Mechanism of Thallium Extraction in Pump Perfused Canine Hearts

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Myocardial extraction of Tl has been postulated to depend on the rate of delivery (flow rate) and the metabolic state of the tissue (ATPase activity). Experiments were performed to assess the role of these factors. In 22 arrested dog hearts the left anterior descending and circumflex coronary arteries were cannulated and pump perfused with oxygenated blood containing ^{204}Tl. Isotope activity was determined in coronary sinus blood. The myocardial extraction ratio (E) of Tl varied inversely with flow, and the permeability-surface area product (PS) increased with increasing flow rates. These findings indicate that Tl uptake is flow dependent and can be analyzed with Renkin's capillary clearance theory. To assess the role of ATPase in Tl uptake, studies were also performed with blood containing ouabain. After introducing ouabain, coronary sinus blood Tl activity increased, approaching arterial activity, and E fell markedly. It was concluded that myocardial Tl uptake is mediated by ATPase.

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Myocardial perfusion scintigraphy with radioactive thallium is widely used in detecting and localizing myocardial ischemia in patients with coronary artery disease (*1,2*). The kinetics of thallium uptake by the myocardium, however, is largely unknown. Studying the plasma-to-interstitium movements of potassium in the myocardium, Conn and Robertson (*3*) found that the kinetics of distribution follows the compartmental theory and is limited by the rate of blood flow. According to the compartmental theory, isotope distribution is a function of permeability constants, and the rate of isotope disappearance from the circulation is a measure of blood perfusion when transcapillary movement of the isotope is rapid compared with the rate at which it is delivered to the capillaries by the circulation (*4*). Renkin (*5*) studied potassium kinetics in the skeletal muscle and found that the distribution is a function of a permeability constant as well as the rate of flow. Sheehan and Renkin (*6*) attributed 70% of the "nondiscriminating" barrier to potassium movements as being in the capillary wall.

Yipintsoi et al. (*7*), employing bolus injections of potassium into the coronary arteries of isolated dog hearts, concluded that the extraction ratio is a function of coronary flow and that Renkin's equations are applicable in the determinations of the extraction ratio, capillary clearance, and permeability-surface area product for this diffusible ion. Strauss et al. (*8*) and Nielsen et al. (*9*) demonstrated that the distribution of thallium, a potassium analog, in the canine myocardium following intravenous administration is proportional to the regional flow as measured with labeled microspheres. Similarly, Weich et al. (*10*) found that the initial extraction of thallium in canine hearts is proportional to myocardial blood flow. On the basis of these studies, thallium scintigraphy is used as a noninvasive means of assessing myocardial ischemia.

In studying the relationship between thallium and potassium uptake in animals, Gehring and Hammond (*11*) referred to a sodium-potassium active transport system which cannot differentiate between potassium and thallium, and suggested that thallium influx into the myocardial cell is ATPase mediated. This has led other investigators (*2,10*) to postulate that the reduction of thallium uptake in ischemic myocardium is primarily due to a decrease in ATPase activity. The existence of such an active transport system correlates with the findings of Gewirtz et al. (*12*) who found that clearance of thallium is independent of flow rate. L'Abbate et al.

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(*13*) also reported that the initial extraction of thallium by myocardium following bolus injection in human subjects does not appear to be influenced by myocardial blood flow. Therefore, conflicting data appear to exist in the literature concerning the role of blood flow in the distribution of thallium in the myocardium

The present experiments were designed to determine the effect of blood flow on myocardial thallium uptake, the applicability of Renkin's equations to describing this uptake, and the role of ATPase in thallium uptake.

MATERIALS AND METHODS

Animal preparation

Twenty-two mongrel dogs (9–20 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated and ventilated with a Harvard respirator. The right femoral artery and vein were cannulated. A left thoracotomy at the fourth intercostal space was performed, the pericardium was opened, and the circumflex and left anterior descending coronary arteries were isolated. Following direct insertion of a catheter into the coronary sinus, heparin (1000 units/kg) was injected intravenously. The heart was stopped by intravenous administration of either saturated KCl or saturated sodium citrate solution. The circumflex and left anterior descending coronary arteries were immediately cannulated and perfused with oxygenated whole blood containing 0.5 μCi/ml thallium-204 (^{204}Tl) using a Harvard syringe pump.

