Separate Effects of Ischemia, Hypoxia, and Contractility on Thallium-201 Kinetics in Rabbit Myocardium

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The effects of hypoxia and ischemia, as well as altered contractility, on thallium-201 (^{201}Tl) kinetics were evaluated in 42 isolated isovolumetrically contracting rabbit hearts. In Group A, three subgroups (n=7 each) were studied that had either normal flow and oxygenation, hypoxia and normal flow, or ischemic flow and normal perfusate oxygen content. In Group B, three subgroups (n=7 each) were studied and all hearts had normal flow but the contractile state was either enhanced with isoproterenol or impaired by hypocalcemia. A hemoglobin-free buffer perfusate was used in all experiments and multiple timed collections of arterial and coronary sinus effluent were used to model myocardial isotope activity during 30 min of constant uptake followed by 30 min of tracer clearance. During ischemia, hypoxia and hypocalcemia peak developed pressure and peak positive and negative dP/dt were all significantly reduced when compared to normal hemodynamic parameters ($p < 0.01$). As expected, isoproterenol significantly elevated these parameters ($p < 0.04$). Myocardial ^{201}Tl kinetics were adequately described utilizing a bi-exponential model having a fast and slow component. Only ischemic hearts had significantly lower rate constants for ^{201}Tl uptake and clearance than normal hearts ($p < 0.001$). The mean (± s.d.) myocardial uptake and clearance rates for ^{201}Tl (%/min) varied between 4.86 ± 0.87 and 7.18 ± 1.45 for the remaining groups of hearts. Therefore, myocardial ^{201}Tl kinetics appear to be dominated by coronary flow and may not reflect marked alterations in the metabolic and contractile state. These data suggest that normal ^{201}Tl uptake in impaired or hypercontractile cells, receiving normal flow, may not represent normal cellular function.

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The utility of thallium-201 (^{201}Tl) imaging in patients to detect ischemic heart disease in conjunction with exercise testing has been clearly documented (*1,2*). However, the comparative effects of ischemia, hypoxia and contractility on these results are unclear. Although previous studies reported that myocardial thallium uptake was related to blood flow (*3,4*), other studies concluded that cellular metabolic alterations could also affect thallium kinetics independent of flow (*5-7*). Specifically, a decrease in the extraction fraction for thallium has been noted in hypoxic dog hearts (*5*). However, coronary perfusion was not held constant during these experiments and the calculated changes in the thallium extraction could have resulted primarily from blood flow changes (e.g., coronary hyperemia secondary to hypoxia would be associated with a decrease in tracer extraction). Therefore, additional work is needed to evaluate the relative effects of perfusion rate and hypoxia on myocardial thallium kinetics in an experimental model which permits independent control of myocardial flow and oxygen delivery.

A better understanding of the relationship between blood flow and cellular function on thallium uptake is

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critical to a correct interpretation of thallium scintigraphic studies. This relationship has particular clinical significance in situations where both the metabolic and contractile state of the myocardial tissue are altered but normal or increased flow is preserved. Such conditions can occur in situations where patients have myocardial thallium imaging in association with intracoronary thrombolysis (*8,9*), or spontaneous release of coronary spasm (*10,11*). In addition, the utilization of clinical exercise and dipyridamole-thallium imaging clearly involves a hyperemic response in myocardium having different contractile states. Therefore, it is critical to know if thallium uptake simply reflects flow, or also implies a certain level of cellular function.

MATERIALS AND METHODS

Surgical and Perfusion Technique

An isolated rabbit heart preparation utilizing methods previously described (*12,13*) was employed in all experiments. Male albino New Zealand rabbits (1.5–2.2 kg) were killed and the thorax was opened. Hearts were quickly removed and placed in a water-jacketed constant temperature chamber, which maintained tissue temperature at 37 ± 1°C throughout all experiments. A drain was placed in the left ventricular apex to decompress the chamber. The aortic root was cannulated and connected to a constant flow pump to provide retrograde coronary artery perfusion with a modified Krebs-Henseleit buffer containing in m*M* concentrations: 118 NaCl, 4.7 KCl, 2.0 $CaCl_2$, 1.2 $MgSO_4$, 25 $NaHCO_3$, 0.4 Na_2 EDTA, 5.5 glucose and 1.0 lactate. Lactic acid was neutralized with NaOH before being added to the buffer and the perfusate was not recirculated.

