Myocardial Uptake of Thallium and Rubidium During Alterations in Perfusion and Oxygenation in Isolated Rabbit Hearts

Jeffrey A. Leppo

Department of Nuclear Medicine and Cardiology, University of Massachusetts Medical Center, Worcester, Massachusetts

The comparative effects of altered cellular function and coronary perfusion on myocardial ^{201}Tl and ^{83}Rb uptake were evaluated in three groups of isolated rabbit hearts having isovolumic contractions. Paired-indication dilution experiments were performed with ^{201}Tl, ^{83}Rb, and ^{111}In-labeled albumin as an intravascular reference marker. In Group A hearts (n = 12), isotope transport was determined during control, hypoxia, and ischemia. In Group B hearts (n = 8), isotope transport was measured at control flow and again at a 50% and 80% reduction. In Group C hearts (n = 8) only ^{201}Tl uptake was determined at control and following coronary reperfusion. Myocardial ^{201}Tl and ^{83}Rb transport were not significantly different and were proportional to flow. Although all interventions caused significant hemodynamic alterations, neither tracer was affected by hypoxia at constant flow. Thallium-201 permeation, however, was transiently decreased immediately after coronary reperfusion. We conclude that myocardial uptake of ^{201}Tl and ^{83}Rb are similar and directly related to flow, but do not reflect hypoxia induced cellular dysfunction.

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Recent clinical and experimental studies have focused on the use of thallium-201 (^{201}Tl) (*1–6*) or rubidium-82 (^{82}Rb) (*7*) to detect changes in regional myocardial perfusion and tissue viability following coronary occlusion and reperfusion. The interpretation of the initial images of cardiac uptake for these isotopes is clearly dependent on the capillary exchange process. However, no previous studies have quantified the exchange of both thallium and rubidium between the intravascular and myocardial cellular space. Specifically, the comparative effects of ischemia, hypoxia, and reperfusion on thallium and rubidium kinetics are unclear. Therefore, the goal of this study is to directly compare both isotopes in an isolated heart model during altered levels of perfusion and oxygenation.

The determination of myocardial blood flow utilizing rubidium or thallium depends on the extraction and permeability × surface area (PS) product. These tracers are diffusion-limited substances and capillary membrane permeability can be estimated from paired indicator-dilution curves (*8–10*). This technique can be used to determine the instantaneous fractional tissue extraction (E) which can be defined as the amount of isotope diffusing from the intravascular space into the tissue during one capillary bed traversal relative to the total injectate delivered into the arterial inflow:

$$E(t) = [h_R(t) - h(t)]/h_R(t), \quad (1)$$

where $h_R(t)$ represents the fraction of the total injected dose for a reference nonpenetrating indicator that is appearing per second in the venous efflux. Similarly, h(t) represents the fraction of injected diffusible indicator that is appearing per second in the venous outflow. If both tracers are equally dispersed in the arterial inflow and tracer backflux from the extra- to intravascular space is negligible, then the fractional extraction can be used to determine the permeability and surface area product (PS):

$$PS = - F \ln (1.0 - E), \quad (2)$$

where F is the flow of the solvent delivering the solute and E is the appropriate extraction fraction (*8*). A variant of Eq. (2) has been developed for solutes with high permeability:

$$PS = - F \ln (1.0 - 1.136\ E_{max}), \quad (2a)$$

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For reprints contact: Jeffrey A. Leppo, MD, Dept. of Nuclear Medicine, University of Massachusetts Medical Center, 55 Lake Ave. North, Worcester, MA 01605.

where E_{max} represents the peak value during the early plateau phase of E(t) which occurs up to the peak of the albumin reference curve. The reasons to utilize E_{max} and the correction for PS (2a) have been previously published (*8–10*).