Relation of myocardial cation extraction to blood flow

In 17 dogs, coronary perfusion was performed for three 3-min periods at flow rates of 14.4, 36.0, and 72.0 ml/min, while the perfusion pressure was monitored continuously. Magnetic stirring bars placed inside the syringes allowed constant mixing of the perfusate. Prior to starting perfusion, a suture, previously inserted beneath the coronary sinus, was ligated to avoid the contamination of the coronary sinus sample by blood from the right atrium. Coronary sinus blood samples (1 ml each) for gamma counting were withdrawn every 15 sec for the duration of each perfusion period. Blood samples were adjusted to a volume of 1 ml and placed in a gamma spectrometer to determine their activity in cpm/ml. An additional 2-ml blood sample was withdrawn at the end of each perfusion period for determinations of PCO_2, PO_2, O_2 saturation, and hemoglobin concentration, as well as hematocrit. Samples were taken directly from the syringe pump prior to and immediately following perfusion and analyzed for PCO_2, PO_2, O_2 saturation, hemoglobin concentration, hematocrit, and ^{204}Tl activity. The extraction ratio (E) for thallium was calculated as:

$$E = (A_a - A_v)/A_a \quad (1)$$

where A_a and A_v are arterial (pump) and venous (coronary sinus) blood isotope activities (in cpm/ml), respectively. The combined thallium permeability-surface area product for the capillary and the cell wall (PS) (*5*) for thallium was calculated as:

$$PS = -Q \ln (A_v/A_a) \quad (2)$$

where Q (in ml/min) is the rate of perfusion.

Role of ATPase in thallium extraction

In a second group of experiments, five mongrel dogs were similarly prepared. Coronary perfusion was studied for three 5-min periods; initially at a rate of 24 ml/min with isotope-free oxygenated blood containing 20 mg/l dipyridamole. This was followed by perfusion with oxygenated blood containing 20 mg/l dipyridamole and 0.5 μCi/ml ^{204}Tl at a rate of 36 ml/min, and a final period of perfusion at a rate of 36 ml/min with oxygenated blood containing ouabain (1 m*M*/l plasma) as well as identical levels of dipyridamole and ^{204}Tl. Coronary sinus samples were taken every 15 sec for the determination of isotope activity. Dipyridamole was used in this portion of the study to insure maximal dilation and stability of the coronary circulation during these prolonged periods of perfusion.

RESULTS

Cardiac arrest was complete within 30 sec after administration of the KCl or sodium citrate solution, with

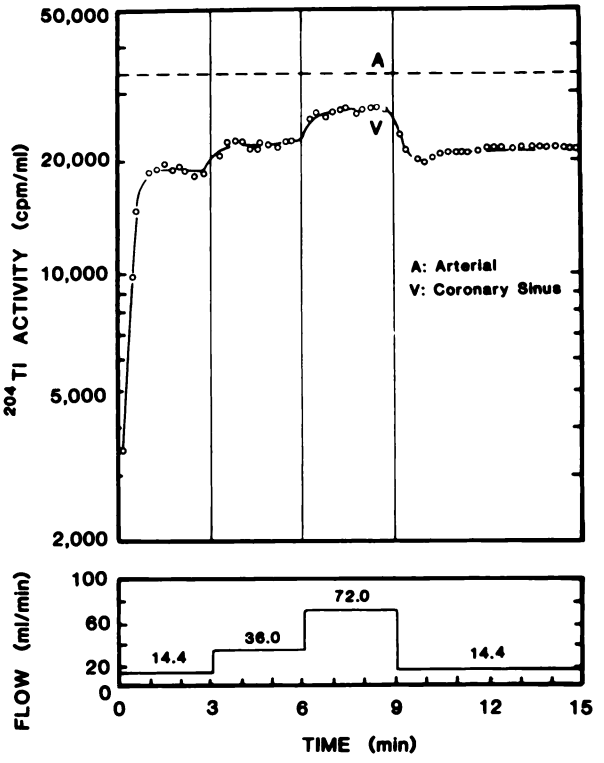

FIGURE 1
Example of arterial (A) and venous (V) ^{204}Tl activities compared with time for different flow rates

