DIFFERENCES IN THE RATE OF RB^{86} UPTAKE BY SEVERAL REGIONS OF THE MYOCARDIUM OF CONTROL DOGS AND DOGS RECEIVING L-NOREPINEPHRINE OR PITRESSIN® [1]

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The rate at which Rb^{86} enters the myocardium from the blood is determined by the rate of coronary blood flow and by the kinetics of potassium within the myocardium. In preparation for a study of the effects of disease on the rate of myocardial Rb^{86} uptake in man, a trial of methods was made in a series of dogs. During this study the rate of Rb^{86} uptake in several regions of the heart of control dogs was measured, and the effects of l-norepinephrine and Pitressin® on differences in regional Rb^{86} uptake were determined, since these drugs respectively increase and decrease overall coronary blood flow (1, 2).

MATERIALS AND METHODS

Details of the materials and methods used have been described elsewhere (3). These data on Rb^{86} uptake of different regions of the heart were obtained from the same dogs in which precordial monitoring was carried out.

Mongrel dogs weighing 6.7 to 14.3 Kg. were anesthetized with sodium pentobarbital and infused intravenously with Rb^{86} at a continuously decreasing rate for periods of 5 to 90 minutes in order to attain nearly constant levels of Rb^{86} in the plasma of arterial blood. The radioactivity of whole blood was monitored in a small external arterio-venous shunt from which samples were taken at 5-minute intervals for determination of plasma Rb^{86} and potassium concentrations. Frequent recordings of heart rate and mean arterial blood pressure were made after 100 to 150 mg. heparin had been given. Four dogs received a mean dosage of 2.5 μgm. per Kg. per min. l-norepinephrine intravenously for 30 minutes and six dogs received a mean of 0.065 pressor units per Kg. per min. Pitressin® for a similar period, during which time they also received Rb^{86}. The dogs were sacrificed by rapidly opening the chest and removing the heart. Specimens were obtained from several regions of the heart, from the lung and liver, and from the skeletal muscle of the pectoral region and spine.

Specimens obtained from the hearts of 29 dogs were as follows: full thickness of the left ventricle in the apical region, full thickness of the left ventricle in the basilar region, full thickness of the mid-portion of the interventricular septum, a portion of the thickest part of the left ventricle divided approximately into outer, middle, and inner thirds, a similar specimen from the right ventricle divided into inner and outer halves, and specimens of the full thickness of the right ventricle and from both auricles. The latter included the appendages and a portion of the adjacent wall of the auricle. The potassium and Rb^{86} concentrations of all specimens were determined after digestion in HNO_3.

METHODS OF ANALYSIS

The rationale of the methods of analysis and the details of the procedure have been presented elsewhere (3). It was assumed that Rb^{86} traced potassium in the myocardium, that the individual portions of the myocardium could be considered homogeneous compartments

TABLE I

Mean potassium concentration of various regions of the hearts of 19 control dogs, and the mean ratio of myocardial Rb^{86}/K to plasma Rb^{86}/K of the same regions of the hearts of eight dogs sacrificed more than 72 hours after Rb^{86} injection

Region of the myocardium	(Myocardial Rb^{86}/K ÷ Plasma Rb^{86}/K) × 100, at equilibrium	K. conc. *mEq. per Kg.*
Mean of six specimens from the left ventricle	106.1 ± 7.6	82.2 ± 4.5
Outer third of left ventricle	108.0	83.3
Middle third of left ventricle	105.8	84.0
Inner third of left ventricle	104.0	80.3
Mean of three specimens from the right ventricle	103.3	81.6
Outer half of right ventricle	104.5	82.2
Inner half of right ventricle	102.9	80.9
Right atrium	115.6	59.5
Left atrium	114.1	67.2

