringe at a speed of 1 ml/min in the left antecubital vein. Simultaneously, arterial blood is drawn from the right brachial or femoral artery at a constant speed of 7 ml/min, through a radicoil inserted into the well counter.

*Calculation of coronary blood flow:*

The calculation of the coronary blood flow is based on the Fick principle, in which flow is calculated as the ratio of the uptake of $^{84}$Rb by the heart to the difference between the specific activities of the isotope in the arterial and coronary venous blood: (14)

$$2.\ F = \frac{dk/dt}{A\text{-}V}, \text{ where:}$$

dk/dt is the first derivative of the myocardial uptake of $^{84}$Rb (dis/min$^2$); A and V are the radioactivity in the arterial and venous blood (dis/min $\times$ ml). By dividing both numerator and denominator by A in this equation, one obtains:

$$3.\ F = \frac{\frac{dk/dt}{A}}{\frac{A - V}{A}} \text{ or Flow} = \frac{\text{clearance}}{\text{myocardial extraction ratio}}$$

To express clearance in absolute units (ml/min), it is necessary to consider the following parameters: The transmission of the left and right sides of the chest to gammas photons, the geometry of a standard vessel containing a known dilution of $^{84}$Rb used as described above, the geometry of the heart as seen by the coincidence pair, the geometry of the scintillation crystals used in the detectors and the properties of the electronic circuits. In addition, the relationship between the singles counts recorded by the well counter, and the coincidence counts have to be considered. These factors, as expressed in the calibration coefficient (C), make it possible to describe clearance in ml/min.[1] Clearance can then be defined.

$$C = \frac{M}{m} \times \frac{CHO}{CHL} \times \frac{Gs}{Gh} \times \frac{Fh}{Fw} \times \frac{Awo}{HO} \times Vs \times Ts, \text{ where:}$$

M is the total mass of the heart, and m is the mass of the heart seen by the pair of detectors. CHO is the coincidence counting rate of the rubidium source measured without the patient on the table; CHL is the coincidence counting rate of the rubidium source placed on the precordial area. Gs is a geometrical factor for the standard container; its value is calculated to be 0.247. Gh is the geometrical factor for the heart. The latter was calculated by assuming that the heart covers the whole cross-sectional area of the detection cylinder. Otherwise, Gh is insensitive to the precise geometrical shape of the heart; its value is 0.23. Fh is the dilution factor used in preparing the source solution in the container (20ml). Fw is the dilution factor used in preparing the source solution for the well counter. Awo is the counting rate of the source solution (Fw) in the well counter. HO is the coincidence counting rate of the source solution (Fh). Vs is the volume of the source (20 ml) and Ts the transmission of the source and its container to 0.51 MeV; its value is 0.761.
by the following equation:

$$4. \ \text{Clearance} = \frac{dk/dt}{A} \text{ or Clearance} = C \times \frac{\frac{d\,(H\text{-}B)}{dt}}{Aw}, \text{ where:}$$

$\frac{d\,(H\text{-}B)}{dt}$ is the first derivative of the myocardial uptake of $^{84}Rb$; C is the calibration coefficient as described in the footnote.

In a previous communication, it was shown on eleven isolated perfused dog hearts and in five tests using the human heart insitu that the extraction ratio declines monotonically with time and the rate of this decline is not influenced by changes in flow and heart rate (11, 12). Consequently, any directional change in myocardial clearance of $^{84}Rb$ related to flow.

For the calculations of coronary blood flow, according to Equation 3, it is essential that the extraction ratio should be known. As the coronary sinus is not intubated, the extraction ratio cannot be obtained directly. However, since the slope of the extraction ratio is approximately constant for each subject and is not altered by changes in flow, it is possible to calculate the coronary blood flow by the logarithmic extrapolation to zero time of the myocardial clearance. At zero time, the activity in the coronary venous blood may be assumed to be zero and; therefore, the extraction ratio is unity. This concept has been verified on nine isolated perfused dog hearts by comparing directly measured with calculated blood flows. The accuracy of the method in these experiments was 93 per cent (12).