A vinyl catheter was placed in the right ventricle by way of the pulmonary artery. A thermistor and a pacing wire were also placed in the right ventricle by way of the right atrium and a fluid-filled balloon was inserted into the left ventricle by way of the left atrium. All catheters and cut surfaces of the heart were ligated so that the perfusate flowing from the pulmonary artery represented coronary sinus drainage and was used for all subsequent isotope samples. Coronary flow was measured by collecting timed samples of coronary sinus effluent in a graduated cylinder. Coronary perfusion pressure was obtained from a side arm of the perfusion cannula connected to a pressure transducer (Statham P23Db). Left ventricular pressure was determined by connecting the fluid-filled balloon catheter to another pressure transducer. All signals were amplified and continuously recorded on a Gould (Series 2000) recorder. The first derivative of left ventricular pressure was obtained by electronic differentiation of the left ventricular pressure signal.

Before starting each experiment, the heart was perfused for 30 min at 30 ml/min coronary flow rate under aerobic conditions (95% 02/5% CO_2), and paced at a heart rate of 180 bpm to permit performance to stabilize. The left ventricular balloon was filled to produce a systolic pressure greater than 80 mmHg with a diastolic pressure in a normal range (<12 mmHg).

Experimental Protocol

A schematic flow diagram is shown in Fig. 1, which outlines all the experimental protocols. The purpose of the protocol in Group A was to measure ^{201}Tl kinetics under normal well-oxygenated conditions and during 60 min of steady-state hypoxia and ischemia. To ensure a constant delivery of isotope, low flow ischemia (20% of control) was used. During the hypoxic period, coronary flow was maintained at control level, but oxygen delivery was reduced to 20% of the normal by reducing the oxygen content of the gassing mixture. Thus, these manipulations permitted a comparison of the control well-oxygenated state with a total coronary flow of 30 ml/min to that of ischemic and hypoxic states. The two interventions were matched for an equal 80% decrease in tissue oxygen delivery but with a fivefold difference in myocardial perfusion.

The purpose of the protocol in Group B was to measure ^{201}Tl kinetics under normal conditions and during 60 min of either isoproterenol infusion or hypocalcemia. Coronary flow and perfusate oxygen content were held constant during all experiments. These two interventions were matched for an approximate 40-50% increase or decrease in cardiac contractility as evaluated by dP/dt determinations.

All hearts were allowed to equilibrate as noted above before switching the perfusate to a similar one containing tracer amounts of ^{201}Tl (25 μCi/l). An estimate of tissue water was determined after each experiment by

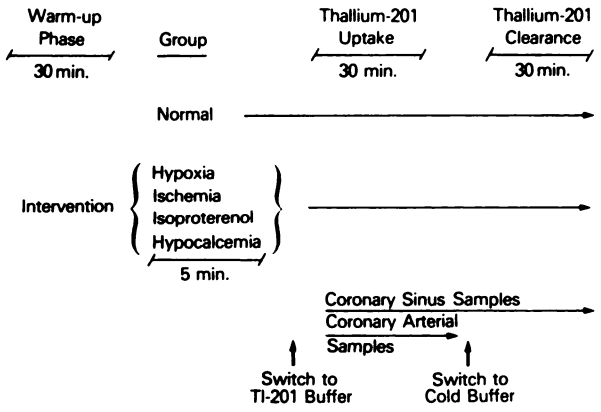

FIGURE 1
Schematic representation of all experimental protocols. Detailed description is provided in text

dissecting a section (0.3-0.4 g) of the left ventricular free wall and measuring its weight immediately and after 2 days in a drying oven. The tissue water fraction was then calculated from the (wet-dry)/wet ratio for each heart.

