Influence of the Rate of Coronary Plasma Flow on the Extraction of Rb\textsuperscript{86} from Coronary Blood

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To determine whether myocardial uptake of Rb\textsuperscript{86} can be used as a useful index of coronary plasma flow, the extraction of Rb\textsuperscript{86} from arterial plasma during one passage through the myocardium of dogs was measured at varying rates of flow. At rates of flow which are encountered in man, changes in the rates of flow and uptake of isotope by the myocardium paralleled each other closely. Rb\textsuperscript{86} uptake is a useful index of coronary blood flow in dogs.

Previous studies have suggested that the rate of coronary blood flow can be estimated in man without cardiac catheterization by the use of a precordial monitor to measure the rate at which the myocardium takes up Rb\textsuperscript{86} from the blood during an infusion of this isotope. The rate of uptake of Rb\textsuperscript{86} by the heart was found to be decreased by intravenous administration of pitressin in dogs and increased by levarterenol (1-norepinephrine).\textsuperscript{1} These changes are in the same direction as those which these drugs produce on coronary blood flow. Differences in the rate of myocardial Rb\textsuperscript{86} uptake in dogs were measured within 20 per cent by placing a scintillation counter over the precordium of the intact animal;\textsuperscript{3} reasonable values for coronary blood flow in man have been obtained with similar methods.\textsuperscript{2} Since this previous evidence is indirect, the present study was undertaken to determine directly the relationship of coronary blood flow and myocardial uptake of Rb\textsuperscript{86}.

METHODS

Dogs weighing 8.3 to 16.7 Kg. were anesthetized with 30 mg./Kg. sodium pentobarbital intravenously, and a right thoracotomy incision was performed, with artificial respiration. After administration of 100 mg. heparin\textsuperscript{*} a flexible cannula of 6.5 mm. outside diameter and 3 mm. inside diameter was passed through the right jugular vein and its tip guided approximately 2 cm. into the coronary sinus. Coronary venous blood flowed through the cannula into the left jugular vein, except when the rate of outflow was measured by timed collection of 10 to 50 ml. in a graduated cylinder.

To provide a stable concentration of Rb\textsuperscript{86} in arterial plasma, a standard intravenous infusion of Rb\textsuperscript{86} in 0.15 M sodium chloride solution was administered at a decreasing rate for 15 to 73 min.\textsuperscript{1} At intervals the rate of outflow of blood from the coronary sinus was measured, and specimens of arterial and coronary sinus blood were collected. The concentration of Rb\textsuperscript{86} in the plasma of these specimens was determined by methods previously described.\textsuperscript{3} Potassium concentration was measured in a 100 fold aqueous dilution of plasma using a Beckman DU flame spectrophotometer. Mean femoral arterial blood pressure was obtained with an indwelling needle and mercury manometer. The hematocrit was determined with a tube of 3 mm. bore and 10 cm. length, which was centrifuged at 2,000 RCF for 45 min. An infusion containing 20 mg. levarterenol per L. 0.15 M sodium chloride solution was administered intravenously, intermittently during the study, in 16 dogs to produce variations in the rate of coronary blood flow. It is possible that levarterenol might have an effect on Rb\textsuperscript{86} extraction, independent of its effect on coronary blood flow. To aid in the detection of such an effect, hypotension was produced in 5 of the dogs by bleeding them 200 ml. prior to the study, during which time they received levarterenol. Thus, observations were made on animals receiving the drug with normal rates of coronary blood flow. The dogs were killed by intravenous injection of

\*Supplied by Upjohn Co.
The weight of the left ventricle was determined, and an aliquot digested in nitric acid for determination of potassium and Rb86 content.4

Since the cannula was introduced a variable distance into the coronary sinus, and since the portion of left ventricular blood flow draining into the coronary sinus varies,5 the amount of myocardium drained by the coronary sinus cannula was calculated in each dog by relating the total amount of Rb86 extracted from the blood which flowed through the cannula to the final Rb86 content of the myocardium measured at the time of killing. On the average, an amount of myocardium equal to 55 ± 13 per cent of the left ventricle was drained by the cannula. In order to calculate the Rb86 concentration present in the myocardium at the time of each successive measurement on an animal, the product of coronary plasma outflow and the arterio-coronary sinus plasma Rb86 difference was accumulated serially.