[1]For the calculation of the calibration coefficient (C), the formula suggested by Paolini is used: (15)

Therefore, at time zero:

$$5.\quad F = \frac{\dfrac{dk/dt}{A}}{\dfrac{A\text{-}V}{A}} \qquad \text{or } F = \frac{dk/dt}{A}$$

As previously described, all calculations are performed in a digital computer. Thus, the first derivative of the myocardial uptake of $^{84}$Rb, its uptake, the coronary flow and the myocardial clearance of Rubidium, as well as the statistical errors are obtained. The formulae used for these calculations are described in detail in another communication (12).

*Selection of patients:*

Coronary blood flow was obtained on 79 individuals varying in age from 18 to 83 years. Fifty-six patients did not have evidences of coronary artery disease while 23 had coronary artery disease according to the criteria previously described (11). Basal conditions were not required for the test. The individuals without coronary artery disease were divided according to age and sex. In 22 patients, two tablets of nitroglycerin (1/150 gr each) were given sublingually after a control period of seven minutes and the coronary blood flow was followed during one or two periods of seven minutes each follwing the administration of the drug.

## RESULTS

Patients without coronary artery disease were divided into two groups, one above and the other below the age of 40. This was done because of the high incidence of coronary artery disease in older individuals. Figure 2 summarizes the results obtained on these individuals. It may be seen that the coronary blood flow in individuals below 40 is 258± 14ml/min; above 40 it is 242± 16 ml/min, these differences are not significant ($P>0.90$).

The patients with coronary artery disease were included in one single group because few patients were younger than 40 years (Table I). Figure 3 illustrates the results obtained in these individuals. The mean coronary blood flow is 222± 16 ml/min. Consequently, there is no significant difference between this group of patients and those without coronary artery disease ($P>0.90$).

The results obtained on individuals without coronary artery disease grouped according to sex are shown in Fig. 4. The mean coronary blood flow in males is 236± 14, and in females is 262± 17; these differences are not statistically significant ($P>0.90$).

These results demonstrate the independence of coronary blood flow on age and sex. In addition, the resting myocardial blood flows in patients with and without coronary artery disease appear identical.

Figure 5 and Table II illustrate the results obtained in 12 individuals without coronary artery disease following the administration of nitroglycerin. In 11 patients the myocardial blood flow increased significantly; in 6 it rose during the first period (7 minutes) following the administration of the drug ($P<0.05$); in 8 it remained elevated or increased further during the second period ($P<0.005$). The average increment in coronary blood flow was 38 ± 25 per cent during the first seven minutes and 70 ± 34 per cent during the remaining seven minutes.

In 9 of 10 patients with coronary artery disease (Fig. 6, Table III), the coronary blood flow remained unchanged or decreased following the administration of nitroglycerin. The average change in coronary blood flow was −14 ± 15 per cent; this was statistically significant ($P<0.025$).

These results demonstrate that nitroglycerin increases the coronary blood flow in patients without coronary artery disease but not in individuals with atherosclerotic hearts.

## DISCUSSION

The main advantage of the method described in this paper is that the radioactivity of the heart muscle can be separated from that of surrounding structures. Other advantages are the elimination of background counting rates, natural radioactivity and cosmic rays. The counting rate does not obey the rule of the inverse square and shielding is not cumbersome when compared with the heavy collimation required with the singles techniques. Finally, $^{84}Rb$ when compared with equal amounts of infused $^{86}Rb$ is five times more efficient.