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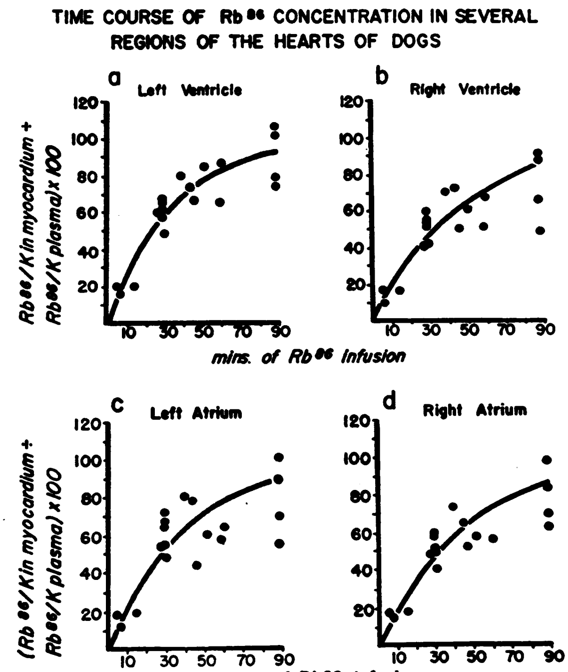

FIG. 1. THE TOTAL Rb^{86} UPTAKE IN THE WALLS OF EACH CHAMBER OF THE HEARTS OF 19 CONTROL DOGS AFTER 5 TO 90 MINUTES OF Rb^{86} INFUSION

The lines indicate the average uptake at any time. This was obtained from the mean of all uptake rates without regard to duration of infusion of Rb^{86}.

which exchanged with plasma at constant rates, and that potassium concentrations did not change during the time that the measurements were being made. A portion of the data which support these assumptions is given in Table I and Figure 1. Rb^{86} uptake has been expressed in terms of the clearance of Rb^{86} by the myocardium and also in terms of the apparent turnover rate of potassium between the myocardium and the circulating plasma, which is defined as the fraction of the myocardial potassium which exchanges with the plasma in one minute. Potassium turnover rates were of interest because the potassium concentration of various regions of the myocardium differed, and it was felt that under some circumstances the potassium turnover rate might reflect the amount of effective plasma flow per unit amount of contractile tissue more accurately than would a simple clearance measurement, which is expressed as uptake per Gm. of tissue.

The turnover rate of potassium within the myocardium was obtained graphically from the following relationship.

$$H = C\ (1-e^{-bt})$$

where

H is the Rb^{86}/K ratio in the myocardium at the time of sacrifice,

C is the Rb^{86}/K ratio of the heart at $t = \infty$ (C is assumed to be equal to the average Rb^{86}/K ratio observed in the plasma.),

t is the duration of Rb^{86} infusion in minutes, and

b is the fraction of total myocardial potassium entering or leaving per minute, *i.e.*, the turnover rate.

If the blood flow is slow in comparison to the flux of potassium into and out of the myocardial fiber, then calculations by this method give a value for apparent potassium turnover which is lower than the true rate of flux.

The initial clearance of plasma Rb^{86} by the myocardium was defined as the amount of arterial plasma which would be required to supply the Rb^{86} taken up during a hypothetical moment before any Rb^{86} had begun to return from the myocardium to the plasma. It was therefore a minimal value for rate of plasma flow.

$$\text{Initial myocardial } Rb^{86} \text{ clearance} = \frac{\text{(b) (Myocardial K conc.)}}{\text{Mean plasma K conc.}}$$

Rb^{86} uptake by organs other than the heart was expressed as clearance of plasma Rb^{86} in ml. per Gm. per 30 min. which is equal to

$$\text{Organ } Rb^{86} \text{ cpm. per Gm.} \div \text{Plasma } Rb^{86} \text{ cpm. per ml.}$$

in dogs given Rb^{86} for a 30-min. period.

No correction has been made in the calculations for differences in the equilibrium ratio of myocardial Rb^{86}/K divided by plasma Rb^{86}/K in the various regions of the heart. These values for 8 dogs are given in Table I.