In these experiments, the PS product of the capillary membrane (PScap) for ^{83}Rb and ^{201}Tl in isolated rabbit hearts was calculated from the E_{max} determined by a bolus injection of indicators into the coronary inflow perfusate. Measurements were made at control and reduced flow levels as well as during hypoxia. Similar determinations were performed during coronary reperfusion in which only thallium was injected.

METHODS

All experiments utilized an isolated isovolumetrically contracting rabbit heart as previously described in detail (*11*). The coronary perfusion rate was controlled by a constant flow pump which was normally set at 30 ml/min. This relatively high perfusion rate is needed to meet myocardial oxygen demand and maintain hemodynamic performance over 2–3 hr. The perfusate consisted of a modified Krebs-Henseleit buffer which was gassed by a 95% O_2/5% CO_2 mixture and not recirculated. A thermistor and pacing catheter were placed in the right ventricle through the right atrium to monitor tissue temperature (37 ± 1°C) and maintain a heart rate of 180 bpm. A vinyl catheter was also placed in the right ventricle through the pulmonary artery to collect coronary sinus drainage for all isotope sample determinations and to measure coronary flow. Finally, a fluid-filled balloon was inserted into the left ventricle through the left atrium. Coronary perfusion and left ventricular pressure were continuously measured and recorded. In addition, the first derivative of left ventricular pressure was obtained by electronic differentiation of the pressure signal.

Experimental Protocol

Three separate experimental protocols were employed. In Group A hearts (n = 12), the effect of reduced oxygen delivery on cellular extraction of rubidium and thallium was evaluated. Oxygen delivery was reduced by either switching to a hypoxic buffer (95% N_2/5% CO_2) while maintaining normal flow, or lowering the perfusion rate by 80% to 6 ml/min. The pO_2 of the hypoxic perfusate was reduced to 35-60 torr and when compared to normal oxygenated values (always > 500 torr) represents a severe reduction in buffer oxygen saturation. In Group B hearts (n = 8), the effect of moderate (15 ml/min) and severe (6 ml/min) flow reductions on myocardial rubidium and thallium extraction was evaluated using a normally oxygenated buffer solution. Finally, in Group C hearts (n = 8), the effect of one and 15 min of coronary reperfusion on only thallium extraction was evaluated.

In all experiments, a control isotope injection was administered into the aortic root after 30 min of hemodynamic stabilization. Each isotope injection consisted of 10–15 μCi of ^{201}Tl, 6–8 μCi of ^{111}In-labeled albumin (*12*), and 1–2 μCi of ^{83}Rb (except for Group C hearts) in a volume of 0.3 ml which was delivered as a bolus over ~0.5 sec. An automatic multiple-sample changer was started simultaneously with the injection and coronary venous effluent was collected into preweighted plastic tubes at 0.6- to 15-sec intervals depending on the flow rate. A total of 40–57 samples were collected over 2–2.5 min and subsequently the full sample weights were determined. An aliquot (0.1 ml) of the injectate was also collected and counted with the coronary venous samples in a gamma well counter with appropriate correction for energy crossover, time, background and physical decay during the counting process as previously described (*11*). In addition, the wet weight of a portion of the left ventricular free wall was determined for subsequent estimation of the tissue water fraction (*11*).

After the control injection in Group A hearts, the hearts were perfused with a hypoxic buffer for 1–1.5 min before another isotope mixture was injected. Two minutes after this injection, the buffer was switched back to a normal one. These hearts recovered over the next 15–20 min and hemodynamic measurements had returned to baseline values. Coronary flow was then reduced to 6 ml/min and a third isotope injection was made 5 min later.

After the control injection in Group B hearts, repeat determinations were made during a progressive reduction in perfusion rate. Initially, flow was reduced to 15 ml/min (moderate) and after an isotope injection it was further reduced to 6 ml/min (severe) prior to the final extraction determination. In Group C hearts, coronary flow was completely stopped after the control injection for a total of 20 min. This period of no flow had been shown to be the minimal time needed to produce subendocardial necrosis (*13*). During this time, tissue temperature and pacing rate were held constant. At 1 and 15 min after returning coronary perfusion to control levels another isotope injection was made.