In normal hearts for Groups A and B (n=7 each), coronary flow, perfusate oxygenation, pacing rate and balloon volume were held constant while isotope extraction and clearance were evaluated. Five to ten seconds after switching to the tracer containing buffer, multiple samples were collected in 1.5 ml vials from the continuous coronary sinus effluent. The sampling rate was initially every 5 to 10 sec over the first 1.5 min and thereafter gradually decreased to one sample every 5 min. In all, 22 samples were collected during the 30-min myocardial uptake phase and a similar sampling rate was used to collect the 22 samples during the 30-min washout phase. Myocardial isotope washout was evaluated by switching the radioactive perfusate back to the original one. During the isotope uptake phase, ten arterial perfusate samples were also collected at 3-min intervals. A similar pattern of sample collection was utilized for all subsequent intervention studies.

In a preliminary series of experiments we observed that these well-oxygenated hearts remained relatively stable hemodynamically and extracted lactate for 150-180 min. However, during the subsequently listed interventions, all the hearts would fail to extract lactate and remained functional for only 60 to 90 min.

In the ischemic heart group (n=7), coronary flow was reduced by 80% (6 ml/min) for 5 min before switching to the isotope containing perfusate, while all other factors remained constant. This short delay period was employed to permit the heart to stabilize at its new flow level. After 30 min of isotope administration, the perfusate was again switched to the original one and flow remained at 6 ml/min throughout this protocol.

In the hypoxic heart group (n=7), the control perfusate was switched to one which had been gased with 20% O_2/5% CO_2/75% N_2 resulting in an 80% reduction in buffer oxygenation. After 5 min of equilibration with hypoxia, the buffer was switched to a similar one having the same isotope concentrations as noted above. The heart rate, balloon volume, and coronary flow remained constant throughout these experiments.

In the isoproterenol group (n=7), the control perfusion was altered by an infusion of 2.1 μg/min of isoproterenol delivered in a volume of 0.2 ml/min. Coronary flow and balloon volume remained constant, but the pacemaker was turned off as the intrinsic heart rate exceeded 190 bpm. After 5 min, the buffer was switched to a similar one containing ^{201}Tl without altering the isoproterenol infusion.

In the hypocalcemia group (n=7), the control perfusate was switched to one containing 1.0 m*M* $CaCl_2$ resulting in a 50% reduction in normal calcium concentration. Coronary flow, heart rate, and balloon volume remained constant throughout the protocol. After 5 min the buffer was switched to a similar one (1.0 m*M* $CaCl_2$) containing ^{201}Tl.

Isotope Uptake and Washout Determinations

After each experiment, 0.5 ml of perfusate was precisely pipetted from each sample cup and placed in a plastic vial for subsequent gamma well counting.* The ^{201}Tl isotope activity was corrected for time, background, and physical decay during counting utilizing a previously described computer program and a computer†(*14*). Before analyzing the coronary venous effluent isotope data, the constancy of the arterial isotope input was evaluated. The mean and s.d. was determined from the ten arterial samples for each isotope and the ratio of s.d./mean was always <2% before any individual experiment would be added to the group results.

The corrected coronary venous isotope activity for each heart was normalized by dividing each timed venous sample value by the peak counts achieved during the protocol. The mean (± s.d.) percentage of peak coronary sinus counts for ^{201}Tl was determined for the 22 uptake and washout samples in each group of hearts. A commercially available derivative-free nonlinear regression analysis (BMDP3R)(*15*) was utilized to determine the biexponential rate constants for the thallium curves, as previously described (*16*). The model for isotope uptake or washout [h(t)] used to fit the data was $h(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda 2t}$, where A_k (k = 1 or 2) are the amplitudes of the exponentials $e^{-\lambda_k t}$ and λ_k are the rate constants. In these fittings each mean point value was weighed by the reciprocal of its variance. The estimated rapid and slow rate constants in each group of hearts were assumed to represent the exchange rate (λ_1, rapid) between the vascular and interstitial space, and the interstitial and cellular exchange rate (λ_2, slow) (*6,16,17*).

Statistical Analysis

All data were expressed as the mean ± s.d. Hemodynamic 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 (*18*).