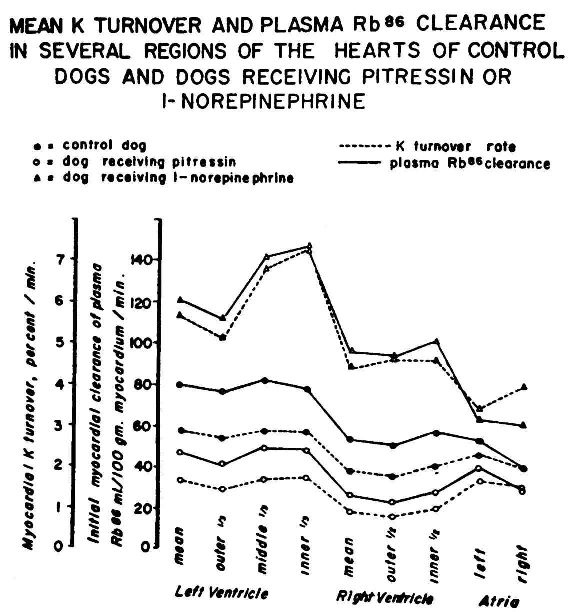

FIG. 2. MEAN POTASSIUM TURNOVER AND CLEARANCE OF PLASMA Rb^{86} IN SEVERAL REGIONS OF THE HEARTS OF CONTROL DOGS AND DOGS RECEIVING PITRESSIN® OR L-NOREPINEPHRINE