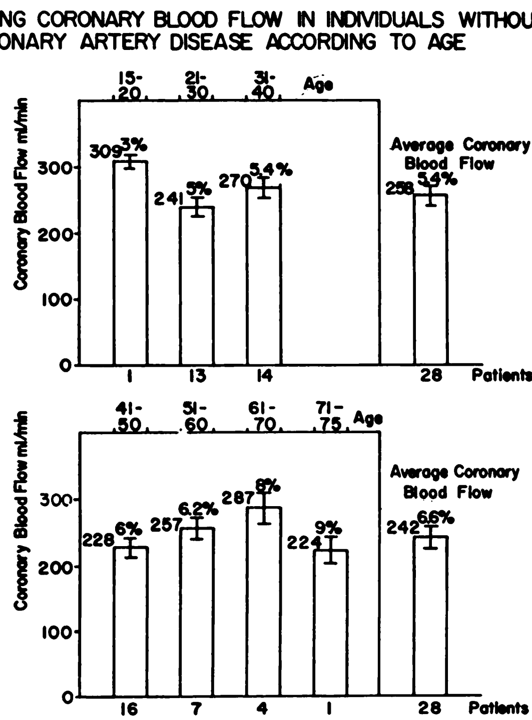


**Fig. 2. Mean resting coronary blood flow in individuals without coronary artery disease according to age. The average coronary blood flow in individuals under the age of 40 is 258 ± 14 (5.4%) ml/min; over 40 years it is 242 ± 16 (6.6%) ml/min. These differences are not significant ($P > 0.90$).**

The accuracy of the method has been greatly improved by elimination of accidental counts, which originate from independent annihilation of positrons from other organs or tissues during the resolving time of the circuit. It was found that shielding with ½ inch lead reduces the accidental coincidence counts to less than 7 per cent.

The method described in this paper is based on the Fick principle and permits the measurement of the coronary blood flow without intubation of the coronary sinus. It is calculated by the extrapolation of the myocardial clearance values to zero time. According to the Fick principle, the uptake of $^{84}$Rb by the heart as well as the coronary arteriovenous difference in activity must be known. Since the coronary sinus is not intubated, the values for the coronary vein blood have to be determined by indirect means. This can be accomplished by extrapolating slopes obtained for various seven minute clearance periods to zero time. At that time, it can be assumed that no rubidium is present in coronary vein blood and that, therefore, the extraction ratio of $^{84}$Rb is unity. Consequently, at zero time, clearance is equal to flow. A prerequisite for this procedure is that the flow is determined solely by changes in clearance and that the extraction ratio is not influenced by changes in flow or heart rate. This supposition has been confirmed in a total of 11 experiments carried out on isolated dog hearts, in which changes in flow failed to alter the slope of the extraction ratio

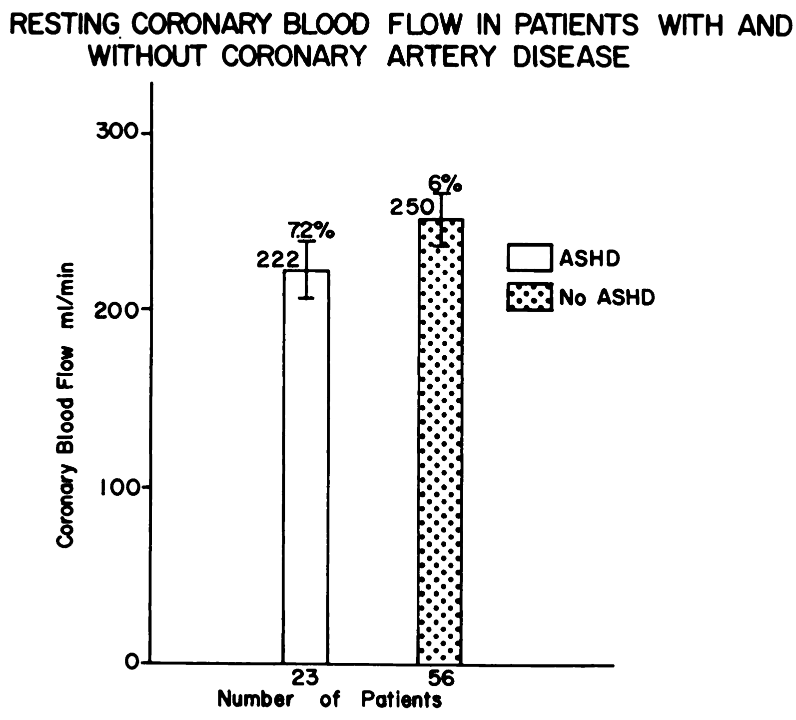


**Fig. 3. Mean resting coronary blood flow in patients with and without coronary artery disease. The average coronary blood flow in arteriosclerotics is 222 ± 16 (7.2%) ml/min; in individuals without coronary artery disease it is 250 ± 15 (6%) ml/min. These differences are not significant (P > 0.90).**

(11, 12). Similar results were obtained in five patients, in whom exercise failed to increase the slope of the extraction ratio (12).