RESULTS

Hemodynamics

Table 1 displays the mean perfusion (aortic), peak developed and diastolic pressures, as well as the maxi-

TABLE 1
Hemodynamic Responses for All Groups*

Group		Control	^{201}Tl uptake	^{201}Tl washout
	Coronary perfusion pressure (mmHg)			
A	Normal	62 ± 21	64 ± 30	68 ± 31
	Ischemia	64 ± 12	12 ± 3	12 ± 4
	Hypoxia	65 ± 18	38 ± 7	43 ± 9
B	Normal	65 ± 9	69 ± 14	73 ± 16
	Isoproterenol	61 ± 10	66 ± 13	82 ± 9
	Hypocalcemia	64 ± 11	57 ± 13	59 ± 18
	Peak developed pressure (mmHg)			
A	Normal	109 ± 8	100 ± 9	92 ± 9
	Ischemia	106 ± 12	28 ± 9	30 ± 13
	Hypoxia	104 ± 13	46 ± 7	48 ± 9
B	Normal	98 ± 9	96 ± 13	90 ± 11
	Isoproterenol	97 ± 6	110 ± 8	106 ± 6
	Hypocalcemia	97 ± 5	70 ± 7	69 ± 9
	LV† end-diastolic pressure (mmHg)			
A	Normal	8 ± 2	10 ± 2	11 ± 4
	Ischemia	11 ± 3	6 ± 9	9 ± 12
	Hypoxia	8 ± 2	15 ± 11	22 ± 14
B	Normal	9 ± 2	9 ± 2	7 ± 3
	Isoproterenol	7 ± 2	15 ± 9	34 ± 15
	Hypocalcemia	9 ± 2	17 ± 7	22 ± 9
	Peak + dP/dt (mmHg/sec)			
A	Normal	2,066 ± 246	1,840 ± 273	1,657 ± 361
	Ischemia	2,120 ± 302	566 ± 115	506 ± 93
	Hypoxia	2,280 ± 351	740 ± 204	660 ± 189
B	Normal	2,317 ± 271	2,285 ± 337	2,016 ± 258
	Isoproterenol	2,126 ± 285	2,988 ± 498	2,625 ± 897
	Hypocalcemia	2,142 ± 108	1,214 ± 153	1,126 ± 234
	Peak − dP/dt (mmHg/sec)			
A	Normal	1,613 ± 109	1,491 ± 174	1,428 ± 177
	Ischemia	1,626 ± 182	331 ± 55	346 ± 21
	Hypoxia	1,520 ± 130	520 ± 160	473 ± 165
B	Normal	1,983 ± 262	1,918 ± 283	1,891 ± 231
	Isoproterenol	1,830 ± 265	2,509 ± 371	2,041 ± 512
	Hypocalcemia	1,932 ± 205	1,240 ± 206	1,073 ± 236

* Values = mean ± s.d.
† LV = Left ventricular.

mal positive and negative dP/dt measurements for both groups. The control measurements are similar in all hearts and represent duplicate determinations made immediately prior to any interventions or tracer administration in the normal group. Compared with control measurements, the mean aortic perfusion pressure significantly decreased with a switch to ischemic and hypoxic conditions ($p < 0.0001$), but no significant change was noted in normal hearts. Ischemic hearts had lower perfusion pressures than either hypoxic ($p < 0.01$) or normal ($p < 0.001$) hearts. Therefore, during constant coronary flow, hypoxia and ischemia reduced coronary vascular resistance compared with their control values. The mean coronary perfusion pres-

sure increased during the isoproterenol infusion ($p < 0.01$) compared with both its control measurements and the relatively stable values noted in the normal and hypocalcemic hearts. This increase in coronary resistance during isoproterenol may be related to the tachycardia (average heart rate increased from 180 bpm to 220 bpm) and the marked increase in the LV end-diastolic pressure.

The mean peak developed pressure significantly decreased in all protocols as a function of time ($p < 0.0001$), except in hearts receiving isoproterenol ($p < 0.03$). Hypoxic, ischemic, and hypocalcemic hearts did, however, develop less peak pressure than normal hearts ($p < 0.0001$) and ischemic hearts had less developed pressure than hypoxic ones ($p < 0.01$). The initial reduction in peak pressure was not progressive during the experimental period of hypoxia, ischemia, or hypocalcemia but a small (8%) progressive fall was noted in normal hearts during this period.