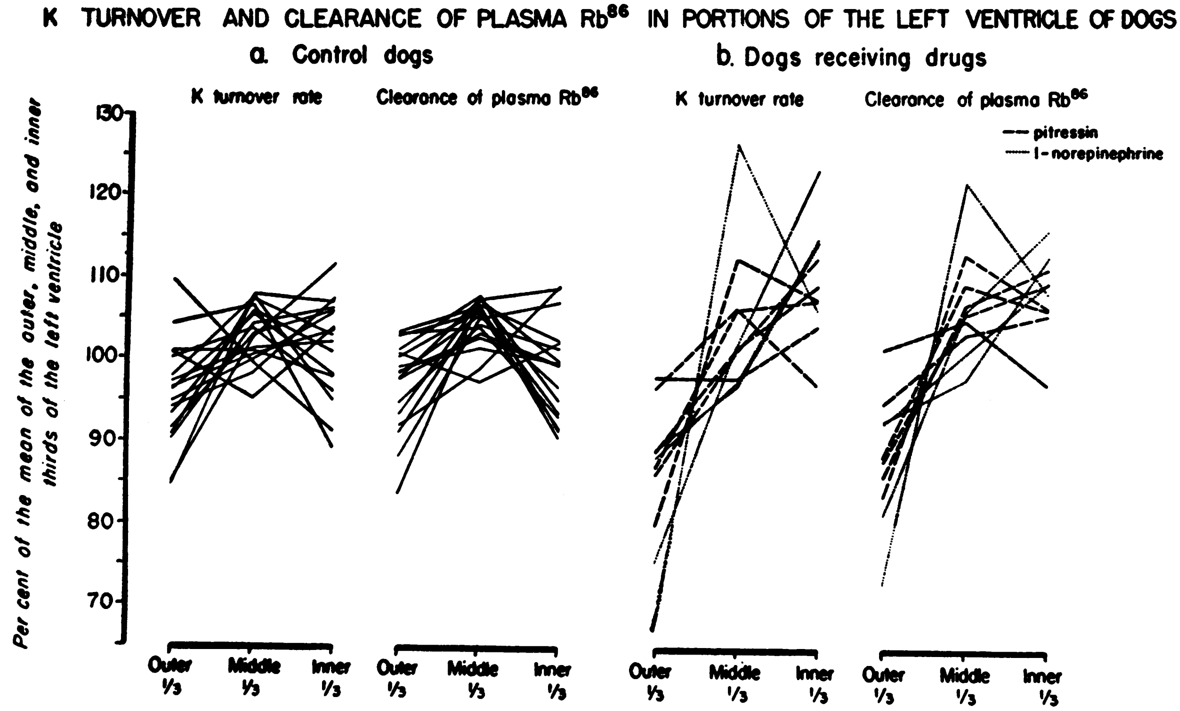

FIG. 3. POTASSIUM TURNOVER AND CLEARANCE OF PLASMA RB86 IN THE OUTER, MIDDLE AND INNER THIRDS OF THE WALL OF THE LEFT VENTRICLE IN CONTROL DOGS (a) AND DOGS RECEIVING INFUSIONS OF L-NOREPINEPHRINE OR PITRESSIN® (b)

RESULTS

The mean values of initial clearance of plasma Rb^{86} and turnover rate of potassium for several regions of the myocardium in control dogs and those receiving Pitressin® or l-norepinephrine are indicated in Figures 2, 3, and 4. Since no significant differences were noted in the results obtained in specimens from the apex of the left ventricle, base of the left ventricle, and from the interventricular septum, these values have not been recorded separately. The statistical significance [2] of some of the differences in Rb^{86} uptake of various regions of the heart is indicated below by the appropriate p value.

COMMENT

Figure 2 indicates that there was a greater clearance of plasma by the left ventricle of control dogs than by the right ventricle ($p < 0.01$). The clearance of plasma Rb^{86} and the turnover rate of potassium in the left ventricle averaged 45 per cent more than in the right, the potassium concentrations of the two being nearly equal (Table I). Clearance of plasma Rb^{86} by the auricles was only slightly lower than by the right ventricle, while the turnover rate of potassium was higher in the atria than in the right ventricle, in association with the relatively low potassium concentration in the atria. Clearance of Rb^{86} ($p < 0.01$) and turnover of potassium ($p = 0.07$) were less in the portion of the right atrium sampled than in the left atrium.

In Figure 3 the small differences in the Rb^{86} uptake by the outer, middle, and inner portions of the left ventricle are apparent. Clearance of plasma Rb^{86} by the middle portion of the wall of the left ventricle averaged 8.0 per cent more than by the outer third ($p = 0.01$) and 5.8 per cent more than by the inner third ($p < 0.01$). Clearance was 2.0 per cent greater by the inner portion than by the outer portion, but this may have been due to chance ($p > 0.4$).

The relationship of the values of turnover of

[2] The Fisher test for unique samples was used where applicable.

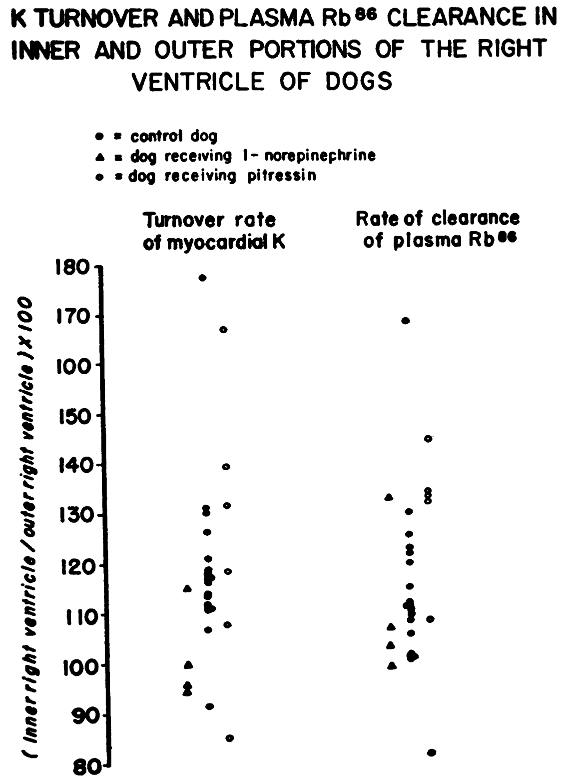

FIG. 4. THE POTASSIUM TURNOVER AND CLEARANCE OF PLASMA Rb^{86} IN THE INNER AND OUTER PORTIONS OF THE RIGHT VENTRICLE OF CONTROL DOGS AND DOGS RECEIVING L-NOREPINEPHRINE OR PITRESSIN®

myocardial potassium were similar, except that the middle and inner portions were nearly the same, and turnover was 6.2 per cent greater in the inner portion than in the outer ($p < 0.05$).