The accuracy of this procedure has been established in nine experiments in which the coronary flow through an isolated dog heart preparation was measured directly and also calculated using the method described in this report; the agreement between the two methods was 93 per cent (12).

At this point a comparison of the coincidence methods with other procedures used in the measurement of coronary flow in man is indicated. The coincidence method has the advantage over that using nitrous oxide in that the coronary sinus does not need to be catheterized (16). In addition, using nitrous oxide, a state of equilibrium between blood and organ mass must be achieved during the period of observation. Some of the gas may transverse the coronary precapillary anastomoses and in ischemic hearts true equilibrium between blood and poor perfused areas may not be achieved. Similar to the nitrous oxide procedure, the coincidence method has the disadvantage that only mean values are obtained during a certain period and that rapid changes in coronary flow cannot be detected. Using $^{86}Rb$, or $^{42}K$, which are single emitters, the arterial level of the isotope must be maintained constant, and changes in coronary flow cannot be measured in the same subject (1).

Several authors have used a single injection of an isotope to determine coronary flow. In the method of Sevelius and Johnson, the precordial activity is

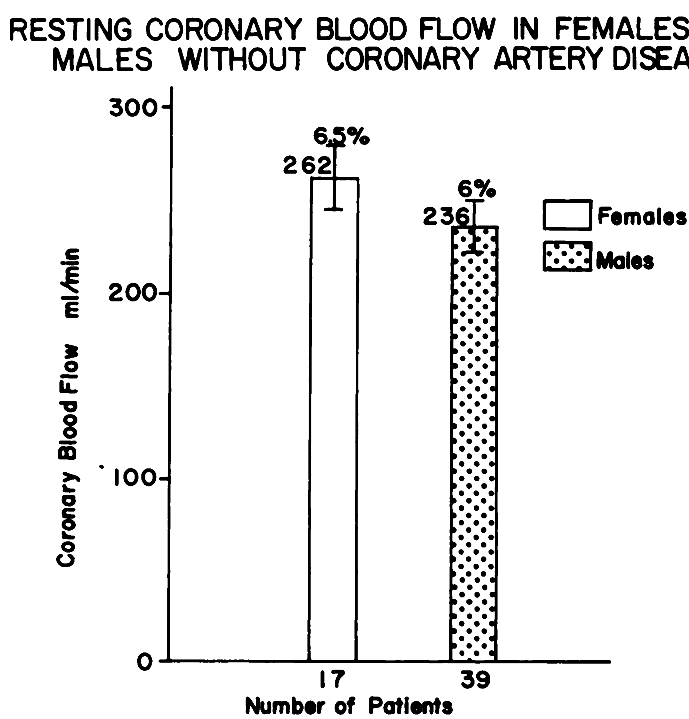


**Fig. 4. Mean resting coronary blood flow in females and males without coronary artery disease. The average coronary blood flow in females is 262 ± 17 (6.5%) ml/min and in males is 236 ± 14 (6%) ml/min. These differences are not significant ($P > 0.90$).**