The mean diastolic pressure in normal hearts remained stable over the course of the entire protocol. Although ischemic hearts tended to experience an initial fall in diastolic pressure, these alterations were not significant over time nor in comparison to normal values. The progressive increase in diastolic pressure noted in hypoxic hearts resulted in a significant ($p<0.01$) alteration as a function of both time and in comparison to normal and hypoxic hearts. There was a significant increase in LV diastolic pressure noted over time and in comparison to normal values in hearts having hypocalcemia or isoproterenol ($p < 0.001$).

The mean peak positive (+) and negative (−) dP/dt values increased in the isoproterenol group ($p < 0.01$) compared to normal. In all other protocols the dP/dt values decreased as a function of time ($p < 0.0001$). However, the fall in + dP/dt and − dP/dt observed in hypoxic, ischemic, and hypocalcemic hearts was significantly greater than the relatively small decrease seen in normal hearts ($p < 0.01$). Although ischemic hearts tended to have lower values compared with hypoxic hearts, these differences were not significant.

Thallium-201 Kinetics

Myocardial thallium uptake and washout are shown in Figs. 2 and 3. Each point of these curves represents the mean fraction of peak coronary venous counts for all hearts in each group. Tracer uptake in normal, hypoxic, hypocalcemic, and isoproterenol hearts was relatively fast, achieving more than 80% of their peak activity after 1 min while ischemic hearts only attained about 40% of their peak activity. The ischemic hearts also appeared to have a reduced slope after 5 min which persisted throughout the observed protocol. The myocardial washout of thallium in normal, hypoxic, isoproterenol and hypocalcemic hearts was also rapid, clearing ~80% of their peak activity within 1 min. The tracer washout in ischemic hearts was again much slower as only 35% of peak activity was cleared after 1 min. It is also clear from the washout curves that the slope of myocardial thallium clearance after 5 to 10 min is relatively flat and essentially the same in all hearts.

The results of the biexponential model for these myocardial thallium curves are shown in Table 2 and these estimated rate constants had a uniformly good fit ($r^2 > 0.96$). Although the fast and slow rate constants for thallium uptake in hypoxic hearts were smaller by 26 and 60%, respectively, when compared with the values determined in the normal hearts, these differences were not significant. In contrast, ischemic hearts had a significant decrease in the fast component of thallium uptake compared to both normal (95% reduction) and hypoxic (93% reduction) hearts. In addition, the slow rate constant during ischemia was also significantly reduced by 94% when compared with normal hearts and by 85% in comparison to hypoxic hearts. During myocardial thallium washout the fast rate constant in