RESULTS

Illustrative data from one dog are shown in figure 1. Previous results have indicated that the uptake of Rb86 by the myocardium is probably an exchange process.1 Therefore the extraction of Rb86 from coronary blood, which is defined as the fraction of Rb86 in arterial plasma removed during one circulation through the myocardium, would be expected to decrease as the isotope content of the muscle increased. The relationship between the radioactivity of the myocardium and the extraction of Rb86 for one dog is shown in figure 2a. Calculations of myocardial radioactivity were made with the assumption that Rb86 traced potassium, the nontracer content being represented by the potassium concentration. Rb86 extraction was also related to the rate of coronary plasma flow, as shown in figure 2b. Since there was evidence that the rate of myocardial uptake of Rb86 was affected by two of the measured variables, the data from all animals were grouped so as to hold one of these factors within a relatively narrow range while evaluating the other.

Effect of Rate of Coronary Plasma Flow on Rb86 Extraction. Figure 3 shows the relation of the rate of coronary plasma flow to the extraction of Rb86 from coronary blood in all dogs. To reduce variation caused by differences in myocardial radioactivity, each measurement is grouped with all of the others made when the Rb86 content of the myocardium was calculated to be within a given range. Measurements made after the Rb86/K ratio of the myocardium had exceeded 30 per cent of the plasma Rb86/K ratio were not included in this chart. In each range of myocardial Rb86 content there was a similar relationship of the rate of coronary flow and the logarithm of myocardial Rb86 extraction. The logarithm of the per cent extraction decreased approximately 0.175 for each 100 ml. increase in the rate of coronary plasma flow. When the rate of coronary plasma flow was
45 ml./100 Gm./min., which is approximately the average rate in man, and the Rb$^{86}$/K ratio of the myocardium was less than 10 per cent of the plasma ratio, the extraction of Rb$^{86}$ averaged 71 per cent. The extraction at very low rates of flow approached 85 per cent, rather than 100 per cent. This supports the idea that anatomical or functional shunts of plasma exist within the myocardium, as they do elsewhere.

Relation of Rb$^{86}$ Uptake and Myocardial Rb$^{86}$ Content. Figure 4 shows the relation of Rb$^{86}$ extraction and myocardial Rb$^{86}$ content. The results have been grouped into 3 ranges of coronary plasma flow to reduce the variation caused by the effect of plasma flow on Rb$^{86}$ extraction. If all of the isotope in the plasma flowing through the myocardium gained access to the cellular pool of Rb and potassium, there should be a 10 per cent fall in extraction for each 10 per cent rise in myocardial Rb$^{86}$ content. However, only approximately an 8.5 per cent fall was observed. This may be caused by the presence of shunts, although a Rb/K ratio in the myocardium approximately 16 per cent higher than that in the plasma would have a similar effect. Values of 14 and of 5 per cent higher relative myocardial Rb concentration have been obtained in two series of dogs (1, 4).

Under the direction of Dr. Lillian R. Elveback, regression relationships were calculated individually for the 15 dogs which were not bled prior to study. The mean of the individual values was essentially the same as the result obtained with pooled data.

Effect of Levarterenol on Rb$^{86}$ Uptake. In figures 3 and 4 measurements made before the animal received this sympathomimetic amine are indicated by a symbol different from that for measurements made during or after the infusion of this drug. Extraction was similar in the 3 groups at the same rate of flow; therefore there was no apparent effect of the drug upon Rb$^{86}$ extraction, which was separate from its effect on plasma flow.