THE EFFECT OF NITROGLYCERIN IN PATIENTS WITHOUT CORONARY ARTERY DISEASE

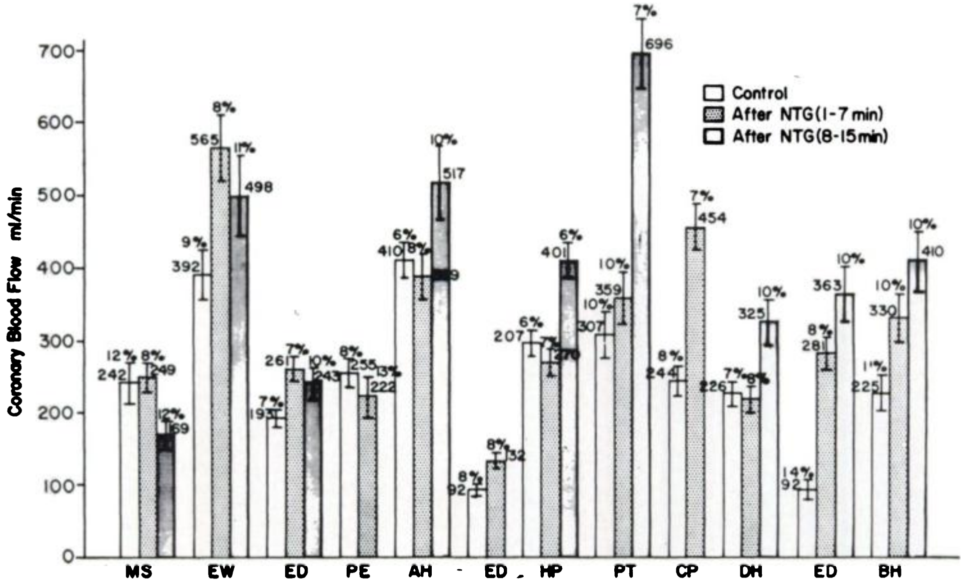


**Fig. 5. Effect of nitroglycerin on the coronary blood flow in patients without coronary artery disease. In six individuals the coronary blood flow increased during the first seven minutes following the administration of the drug (P < 0.05); in eight it remained elevated or increased further during the additional seven minutes of the test (P < 0.005). Figure on the top of column represents the coronary blood flow and its standard deviation.**

THE EFFECT OF NITROGLYCERIN IN PATIENTS WITH CORONARY ARTERY DISEASE

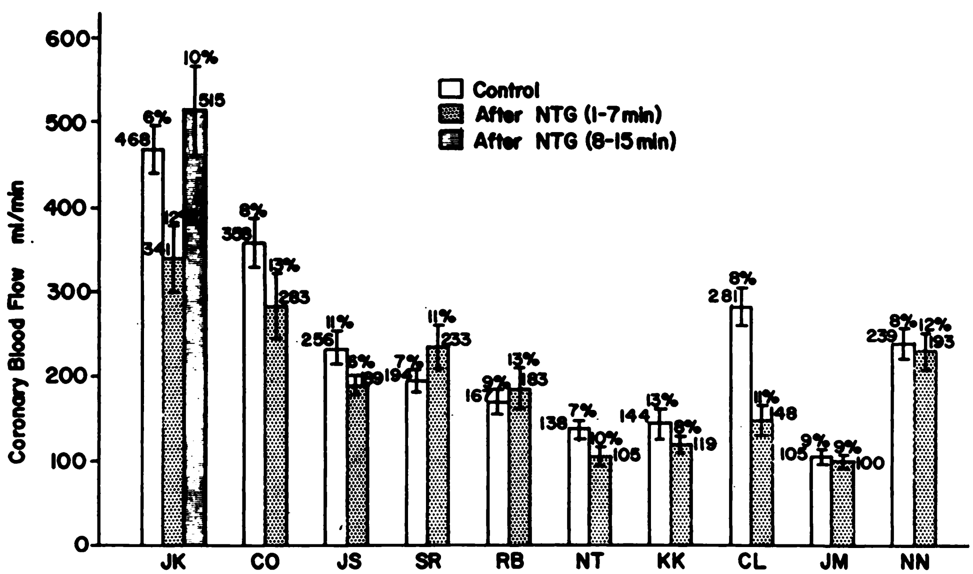


**Fig. 6. Effect of nitroglycerin on the coronary blood flow in patients without coronary artery disease. In nine patients the coronary blood flow failed to increase after the administration of the drug (P < 0.025). Figure on the top of column represents the coronary blood flow with its standard deviation.**

measured after a bolus injection of radioiodinated serum albumin (8,17). The "coronary peak" as described by these authors is difficult to differentiate due to the passage of the isotope through the ventricular chambers. The method of computation is subjective and the extrapolation of this small "coronary peak" is difficult. In addition, the errors inherent due to the Poisson's distribution are not considered (18). Mena, using a similar technique, found that the ratio of the disappearance slope of the precordial and arterial activities was blood flow related (7). However, flows could not be determined because units are lacking. The criticism applied to the method of Sevelius and Johnson is also applicable