In each experiment, three sets of individual samples of coronary venous effluent obtained at timed intervals after intra-aortic tracer injection were available. The time of collection (t) and corrected isotope activity (C(t)) in each sample as well as the injected dose of each tracer (D_i) and coronary flow (F) was known. Therefore, $h_R(t)$ was calculated for ^{111}In-labeled albumin and h(t) for ^{201}Tl and ^{83}Rb by the general equation:

$$h(t) = \frac{F}{D_i} \cdot C(t).$$

From hR(t) and h(t), the instantaneous fractional extraction E(t), the peak plateau value E_{max} was picked as the best estimate of the average fractional extraction and was used to calculate PScap using Eqs. (2) and (2a) (*9*).

All data were expressed as the mean ± s.d. Serially collected hemodynamic and isotope data were evaluated by an analysis of variance and covariance with repeated measures. In addition, a Bonneferroni correction for multiple comparisons was made to evaluate significance, and other comparisons between groups of a single numeric variable were performed by an analysis of variance and appropriate t-statistic.

RESULTS

Table 1 displays the mean perfusion (aortic), peak developed and diastolic pressures, as well as the maximal positive and negative dP/dt measurements for all three groups. The control measurements are similar in

TABLE 1
Hemodynamic Results

	Group A (n = 12)			Group B (n = 8)			Group C (n = 8)		
	Control	Hypoxia	Ischemia	Control	Moderate	Severe	Control	Reflow 1′	Reflow 15′
Aorta (mmHg)	58 ± 13	51 ± 18 *	12 ± 3 *	48 ± 7	26 ± 4 *	12 ± 3 *	53 ± 6	71 ± 16 Δ	68 ± 12 Δ
LVPSP (mmHg)	102 ± 5	48 ± 13 *	21 ± 5 *	98 ± 10	58 ± 7 *	27 ± 6 *	100 ± 6	73 ± 26 *	76 ± 13 *
LVEDP (mmHg)	8 ± 3	22 ± 8 Δ	3 ± 3 Δ	8 ± 2	2 ± 2 *	2 ± 2 *	7 ± 3	49 ± 30 Δ	45 ± 24 Δ
+dP/dt (mmHg/sec)	2,439 ± 155	836 ± 184 *	557 ± 120 *	2,314 ± 361	1,394 ± 150 *	702 ± 113 *	2,432 ± 226	867 ± 612 *	623 ± 346 *
−dP/dt (mmHg/sec)	2,029 ± 97	581 ± 207 *	350 ± 98 *	2,114 ± 300	1,330 ± 166 *	582 ± 97 *	2,012 ± 300	607 ± 402 *	759 ± 402 *

Mean ± s.d., * = $p < 0.001$, Δ = $p < 0.03$.
LVPSP, LVEDP = left ventricular peak systolic pressure, end diastolic pressure.

all hearts and were made just prior to the initial bolus isotope injection. All subsequent group measurements were made just prior to repeat isotope injections. Compared to control values, mean aortic perfusion pressure significantly decreased during ischemia (including moderate and severe) but increased with coronary reflow at 1 and 15 min. The slight fall in mean aortic pressure after 1–15 min of hypoxia did not achieve statistical significance. Therefore, a reduced level of coronary perfusion was associated with a corresponding fall in coronary vascular resistance, while coronary reperfusion resulted in an increase in resistance.

The mean peak developed pressure significantly decreased during all interventions. Although mean peak pressures were higher during hypoxia and reperfusion compared to ischemia, developed pressure (LVPSP-LVEDP) was similar among all these interventions. Compared to control values, the mean left ventricular end diastolic pressure significantly decreased during flow reductions but increased during hypoxia and especially with reperfusion. These observations suggest that during ischemia, hearts are relatively more compliant than normal, while hypoxia and reperfusion result in relatively stiffer (contracture) hearts. It is important to note that this decreased compliance associated with a brief hypoxic episode was completely reversed, but the initial hemodynamic alterations associated with early reperfusion were essentially constant over the next 15 min.