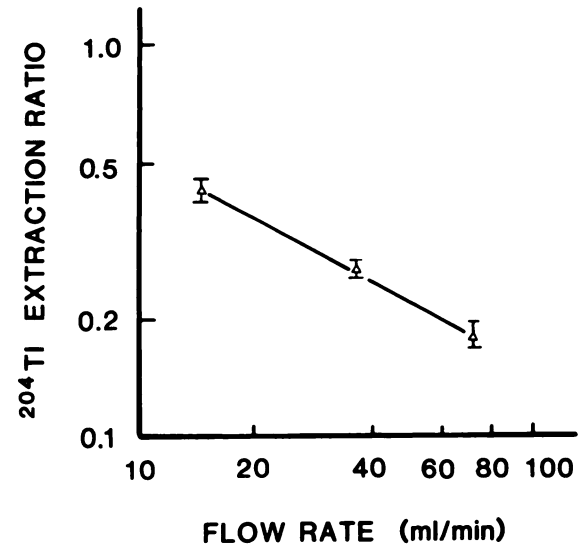

FIGURE 2
Relationship between logarithm of extraction ratio for ^{204}Tl and logarithm of flow rate. Vertical bars represent s.e.m.

no appreciable fibrillation or contractions occurring during the course of the perfusion experiments. Comparison of O_2 saturation and PO_2 levels between the perfusate and the venous effluent indicated negligible tissue oxygen consumption, with oxygen extraction averaging only 2% to 3%.

Relation of myocardial thallium extraction to blood flow

An example of the change in ^{204}Tl activity in the coronary sinus blood following variations in the rate of perfusion is shown in Fig. 1. The relationship between the extraction ratio and flow rate in all 17 experiments is summarized in Fig. 2. The extraction ratios for ^{204}Tl at flow rates of 14.4, 36.0, and 72.0 ml/min were 0.426 ± 0.024, 0.266 ± 0.011, and 0.179 ± 0.012, respectively.

The effects of changes in blood flow on the PS product for thallium are shown in Fig. 3. At flow rates of 14.4, 36.0, and 72.0 ml/min, the PS values were 8.20 ± 0.26, 11.27 ± 0.59, and 14.32 ± 1.12, respectively. Thus, the PS product for thallium varies directly with flow.

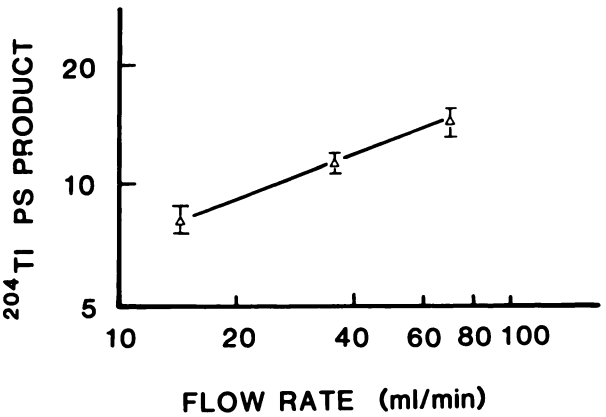

FIGURE 3
Relationship between the logarithm of PS products for ^{204}Tl and the logarithm of flow rate. Vertical bars represent s.e.m.

Role of ATPase in thallium extraction

During the first minute of perfusion with ouabain-free blood containing ^{204}Tl at 36 ml/min, the extraction of this cation fell rapidly. The fall in extraction reflects the rising phase of the venous concentration curve for the isotope as measured in the coronary sinus. A steady state extraction of 0.44 ± 0.09 was attained in about 2 min. Following the introduction of ouabain the coronary sinus ^{204}Tl activity increased to approach the arterial activity, and extraction decreased to a low level (Fig. 4). The time constant for the effect of ouabain on E of ^{204}Tl was calculated as the time needed for E to decrease to 36.8% of the pre-ouabain value; this time constant was of the order of 100 sec.