The Effect of Other Factors on Rb$^{86}$ Extraction. The pulse rate and the myocardial extraction of Rb$^{86}$ were measured essentially simultaneously 26 times in 10 dogs. Pulse rate ranged from 84 to 216 beats/min., but no relation of pulse rate to Rb$^{86}$ extraction could be demonstrated, even when a correction was made for the effects of the rate of coronary plasma flow and the myocardial Rb$^{86}$ content on the degree of extraction of isotope. In a group of dogs studied previously, no relation of pulse rate to the rate of Rb$^{86}$ uptake was demonstrable. The rate of net uptake or loss of potassium by the myocardium at the time of each measurement of coronary blood flow was calculated from the coronary arteriovenous difference. The net exchange of potassium by the heart must affect the fraction of the Rb$^{86}$ extracted from coronary plasma, if Rb$^{86}$ traces potassium in the myocardium. However, no such effect was demonstrated in this group of dogs. This was probably caused by the small net exchanges present and by the low specific activity of potassium entering the plasma from the myocardium during the initial portion of the study. In these experiments, the fraction of the Rb$^{86}$ which was extracted from coronary plasma was not related to variations in plasma potassium concentration, or to the Rb concentration of the injectant.

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DISCUSSION

From these data it is possible to obtain a value for the effective rate of flux of potassium between the myocardial cell and capillary lumen, by the assumption, as an approximation, that Rb$^{86}$ traces the movements of potassium within the myocardium. If the amount of shunting at low rates of plasma
Flow is 10 per cent of the total flow, and 81 per cent of the total Rb\textsuperscript{86} entering 100 Gm. of myocardium in the coronary arterial plasma is removed at a flow of 25 ml. plasma/min. (fig. 3, with correction for myocardial Rb\textsuperscript{86}), then 90 per cent of the isotope in the plasma which was not shunted must have entered the myocardium. To reach an uptake of 90 per cent, the rate at which potassium flows out of the capillary must be approximately 9 times the rate at which it is delivered by the blood. With a plasma potassium of 4.5 mEq./L, this would amount to a capillary flux of 0.91 mEq./100 Gm. myocardium/min. in one direction, or approximately 10 per cent of the cellular potassium content. If the potassium flux across the capillary wall remains constant with increasing flow, then the per cent of the plasma shunted would have to increase approximately 3 per cent for each 25 ml. increase in coronary plasma flow, to account for the data of figure 3. The resulting value for potassium flux is twice that reported by Conn and Robertson.\textsuperscript{7} Their data obtained with K\textsuperscript{42} were analyzed, with all of the isotope being considered to gain access to the interstitial space, and without parallel measurements of the rate of coronary blood flow. The difference in the rates is not caused by a difference in isotopes used, since the extraction of K\textsuperscript{42} in their study was approximately the same as the extraction of Rb\textsuperscript{86} found in the animals reported here. Previous studies in dogs have demonstrated that the amount of plasma potassium gaining access to the myocardial cell is a function of the plasma potassium concentration.\textsuperscript{1} This would not be true if there were a small fixed cellular potassium flux, such as is present in the erythrocyte.\textsuperscript{5, 9} It seems probable that all estimates of potassium movements in and out of the cells of the myocardium, which are based on uptake of isotope from the blood, are too low. The observed rates of exchange between the plasma and myocardium could be limited by incomplete mixing within the myocardium or by a membrane barrier, with increased shunting of plasma at high rates of flow because of axial streaming, etc. Under these circumstances the rate of uptake of potassium from the blood would not accurately reflect the rate of flux of potassium into and out of the myocardial cell. The result obtained may approximate closely the diffusing capacity of the myocardial capillary bed for Rb\textsuperscript{86} and potassium. Expressing the results in these terms, the diffusing capacity of the dog myocardium would be approximately 200 ml. plasma/min./100 Gm. From results of measurements of plasma flow and Rb\textsuperscript{86} extraction in other areas of the dog,\textsuperscript{10} it is possible to calculate similar rates of 500 ml. for the kidney, 95 ml. for the combined liver and portal bed, 13 ml. for the lower extremity, and 62 ml. for the lung. The extent to which Rb\textsuperscript{86} uptake is limited by capillary permeability undoubtedly varies from tissue to tissue, so that these values may have no meaning in these terms for some tissues.