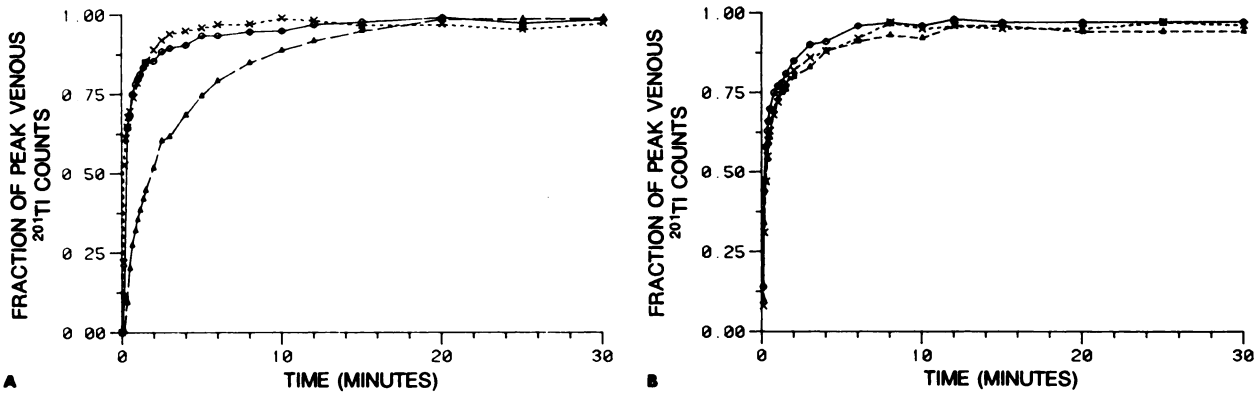

FIGURE 2
A: Mean normalized myocardial uptake of ^{201}Tl in group A rabbit hearts over 30 min of continuous tracer infusion. (x) Normal; (o) Hypoxia; (Δ) Ischemia. B: Mean normalized myocardial uptake of ^{201}Tl in Group B rabbit hearts over 30 min of continuous tracer infusion. (x) Normal; (o) Isoproterenol; (Δ) Hypocalcemia

TABLE 2
Thallium-201 Rate Constants (Percentage · min^{-1})

	Uptake			Clearance		
		Fast component	Slow component		Fast component	Slow component
Group A						
Normal	p = N.S.†	6.61 ± 1.03	0.32 ± 0.07	p = N.S.	7.08 ± 1.45	0.18 ± 0.01
Ischemic		0.32 ± 0.04	0.04 ± 0.01		0.89 ± 0.08	0.10 ± 0.02
Hypoxic		4.86 ± 0.87	0.28 ± 0.04		5.32 ± 0.76	0.30 ± 0.05
Group B						
Normal	p = N.S.	6.33 ± 1.01	0.29 ± 0.06	p = N.S.	6.97 ± 1.31	0.31 ± 0.06
Isoproterenol		6.92 ± 1.15	0.45 ± 0.08		6.19 ± 1.19	0.17 ± 0.03
Hypocalcemic		5.12 ± 0.82	0.23 ± 0.06		5.53 ± 0.81	0.24 ± 0.03

* = $p < 0.001$.
† N.S. = Not significant.

hypoxic hearts was reduced by 25% when compared with normal, but this was not a significant difference. Ischemia also caused a reduction in the fast rate constant in comparison to normal (87%) and hypoxic (83%) hearts which did attain statistical significance. Although ischemic hearts also tended to have a reduced slow rate constant, there were no significant differences in these values among the three groups during tracer washout.

Although there was a variation of ~20% among the estimated fast components of thallium uptake and washout for the Group B hearts, these differences were not significant. Similarly, the 50% variation in the estimated slow component of thallium uptake and washout also did not achieve statistical significance. In addition, a comparison between the rate constants for all Group B hearts and those for hypoxic and normal hearts in Group A did not demonstrate any statistical differences.

To evaluate the possible effect of edema formation on the different rate constants calculated for each group, the tissue water fraction was also determined. The mean fraction of water in all groups of hearts varied between 0.82±0.02 and 0.85±0.03 and no significant differences were noted. This suggests that edema formation did not selectively affect any group of hearts.

DISCUSSION

These observations support the dominant effect of coronary perfusion above that of hypoxia and altered contractility on myocardial kinetics, and suggest that normal thallium uptake in damaged cells receiving normal flow may not imply normal cellular function. The use of an isovolumetrically contracting heart model with constant isotope infusion, cold washout, and precise gamma well detection of radioactivity has not previously been reported, but our results do support earlier data utilizing some different techniques. Specifically,