TABLE I

RESTING CORONARY BLOOD FLOW IN PATIENTS WITH CORONARY ARTERY DISEASE

| *Patient Initials* | *Age and Sex* | *Diagnostic Criteria** | *Flow ml/min* | *G Flow* |
|---|---|---|---|---|
| J.K. | 54 F | 2 | 468 | ± 28 |
| C.O. | 67 M | 2 | 358 | ± 29 |
| J.S. | 48 M | 2 | 256 | ± 18 |
| S.R. | 56 M | 2 | 194 | ± 14 |
| R.B. | 36 M | 2, 3 | 167 | ± 15 |
| N.T. | 67 M | 2 | 138 | ± 10 |
| K.K. | 51 M | 2 | 144 | ± 19 |
| C.L. | 62 M | 3 | 281 | ± 22 |
| J.M. | 71 M | 2, 3 | 105 | ± 9 |
| O.M. | 37 M | 3 | 149 | ± 5 |
| G.M. | 66 M | 2, 3 | 355 | ± 7 |
| I.K. | 72 M | 3 | 270 | ± 8 |
| E.G. | 65 F | 2, 3 | 160 | ± 6 |
| J.P. | 83 M | 3 | 194 | ± 5 |
| B.J. | 52 M | 2, 3 | 193 | ± 12 |
| W.M. | 62 M | 2 | 310 | ± 18 |
| B.B. | 59 M | 3 | 166 | ± 17 |
| N.N. | 59 F | 3 | 239 | ± 19 |
| W.L. | 71 M | 2, 3 | 105 | ± 15 |
| G.S. | 65 M | 1 | 193 | ± 7 |
| L.B. | 49 M | 2 | 212 | ± 17 |
| W.F. | 50 M | 2 | 160 | ± 10 |
| A.S. | 62 M | 3 | 276 | ± 28 |
| Average Coronary Blood Flow | | | 222 | ± 16 |

*See Text
1. Coronary arteriography.
2. History of recent infarct, electrocardiogram and enzymatic studies.
3. Previous infarct suspected on the basis of history and electrocardiogram.

TABLE II

EFFECT OF NITROGLYCERIN IN PATIENTS WITHOUT CORONARY ARTERY DISEASE

| *Patient Initials* | *Age and Sex* | | *Period* | *Flow ml/min* | *% Change of Flow* |
|---|---|---|---|---|---|
| M.S. | 42 | F | Before | 242 ± 29* | ——— |
| | | | After I | 249 ± 20 | 3 ± 18 |
| | | | After II | 169 ± 20 | −30 ± 19 |
| E.W. | 36 | F | Before | 392 ± 35 | ——— |
| | | | After I | 565 ± 45 | 44 ± 38 |
| | | | After II | 498 ± 54 | 27 ± 25 |
| E.D. | 22 | F | Before | 193 ± 13 | ——— |
| | | | After I | 261 ± 18 | 35 ± 18 |
| | | | After II | 243 ± 24 | 26 ± 21 |
| P.E. | 35 | F | Before | 255 ± 20 | ——— |
| | | | After I | 222 ± 29 | −13 ± 18 |
| A.H. | 50 | M | Before | 410 ± 24 | ——— |
| | | | After I | 389 ± 31 | −5 ± 13 |
| | | | After II | 517 ± 51 | 26 ± 21 |
| E.D. | 29 | F | Before | 92 ± 7 | ——— |
| | | | After I | 132 ± 11 | 44 ± 21 |
| H.P. | 32 | M | Before | 297 ± 18 | ——— |
| | | | After I | 270 ± 19 | −9 ± 11 |
| | | | After II | 401 ± 24 | 35 ± 16 |
| P.T. | 63 | F | Before | 307 ± 31 | ——— |
| | | | After I | 359 ± 36 | 17 ± 24 |
| | | | After II | 696 ± 49 | 126 ± 39 |
| C.P. | 74 | M | Before | 244 ± 20 | ——— |
| | | | After I | 454 ± 32 | 86 ± 28 |
| D.H. | 22 | M | Before | 226 ± 16 | ——— |
| | | | After I | 219 ± 18 | −3 ± 15 |
| | | | After II | 325 ± 32 | 44 ± 26 |
| E.D. | 29 | M | Before | 92 ± 13 | ——— |
| | | | After I | 281 ± 22 | 205 ± 68 |
| | | | After II | 363 ± 37 | 295 ± 98 |
| B.H. | 53 | F | Before | 225 ± 25 | ——— |
| | | | After I | 330 ± 33 | 46 ± 31 |
| | | | After II | 410 ± 41 | 82 ± 39 |
| | | | | | Significance of |
| | | | Average Flow | 248 ± 21 | Change from Before |
| | | | | 311 ± 27 | ($P < 0.05$) After I |
| | | | | 402 ± 36 | ($P < 0.005$) After II |
| | | | Average % of Change of Flow | | 38 ± 25 |
| | | | | | 70 ± 34 |