The mean peak positive and negative dP/dt values significantly decreased during all interventions. This decrease was significantly greater during ischemia compared to hypoxia suggesting that ischemia has a greater negative effect on this index of contractility than hypoxia in the same hearts.

Myocardial Isotope Extraction

Figure 1 shows the thallium and rubidium curves for h(t) and E(t) from a Group A heart. The h(t) and E(t) curves for these diffusible isotopes were remarkably similar during control and hypoxia. Although the initial portion of the h(t) and E(t) curves were similar during ischemia, there was a higher peak h(t) value and corresponding lower E(t) curve for rubidium compared to thallium. This difference in the tail of both curves was a constant observation in all Group A and B hearts during low flow. The instantaneous fractional extractions [E(t)] calculated from Eq. (1), typically increased to a maximum (E_{max}) at about the peak of h(t) and E_{max} for both isotopes and was approximately the same in all hearts.

The mean group values for E_{max} and PScap [Eq. (2a)] are shown in Table 2. Control measurements were approximately the same in all groups for thallium and rubidium. During hypoxia, mean E_{max} and PScap values did not significantly change for either isotope. In contrast, E_{max} for both isotopes increased significantly by ~21% in Group A hearts during ischemia. However, PScap decreased by an average of 62% for both isotopes following ischemia. Therefore, the increase in first-pass extraction associated with ischemia is not proportional to the absolute decrease in coronary perfusion which results in a net reduction of tracer transport across the capillary membrane.

The inverse relationship between coronary flow and isotope extraction is further demonstrated in Group B hearts. Myocardial extraction of thallium and rubidium significantly increased during a 50% and 80% reduction in perfusion rate. However, the corresponding PScap values for both isotopes significantly decreased by about 38% and 66%, respectively. As noted above in the Group A hearts, the rise in the extraction fraction during reduced perfusion rates does not result in an increase in net isotope transfer as determined by PScap. Both tracers, in fact, demonstrate a fairly linear relationship between coronary flow and PScap values.

Only thallium data is available in Group C hearts. Although global coronary flow was held constant during all three isotope injections, the extraction and PScap values significantly decreased after 1 min of reperfusion. Despite continued hemodynamic impairment during reperfusion, E_{max} and PScap returned to control values 15 min later. These data suggest that there is decreased (~36%) cellular uptake of thallium immediately after coronary reperfusion, which underestimates the total amount of organ flow. However, this reduced uptake is transient and may well represent arterial-venous shunting due to a failure in capillary bed reperfusion. It does appear that a normal amount of capillary exchange is available after 15 min. Therefore, myocardial thallium uptake may not reflect the full extent of coronary reperfusion immediately after reperfusion.

The mean water content percentage for Group A hearts was 82 ± 2%, and was 83 ± 2% for Group B and 83 ± 1% for Group C. There were no significant differences between groups as all hearts demonstrated increased water content during these experiments.

DISCUSSION

Thallium Kinetics

Although there have not been any previous reports that evaluated myocardial thallium and rubidium simultaneously, our observations are consistent with previous results which utilized different techniques and analyses. Specifically, the dominant effect of coronary flow on thallium kinetics has been demonstrated by several investigators utilizing external myocardial probe detectors (*14,15*) and coronary venous sampling (*11, 16*) techniques. One of these studies (*16*) determined thallium extraction by utilizing an indicator-dilution technique, but there was relatively poor temporal resolution of the venous samples and coronary flow was not held constant nor precisely calculated. Despite all