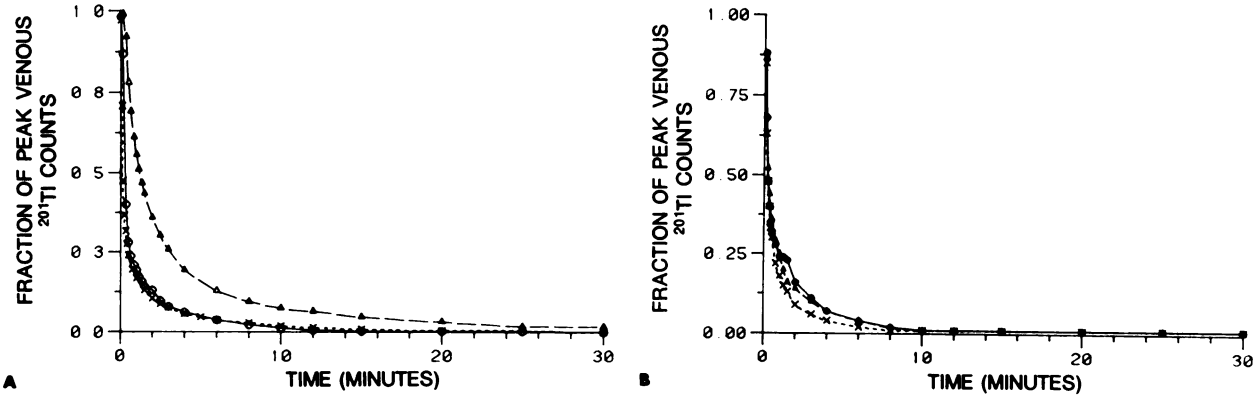

FIGURE 3
A: Mean normalized myocardial clearance of ^{201}Tl in Group A rabbit hearts over 30 min of tracer washout. (x) Normal; (o) Hypoxia; (Δ) Ischemia. B: Mean normalized myocardial clearance of ^{201}Tl in Group B rabbit hearts over 30 min of tracer washout. (x) Normal; (o) Isoproterenol; (Δ) Hypocalcemia

the combination of previous data (*4,16*) suggesting that flow effects significantly alter thallium kinetics with our observations, leads one to conclude that marked alterations in oxygen saturation, cardiac workload, and contractility do not have such an effect on thallium kinetics. Overall, our experiments could determine myocardial thallium kinetics more precisely than standard imaging techniques, and do have important implications in the interpretation of thallium perfusion imaging.

Thallium scintigraphy is generally used as an evaluation of myocardial perfusion and viability, but its current use (*8-11*) in conjunction with coronary reperfusion raises some important questions. Specifically, if thallium imaging is used to evaluate both myocardial perfusion and viability, its uptake should independently reflect ischemic, hypoxic, or enhanced or depressed contractile state changes that are associated with a prolonged insult and permanent damage. Accordingly, our experimental design permitted the independent assessment of decreased perfusion and oxygen content as well as increased or decreased contractility so that isotope kinetics could also be determined under these separate conditions.

Thallium Kinetics in an Isolated Heart Model

The use of the arterial and venous sampling to determine organ tracer uptake and clearance in this study was based on work by Kety and Schmidt (*19*). The computer model used to fit the rate constants was similar to several previous reports (*7,14,16*) that estimated mono- or bioexponential functions from isotope time activity curves. It is of interest to note that the three-compartment model (vascular, interstitial, and cellular) and estimated fast and slow rate constants provided a very adequate fit for the thallium data. Although the use of a three-compartment model to describe thallium kinetics is relatively simplistic, this model has been previously published (*6,16,17*) and provides some means for comparison. Specifically, Goldhaber and co-workers utilized an isolated rat heart to monitor thallium kinetics during normal (12 ml/min) and reduced levels of coronary perfusion (*16*). An external radiation detector was utilized and they noted a progressive decrease (67-75%) in estimated rate constants as coronary perfusion was decreased (85%). During ischemia, we also noted that myocardial thallium uptake and clearance rate constants were reduced by an average of 83 to 95% (80% reduction in flow) compared to normal and hypoxic hearts. The absolute values for the rate constants were higher in this study than previously observed (*16*) which may well be related to the higher level of perfusion, constant rapid heart rate, isovolumic contractions, and higher temporal resolution of data points collected during our experiments. In another study, Bergmann and co-workers reported that the residual fraction for thallium in isolated rabbit hearts was affected by flow but not by increased myocardial work or hypoxia (*4*).