*Standard Deviation of Flow

I—1 to 7 minutes

II—8 to 15 minutes

to that of Weinberg *et al* (9). In the method of Donato *et al,* using singles, such as $^{84}$Rb and/or $^{42}$K, iodinated albumin must also be injected in order to separate the activity of blood in the heart chambers from the myocardial activity (5). In addition, use of singles makes separation of the activity of the heart from that of surrounding structures difficult.

TABLE III

EFFECT OF NITROGLYCERIN IN PATIENTS WITH CORONARY ARTERY DISEASE

| *Patient Initials* | *Age and Sex* | *Diagnostic Criteria*** | *Period* | *Flow ml/min* | *% Change of Flow* |
|---|---|---|---|---|---|
| J.K. | 54 F | 2 | Before | 468 ± 28* | ——— |
| | | | After I | 341 ± 41 | −27 ± 12 |
| | | | After II | 515 ± 52 | 11 ± 6 |
| C.O. | 67 M | 2 | Before | 358 ± 29 | ——— |
| | | | After I | 283 ± 37 | −21 ± 17 |
| J.S. | 48 M | 2 | Before | 256 ± 18 | ——— |
| | | | After I | 189 ± 11 | −26 ± 10 |
| S.R. | 56 M | 2 | Before | 194 ± 14 | ——— |
| | | | After I | 233 ± 26 | 20 ± 23 |
| R.B. | 36 M | 2, 3 | Before | 167 ± 15 | ——— |
| | | | After I | 183 ± 2 | 10 ± 16 |
| N.T. | 67 M | 2 | Before | 138 ± 10 | ——— |
| | | | After I | 105 ± 11 | −24 ± 13 |
| K.K. | 51 M | 2 | Before | 144 ± 19 | ——— |
| | | | After I | 119 ± 10 | −17 ± 18 |
| C.L. | 62 M | 3 | Before | 281 ± 22 | ——— |
| | | | After I | 148 ± 16 | −47 ± 10 |
| J.M. | 71 M | 2, 3 | Before | 105 ± 9 | ——— |
| | | | After I | 100 ± 9 | − 5 ± 18 |
| N.N. | 59 F | 3 | Before | 239 ± 19 | ——— |
| | | | After I | 229 ± 27 | − 4 ± 16 |
| | | Average Flow | | 229 ± 18 | Significance of |
| | | | | 193 ± 21 | Change from Before |
| | | | | | (P < 0.025) After I |
| | | Average % of Change of Flow | | | −14 ± 15 |

*Standard Deviation of Flow
I—1 to 7 minutes
II—8 to 15 minutes
**See text

Krypton-85 and/or $^{133}Xe$ have been used for the measurement of coronary blood flow by the injection of the isotopes into the coronary arteries directly; coronary blood flow is then determined from the washout of the precordial activity (19). This method has the advantage that radioactivity is restricted to the heart, but it also requires equilibrium between the gas in the blood and in the muscle. The technique necessitates catheterization of a coronary artery. As Rowe pointed out, with the use of any of the singles techniques the measurement of flow through both free walls of the ventricles and septum becomes very difficult, because these areas lie at different distances from the detectors, making the resultant precordial count inaccurate (20). With the coincidence method, this difficulty has been eliminated.