At a constant flow rate of 36 ml/min, PS decreased significantly from 21.14 ± 2.49 to 1.30 ± 0.34 with the introduction of ouabain.

DISCUSSION

Several studies have shown that the distribution of thallium is a flow-dependent process, and this is the basis

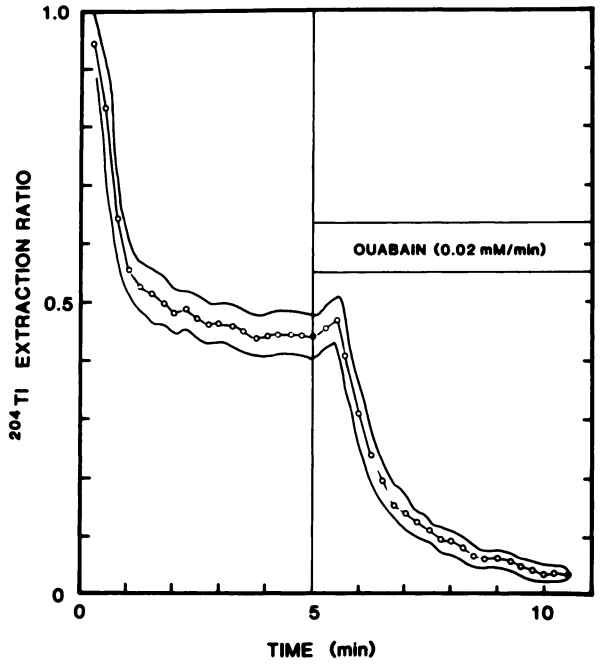

FIGURE 4
Changes in extraction ratio of ^{204}Tl accompanying administration of ouabain (0.02 m*M*/min). Perfusion flow rate is 36 ml/min). Upper and lower curves represent s.e.m.

for the clinical use of thallium as a noninvasive means of assessing myocardial ischemia. The exact nature of the relationship between flow rate and thallium extraction, however, has not been ascertained. In the present study, we examined the extraction of ^{204}Tl from the coronary circulation supplying the left ventricle of the dog. The sodium citrate or potassium arrested heart was utilized to minimize myocardial oxygen consumption and avoid the formation of ischemic tissue at low perfusion rates. The finding that coronary sinus blood PO_2 was always in excess of 90 mmHg indicates that these aims were achieved. The extraction ratios reported here differ somewhat from previously reported values (*10,13,14*). This difference is most likely attributable to the experimental design, an in situ preparation employing constant flow perfusion of the arrested heart.

Experiments in which the perfusion flow rate was varied (Fig. 2) demonstrate that the extraction (E) of thallium varies inversely with flow rate, i.e., directly with transit time. According to Renkin (*5*):

$$E = (A_a - A_v)/A_a = 1 - e^{-PS/Q} \quad (3)$$

where e is the base of natural logarithm, and the clearance (C) is given as

$$C = QE. \quad (4)$$

The findings from the present investigation (Fig. 2) indeed indicate that thallium extraction by the myocardium is flow-dependent and follows the capillary clearance theory of Renkin (*5*).

The rate of isotope uptake by the myocardium (J) can be calculated as the product of the arterial or input activity times the clearance of the isotope:

$$J = A_aQE. \quad (5)$$

Myocardial uptake (U_m) at time T can be described as the integral of the rate of uptake from time zero (t = 0) to time T (t = T) as follows:

$$U_m = \int_0^T A_aQE\,dt. \quad (6)$$

Equation 6 indicates that U_m is determined primarily by three terms: Q, E, and A_a. If the flow rate and extraction ratio remain relatively constant, then combination of Eqs. 3 and 6 yields:

$$U_m = Q(1 - e^{-PS/Q}) \int_0^T A_a\,dt. \quad (7)$$

Therefore, U_m depends on the relative values of PS and Q. It is interesting to note that the current theories on the mechanism of thallium uptake by myocardium are based on either the role of Q (*1*), which affects both the first and second terms, or the permeability of myocardial membrane to thallium (*15*), which only determines the second term in Eq. 7. In our experiments, E varies