An estimate of the relationship of the rates of coronary plasma flow and myocardial uptake of Rb\textsuperscript{86} in man can be obtained by applying these data to the rates of flow expected in human subjects with and without heart disease. In figure 5 the changes in Rb\textsuperscript{86} uptake which would be expected from variation in coronary plasma flow are indicated.
In these calculations the reference flow was 75 ml. of whole blood/100 Gm. of myocardium/min., a reasonable value for normal man. The relationship of coronary flow, and Rb<sup>86</sup> uptake is especially close at low rates of flow, which are the chief clinical concern. Because of the rise in myocardial Rb<sup>86</sup> concentration, the extraction of Rb<sup>86</sup> would fall approximately 10 per cent during a study lasting 7 min. at normal rates of flow. The variability in Rb<sup>86</sup> extraction from dog to dog at a given rate of coronary plasma flow cannot be evaluated adequately from these data, because the size of the errors in measurements of coronary flow, isotope extraction, and myocardial radioactivity are not known. Because of these experimental errors, the variability must be less than that shown in figure 3. Extraction of Rb<sup>86</sup> by the myocardium in man has not yet been studied, and the possible effects of disease are not known. However, any factor which increases the quantity of potassium passing from capillary lumen to myocardial cell would improve the correlation between Rb<sup>86</sup> uptake and coronary plasma flow. A doubling of this rate would increase extraction by only 5 per cent. Although a reduction in this rate would make the correlation less close, substantial changes would have relatively little effect. If the exchange of potassium between myocardium and capillary plasma fell by one half, the extraction of isotope would be decreased by but 8 per cent.

An important limitation to the clinical use of Rb<sup>86</sup> uptake to measure coronary blood flow is the error caused by poor collimation of precordial monitors used to measure myocardial Rb<sup>86</sup> concentration. Previous measurements, made by monitoring from two sites over the precordium and remonitoring 24 hours after the infusion of isotope, have yielded reasonable values for coronary blood flow, but this result may have been partially caused by parallel variations in the rates of uptake of the several tissues under the monitor. An accurate method of clinically determining myocardial radioactivity must be developed before the validity of myocardial Rb<sup>86</sup> uptake as an index of coronary blood flow can be adequately tested in man.

**Summary**

Because of previous evidence indicating that the myocardial uptake of Rb<sup>86</sup> is determined by the rate of plasma flow, coronary blood flow and the degree of extraction of Rb<sup>86</sup> by the myocardium were measured at intervals during an intravenous infusion of isotope in 19 dogs. Myocardial Rb<sup>86</sup> extraction was found to be logarithmically related to coronary plasma flow. (log. per cent Rb<sup>86</sup> extracted = 1.93 - 0.00175 coronary plasma flow, ml./100 Gm. myocardium/min.)

If these results apply to man, a 50 per cent increase or decrease in the average rate of coronary plasma flow would produce respectively a 38 per cent rise or 44 per cent fall in Rb<sup>86</sup> uptake rate. It will be feasible to make estimates of the rate of coronary plasma flow by this method in man without cardiac catheterization, if myocardial radioactivity can be measured accurately with an external monitor.

**Summario in Interlingua**

A causa del observation, previemente facite, que le acceptation myocardial de Rb<sup>86</sup> es determinate per le intensitate del fluxo de plasma, le presente studio esseva interprente, mesurante le fluxo de sanguine coronari e le grado de extraction de Rb<sup>86</sup> per le myo-cardio a varie intervallos durante le infusion intravenose del isotope in 19 canes. Esseva trovate que le extraction myocardial de Rb<sup>86</sup> es logarithmicamente relationate al fluxo coronari de plasma (i.e. log pro cento de Rb<sup>86</sup> extrahite = 1.93 - 0.00175 de fluxo coronari de plasma, in ml per 100 g de myocardio per minuta).

Si iste resultatos es valide pro humanos, un augmento o un reduction de 50 pro cento in le valor medie del fluxo coronari de plasma producerea, respectivamente, un augmento de 38 pro cento o un reduction de 44 pro cento in le acceptation de Rb<sup>86</sup>. Il es possibile in le practica usar iste metodo pro estimar le intensitate del fluxo coronari de plasma sin
catheterismo cardiac, providite que le radio-activitate myocardial pote esser measure accuratemente per medio de un coitator externe.

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