Finally, the method of calculation used here takes into account the various statistical errors arising from radioactive processes of disintegration which are mutually independent and randomly distributed in time. The Poisson distribution is characterized by a single independent parameter, the mean value alone (18). Equations dealing with standard deviations are based on the Poisson statistics (12). The method of least square is used to compute the first derivative of the myocardial uptake of rubidium and the extrapolation of the clearance to zero time. All calculations are carried out objectively by computer analysis.

The results reported here demonstrate that the coronary blood flow is independent of age and sex. In patients above or below 40 years, the mean coronary blood flow is $242\pm 16$ ml/min and $258\pm 14$ ml/min, respectively; this difference is not statistically significant ($P>0.90$). The mean coronary blood flow in males is $236\pm 14$ ml/min and in females $262\pm 17$ ml/min ($P>0.90$). Rowe, utilizing the nitrous oxide method, reported that the coronary blood flow per 100 gm of left ventricular muscle is higher in females (20, 21). It is possible that if the results reported here could also be expressed per 100 gm of myocardium, the differences in coronary flow would be more apparent.

There is no statistical difference in coronary flow between patients with and without coronary artery disease ($P>0.90$). In patients without and with coronary artery disease the coronary blood flow is $250\pm 15$ and $222\pm 16$, respectively. In contrast, using the nitrous oxide method, Gorlin reported a higher resting coronary flow in patients with coronary artery disease due to maximal dilatation of the coronary vessels (22). However, Sapirstein and Ogden have pointed out that this may have been due to poor equilibration between blood and perfused ischemic areas (23).

In 12 individuals without coronary artery disease, nitroglycerin increased the coronary blood flow in all but one individual. The average rise during the first seven minutes after the administration of the drug was 38 percent ($P<0.05$). It was 70 percent for the remaining seven minutes ($P<0.005$).

In ten patients with coronary artery disease, the administration of nitroglycerin failed to raise the coronary blood flow in all but one. The average decline was $-14$ percent ($P<0.025$).

The results reported here demonstrate a marked difference in the effect of nitroglycerin in patients with and without coronary artery disease and confirm similar reports by others using the nitrous oxide method or isotope procedures

(5, 22, 24). Because of this different response to nitroglycerin, the coincidence method has already been successfully employed as a diagnostic aid in the recognition of coronary artery disease (12, 25).

Despite obvious advantages of the coincidence counting method, certain improvements could make this procedure of even greater value. In the first place, rapid changes in coronary flow cannot be detected, because the statistical error is too great when periods of flow of less than five minute duration are computed. Secondly, because the half-life of the isotope is 33 days, repeated studies at intervals of less than one month are not advisable. Thirdly, coronary flow measurements exceeding 30 minutes cannot be carried out, because of the progressive decrease in myocardial uptake of $^{84}$Rb.

## SUMMARY

The concepts underlying a coincidence counting method for the measurement of coronary blood flow using $^{84}$Rb, a positron emitter, is described. Coronary blood flow is calculated by the logarithmic extrapolation of the myocardial clearance values of $^{84}$Rb to zero time. At this time, the myocardial extraction ratio is unity. The accuracy of the method has been established in experiments on the isolated dog heart. All calculations are objectively performed by a digital computer.

The resting coronary blood flows in individuals above and below the age of 40 and in males and females were not statistically different. In addition, there were no significant differences in the resting coronary blood flows in patients with and without coronary artery disease.

The observation that sublingual administration of nitroglycerin increases the coronary blood flow in individuals without coronary artery disease while failing to increase it in patients with coronary artery disease has been used as a diagnostic test in the recognition of coronary artery disease.

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