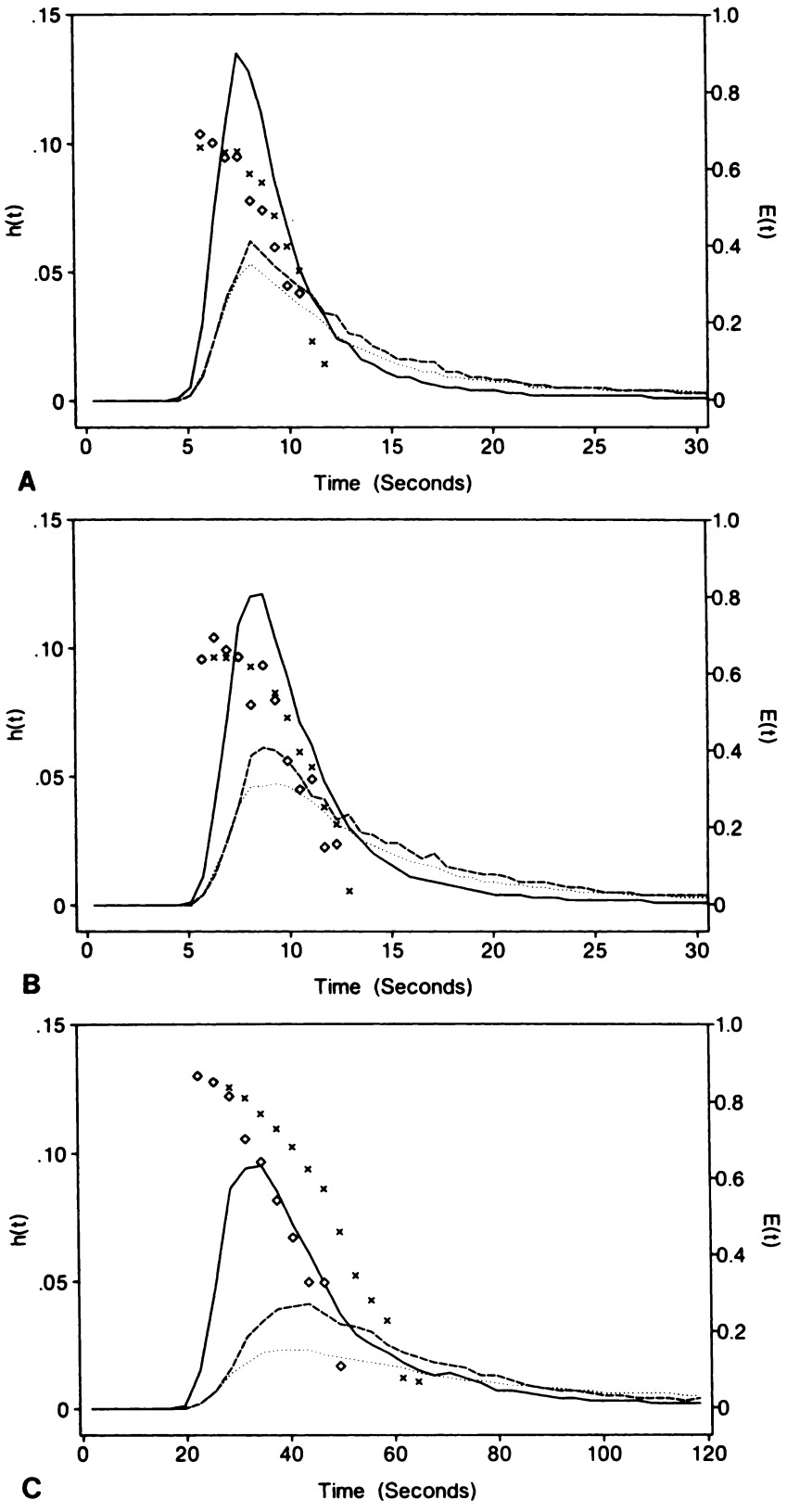

FIGURE 1
The transport function curves [h(t)] for albumin (Alb), ^{201}Tl, and ^{83}Rb are shown for a Group A heart during control (1A), hypoxia (1B) and ischemia (1C) utilizing the left sided scale. In addition, the right sided scale [E(t)] is the instantaneous extraction fraction (EXF) for the diffusible tracers and only the data points (symbols) are shown. Key: (—) Alb; (· · ·) ^{201}Tl; (---) ^{83}Rb; (×) ^{201}Tl EXF; (◇) ^{83}Rb EXF.