The clearance of plasma Rb^{86} and the turnover of myocardial potassium in the right ventricle were higher in the inner than in the outer portion ($p < 0.01$), the difference averaging 15 per cent (Figure 4).

Clearance of plasma Rb^{86} and turnover of myocardial potassium were increased in all regions of the myocardium by the infusion of l-norepinephrine (Figure 2). The rate of Rb^{86} uptake was increased more in the ventricles than in the atria ($p < 0.02$), and more in the right ventricle (77 per cent) than in the left (50 per cent) ($p = 0.2$). In the left ventricle the increase in clearance was greater in the inner portion than in the outer portion ($p < 0.02$). This accentuated the difference between the clearance in inner and outer portions noted in the controls from a value of 2 per cent to one of 29 per cent. This difference in inner and outer portions was probably not due to chance ($p < 0.02$). Since myocardial potassium concentration was low in three of four dogs receiving l-norepinephrine, the change in rate of turnover of myocardial potassium was proportionately greater than the change in clearance of plasma Rb^{86}.

Infusion of Pitressin® reduced the turnover rate of myocardial potassium and the clearance of plasma Rb^{86} in all the regions of the myocardium sampled (Figure 2). As in the dogs that received l-norepinephrine, the changes occurring in the right ventricle were greater than those in the left, clearance of plasma Rb^{86} by the right ventricle having decreased an average of 49 per cent and the left ventricle 40 per cent ($p = 0.3$). Changes occurring in the auricles were in the same direction as those in the ventricles, but smaller ($p < 0.06$), averaging 20 per cent less. Clearance of plasma Rb^{86} was decreased 20 per cent less in the inner portions of the left ventricle than in the outer ($p < 0.03$), and the 2.0 per cent difference between these regions

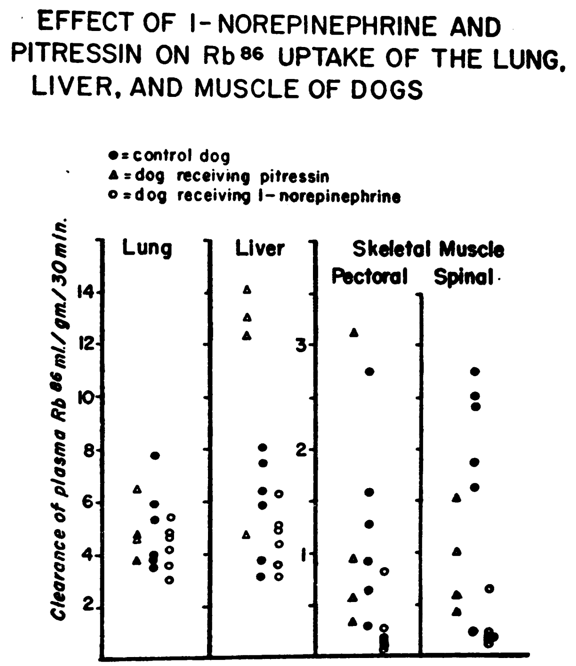

FIG. 5. CLEARANCE OF PLASMA Rb^{86} BY THE LUNGS, LIVER, AND SKELETAL MUSCLE FROM THE PECTORAL AND SPINAL REGIONS OF CONTROL DOGS AND DOGS WHICH RECEIVED INFUSIONS OF L-NOREPINEPHRINE OR PITRESSIN®

noted in the normal dogs was increased to 17 per cent, which was probably a qualitatively reproducible difference ($p < 0.02$).