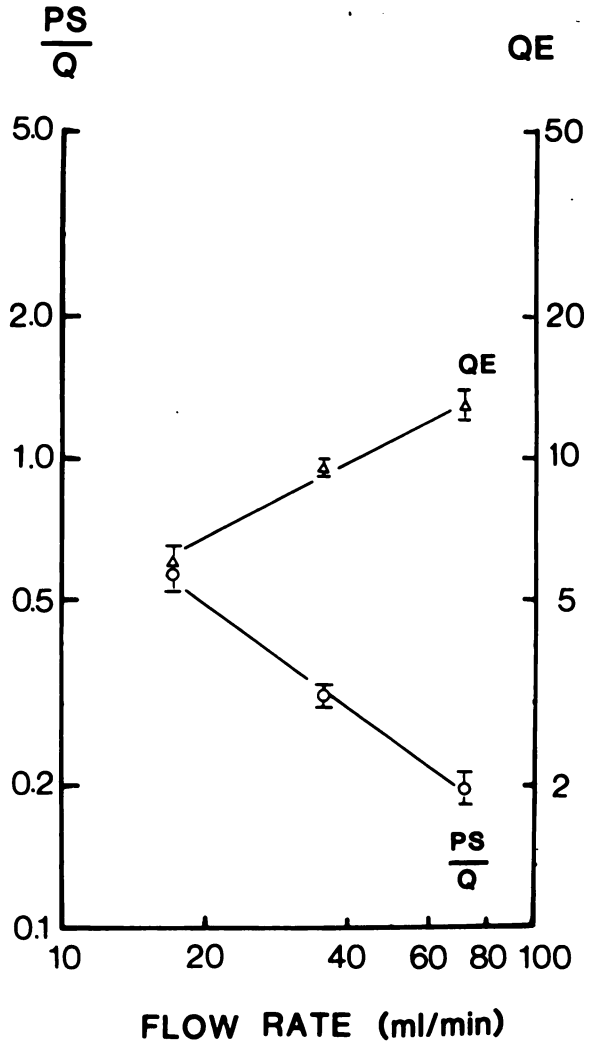

FIGURE 5
Variations in ratio PS/Q and QE product for ^{204}Tl with flow rate as shown on log-log plot. Vertical bars represent s.e.m.

inversely (Fig. 2) while PS varies directly with Q (Fig. 3), and the ratio PS/Q decreases with increasing Q (Fig. 5). Accordingly, $Q(1 - e^{-PS/Q})$, i.e., QE, increases less than proportionally with increasing Q (Fig. 5). Prokop et al. (*16*) found that reactive hyperemia causes an increase in myocardial potassium uptake, but the increase is less than proportional to Q. Since the myocardial thallium uptake correlates well with potassium uptake (*1*), these findings, together with the data obtained from the present investigation, suggest that both Q and E play significant roles in determining myocardial thallium uptake.

Extrapolation of this data to the physiologic heart must be done with caution. If our findings can be extrapolated to the normal beating heart, E would vary inversely with flow rate when the ATPase mediated transport system is intact. In the ischemic areas of the myocardium, however, the ATP depletion may result in

a disproportionate decrease in the PS product due to ischemia, thus lowering the value of $(1 - e^{-PS/Q})$. This mechanism would act together with the reduction in Q to reduce the QE product and hence U_m.

According to Pohost et al. (*15*), the flow-dependent behavior of thallium is the result of the active uptake of thallium by myocardium. This uptake is by means of an active sodium-potassium transport system which cannot differentiate between potassium and thallium and where the rate of transport is a function of ATPase activity (*11*). Ouabain is a well-established selective ATPase inhibitor (*17*). Switching of myocardial perfusion to a perfusate containing 1 m*M*/l plasma ouabain caused pronounced decreases in E (Fig. 4) and PS. The large decrease in extraction following ouabain administration demonstrates that the high value of E in the control state is, indeed, mainly due to an active transport mechanism which is mediated by ATPase. The decrease in E at a constant Q following ouabain administration would lead to a decrease in myocardial uptake of thallium. This concept, while demonstrated in the nonbeating, nonischemic heart, should also in theory be applicable to the intact heart.

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