these differences in technique, our study confirms the observation that myocardial thallium extraction has an inverse relationship to flow and we have also shown that PScap has a direct relationship. Therefore, although net capillary exchange of thallium will reflect alterations in coronary perfusion, the observed changes in first-pass extraction will result in underestimation of higher flow levels and overestimation of lower flow.

TABLE 2
^{201}T1 and ^{83}Rb Extraction (Emax) and PScap

	Group A				Group B					Group C				
Emax	Control	Hypoxia		Ischemia	Control		Moderate		Severe	Control		Reflow 1′		Reflow 15′
^{201}T1	0.73 ± 0.04	0.71 ± 0.06	-•-	0.87 ± 0.03	0.66 ± 0.05	-•-	0.74 ± 0.05	-•-	0.80 ± 0.05	0.71 ± 0.02	-•-	0.57 ± 0.08	-Δ-	0.70 ± 0.08
^{83}Rb	0.71 ± 0.05	0.72 ± 0.08	-•-	0.86 ± 0.06	0.69 ± 0.04	-•-	0.72 ± 0.04	-•-	0.81 ± 0.07					
PScap (ml/min/g)														
^{201}T1	5.97 ± 1.48	5.75 ± 1.83	-•-	2.17 ± 0.58	5.62 ± 0.68	-•-	3.55 ± 0.34	-•-	1.96 ± 0.35	6.62 ± 1.12	-Δ-	4.26 ± 1.95		6.20 ± 1.46
^{83}Rb	5.46 ± 1.50	5.51 ± 1.86	-•-	2.15 ± 0.76	6.16 ± 0.59	-•-	3.82 ± 0.43	-•-	2.10 ± 0.50					

Mean ± s.d., • = $p < 0.001$, Δ = $p < 0.03$.
PScap = capillary permeability-surface area product.

The effect of hypoxia on thallium extraction has been controversial. A previous study showed extraction decreased from a control of 0.89 to 0.78 ($p < 0.01$) during hypoxia, but coronary flow was increased by 70% (*16*). In another series of experiments performed in isolated rabbit hearts the first-pass thallium residual fraction remained at 0.34 during hypoxia and constant flow (*14*). In addition, myocardial uptake of thallium during a constant infusion into an isolated rabbit heart was unaffected by hypoxia when coronary flow was constant (*11*). This present study clearly demonstrates that E_{max} and PScap for thallium are not affected by cellular hypoxia which caused severe cardiac hemodynamic dysfunction.

Considering that these previous studies (*11,14–16*) on the effect of hypoxia and flow alteration on thallium kinetics did not have the temporal resolution and/or intravascular reference tracer to determine E_{max}, it is still possible to combine this earlier work with our present study. Specifically, it appears that coronary flow rather than cellular oxygenation determines thallium extraction. It is possible, however, that cellular metabolic dysfunction would affect thallium washout as noted previously in fetal mouse hearts (*17*). Our data do not provide enough information to evaluate myocardial clearance patterns for thallium.

It is interesting to note that during the initial phase of coronary reperfusion E_{max} and PScap for thallium were significantly decreased, despite the fact that coronary flow had returned to baseline. There was also a significant deterioration in hemodynamic function which did not improve over the next 15 min when a repeat determination showed that E_{max} and PScap returned to control values. At a similar flow rate and functional impairment hypoxic hearts did not have altered thallium extraction compared to Group C hearts after 1 min of reperfusion. Therefore, it would appear that myocardial capillary recruitment is not complete immediately after reperfusion and there may be enough arterial-venous shunting to explain the decrease in isotope conductance across the capillary wall. It is also possible that rapid changes in cellular water content (tissue turgor) or metabolites could also account and/or contribute to a transient decrease in tracer extraction. The remarkable observation that thallium extraction returns to control value, despite persistent functional impairment, does favor capillary recruitment as a more likely explanation.