The Rb^{86} uptake of the lung, liver, and skeletal muscle of the pectoral and spinal regions was calculated in the 6 control dogs which were infused with Rb^{86} for 30 minutes and, in the dogs receiving drugs, in order to compare the effect of these drugs on the myocardium with their effect on the other organs sampled (Figure 5). It was found that neither drug had any noticeable effect on clearance of plasma Rb^{86} by the lung, but that Pitressin® greatly decreased Rb^{86} clearance by both the muscles tested ($p < 0.01$). l-Norepinephrine decreased Rb^{86} uptake by the skeletal muscle of the spine ($p < 0.05$), but its effect was less marked than that of Pitressin®. The decrease in skeletal muscle clearance of plasma Rb^{86} caused by Pitressin® was more than twice that produced in cardiac muscle. Clearance of plasma Rb^{86} by the liver was not apparently affected by Pitressin®, but Rb^{86} uptake was greatly elevated in the livers of three of the four dogs that received l-norepinephrine.

GENERAL DISCUSSION

These variations in Rb^{86} uptake rate reflect differences in the rate at which Rb^{86} is brought to the area by the blood, or the actions of unknown factors affecting the flux of rubidium across the walls of the capillary and myocardial fiber or affecting the mixing of rubidium within the interstitial fluid and cell. A variety of evidence favors the view that the flux of potassium and Rb^{86} across cellular membranes in the heart is rapid by comparison with the rate at which these substances can be delivered by the coronary blood, and that therefore the rate of coronary blood flow is ordinarily the factor most likely to limit Rb^{86} uptake (3). In the case of organs other than the heart, it has been found that blood flow is a major factor limiting the rate of uptake of water and inert gases, as well as electrolytes (4–6). Rb^{86} is taken up rapidly by the vascular thyroid and adrenal glands (7), even though these organs are not known to have unusually high cellular exchange rates of potassium or rubidium. The effects of Pitressin® and l-norepinephrine on Rb^{86} uptake of resting muscle in the dogs reported here are in the directions which would be expected if regional blood flow affected uptake. This obviously is not true of all organs since the brain has a very slow uptake despite a rapid blood flow (7), and the erythrocytes have a slow uptake despite the absence of any limitation imposed by blood flow. It is reasonable to suppose that there is a rapid flux of potassium in and out of the individual cardiac muscle fiber, because the movement of potassium ions is believed to be involved in the process of contraction. The mechanical kneading action of the heart would be expected to promote mixing within the myocardium. The effects of l-norepinephrine and Pitressin® on Rb^{86} uptake are in the same directions as their effects on coronary blood flow.

The demonstration that in control dogs Rb^{86} uptake is more rapid in the inner than in the outer portion of the wall of the right ventricle, while the differences in the left ventricle were much less definite, suggests the possible role of the Thebesian circulation in Rb^{86} uptake, because these vessels are known to be more numerous in the right ventricle of the dog than the left (8). Quantitative variations in the effects of Pitressin® and l-norepinephrine on different regions of the heart may indicate variations in local blood flow caused by the humoral control of blood vessels within the myocardium.

SUMMARY

1. When control dogs were given Rb^{86} intravenously, the mean rate of Rb^{86} uptake by the left ventricle was 45 per cent faster than by the right ventricle.

2. The rate of Rb^{86} uptake in the atria was similar to that in the right ventricle.

3. The inner portion of the right ventricle consistently took up Rb^{86} more rapidly than did the outer portion.

4. In dogs receiving l-norepinephrine or Pitressin®, the uptake was significantly more rapid in the inner portion of the left ventricle than in the outer portion.

5. Pitressin® and l-norepinephrine produced changes in Rb^{86} uptake rate which were in the same direction as their known effects on the rate of coronary blood flow.

6. These differences in the rate of Rb^{86} uptake are believed to be related to differences in the rate of effective blood flow, although other factors have not been eliminated.

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