The observation that coronary venous activity remained below its peak for a relatively longer period of time implies that tracer extraction during ischemia was greater than normal or hypoxic hearts. This inverse relationship between flow and extraction confirms previous observations (*4,5*). In contrast to ischemia, our data also suggest that normal and hypoxic hearts, as well as hearts with altered contractility, having the same coronary perfusion, quickly attain peak thallium activity during a constant isotope infusion. Thallium clearance from the fast vascular-interstitial space was also reduced during ischemia but the reduction in slow interstitial-cellular exchange was not significant. Despite significant alterations in hemodynamic function in hypoxic, hypocalcemic, and isoproterenol hearts, thallium uptake and clearance were not significantly depressed compared with normal hearts. Thus these results show that thallium uptake reflects flow but is not significantly influenced by significant alterations in cellular or metabolic function.

It is important to note that the differences observed in isotope kinetics were not related to tissue water changes in our experiments because impaired thallium uptake has been reported in edematous myocardium (*20*). We noted that the average water content in all groups of hearts was ~83%. A protein-free perfusate would be expected to cause edema formation and, therefore, the rate constants measured in our hearts are not directly comparable to those determined from in vivo hearts having a normal water content of 78 to 80%. However, despite the lack of a direct measurement of extracellular volume, tissue edema would not account for the intergroup differences in estimated rate constants.

Limitations and Clinical Implications

There are always limitations in extrapolating data from in vitro heart models to determine myocardial isotope kinetics. The use of a hemoglobin-free buffer perfusate and consequently the need for a higher than normal perfusion rate makes comparisons to in vivo situations more difficult. There is also a lack of autonomic innervation and only isovolumic contraction is permitted. However, the use of such a model does allow global myocardial perfusion to be held constant and the metabolic and contractile state can be varied independent of coronary perfusion. The constant level of arterial isotope input and the directly determined isotope washout with a cold buffer solution facilitates statistical modeling as well. In addition, the use of precise volume sampling and gamma well counting avoids some of the problems of external radiation detection in similar types of experimental preparations. Specifical-

ly, external detection of myocardial isotope activity is limited by temporal resolution, geometric and background corrections during the cardiac cycle.

Despite the above-mentioned limitations, our overall results concerning the dominance of coronary perfusion over cellular metabolism on thallium kinetics during metabolic alterations are consistent with observations reported in intact dog hearts after coronary reperfusion (*21*). Another study performed in dog hearts also concluded that thallium uptake was dominated by blood flow and that intracellular accumulation was relatively independent of Na-K ATPase (*22*). Therefore, the external detection of regional myocardial thallium content as performed during standard clinical imaging is likely to reflect regional coronary perfusion at the time of tracer administration and not regional cellular function. Consequently, clinical images of normal thallium uptake may occur in severely impaired myocardium receiving elevated or normal perfusion.

Although it appears clear that coronary flow dominates myocardial thallium uptake and clearance, the extrapolation of these data to the process of thallium redistribution must be made with caution. Specifically, in the intact animal, thallium redistribution is a complex interaction of continuous cardiac uptake and clearance which is coupled to an arterial input concentration that is continually decreasing over time. As with all isolated heart models, ours is not well suited to study the redistribution process. However, since regional differences in myocardial thallium kinetics must exist in order to visualize redistribution, some extrapolation does appear justified. The large reduction in both uptake and clearance of myocardial thallium activity noted during ischemia would account for transient defects on serial images. This could be due to a combination of a slower net uptake of thallium in the ischemic region and faster clearance of activity from the normal region as our data suggests. Such a mechanism has been demonstrated in intact experimental studies (*14*). There have been no previous reports on the specific effects of hypoxia and altered contractility on thallium redistribution in intact animal models for comparison to our data. It is possible that the small differences in the rate constants for thallium uptake and interstitial clearance during different interventions noted in our report, coupled with the slightly faster cellular clearance compared to normal rate constants may have significant effects on the redistribution process. However, such an effect would require further extensive investigations involving a single i.v. bolus injection of thallium in an intact animal having regional metabolic impairment.

FOOTNOTES

* Packard Instrument Company, Downers Grove, IL. (Auto-Gamma Spectrometer interfaced with a Canberra Series 40 multichannel analyzer). Canberra Industries, Meridan, CT.

† Digital Equipment Corporation, Maynard, MA (Vax 11/780 computer).

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