Rubidium Kinetics

The rubidium kinetics in this report are the first which utilized the paired indicator dilution technique to derive E_{max} and PScap. The data showed that first-pass myocardial extraction of rubidium is inversely related to flow but capillary exchange (PScap) is directly proportional to flow. Our observation that rubidium extraction is inversely related to flow confirms earlier reports which utilized positron imaging techniques (*18, 19*) and external epicardial detectors (*20*). Other investigators have evaluated myocardial rubidium uptake with simultaneously injected microspheres and except at high and low blood flow, noted a relatively linear relationship. However, all these type of measurements did not include a vascular reference tracer in the protocol and derived extraction values from the myocardial time activity curves. There was a wide variation in these calculated ^{82}Rb extraction fraction among these reports which resulted from using different methods of data collection and analysis. Ziegler and Goresky (*23*) reported that the rate constant across the capillary wall increased with perfusion, but that myocardial cellular uptake appeared relatively constant. Although these authors utilized an experimental model and technique similar to ours, calculations for E_{max} and PScap were not performed which limits more direct comparisons.

The direct comparison of rubidium and thallium transcapillary exchange was a specific goal of this report and our results demonstrated that myocardial uptake of both tracers is quite similar. Both tracers appear to have fairly high capillary permeation which is independent of hypoxic perfusion. Therefore, either tracer should be an excellent marker of regional coronary blood flow, despite the differences in imaging techniques. Although, our report did not directly calculate parenchymal cellular uptake and washout, we did note at lower flow that each Rb h(t) curve was higher than the Tl h(t) curve after the albumin peak was reached. This difference in the tail portion of the h(t) function was not apparent in the E_{max} and PScap calculations because both tracers had similar initial h(t) curves. One can assume from this constant observation that the extravascular back-diffusion of rubidium is greater than that for thallium and consequently, the cellular volume distribution for rubidium is smaller than thallium. Additional experiments and more direct calculations would be needed to further validate this assumption.

Limitations and Clinical Implications

The use of a buffer perfused isolated heart permitted us to measure transcapillary transport of rubidium and thallium but there are several limitations to consider in this type of model. The water content of these hearts is ~83% which represents an increase in interstitial fluid volume (edema) when compared with in vivo hearts (78–79%). The presence of this edema especially when combined with the need for high perfusion rates (to maintain adequate tissue oxygenation), make the extrapolation of our kinetic calculations to in vivo hearts more difficult. It is likely that a greater interstitial fluid volume and high perfusion rate make less tracer available for exchange at the parenchymal cell membrane. Therefore, qualitative directional changes, rather than quantitated uptake rates, may be more comparable to in vivo blood perfused hearts.

The clinical implications of these results strongly support the dominance of coronary flow on myocardial uptake of thallium and rubidium. Both tracers have relatively high capillary permeation which is proportional to flow and the exchange rate at the capillary level is similar. Therefore, cardiac images of thallium and rubidium are primarily a reflection of regional coronary perfusion at the time of injection and are not particularly sensitive to regional cellular function. An important exception is noted immediately (at 1 min) after coronary reperfusion, when thallium extraction shows a transient decrease. We would suggest that the clinical evaluation of coronary perfusion after reperfusion be delayed for 10–15 min. These observations support previous studies (*4–6*) suggesting that thallium imaging after coronary reperfusion reflects flow changes and may not indicate viability. Overall, it appears that clinical images of thallium and rubidium uptake would appear normal during homogeneous flow despite the presence of regional myocardial cellular dysfunction.

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