INVESTIGATIVE NUCLEAR MEDICINE

Partition of Thallium-201 in Isolated Myocardial Tissue of Rats Previously Injected at Rest or After Exercise

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The kinetics and distribution of Tl-201 in isolated myocardial tissue of rats injected i.v. with this radionuclide are compared at rest and after exercise (2 hr of forced swimming). At 1/2 and 3 hr after injection, a myocardial segment was obtained and subjected to continuous washout with the radioactivity remaining in the tissue recorded each 10 sec for 1 hr. Altogether there were four groups of ten animals each. A three-compartment model (extracellular, main intracellular, and subcellular) was found to describe adequately the kinetics of Tl-201. In the groups studied 1/2 hr after Tl-201 injection the most dramatic effect of exercise was a translocation of Tl-201 into the subcellular compartment. The change was also present but less marked in samples from exercised rats obtained 3 hr after Tl-201 injection, which suggests a transition to the resting stage. The findings suggest the possibility of structural subcellular differences in myocardial uptake for Tl-201 in clinical images visualized after exercise and at rest.

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Myocardial scintigraphy after i.v. injection of Tl-201 has proved of clinical value in the noninvasive diagnosis of myocardial infarction and ischemia. It is currently customary to compare images obtained shortly after exercise with those at rest. Distribution of Tl-201 in myocardium is related to (a) regional blood flow and (b) efficiency of extraction by myocardial cells (*1–4*). In a preliminary study (*5*) we found evidence that intracellular distribution of Tl-201 in myocardium is not uniform but is subpartitioned into two compartments, one attributable to the main cytoplasm and the other to a subcellular structure, presumably mitochondria. Since it appears that no quantitative study has hitherto been carried out to assess the effects of exercise on myocardial cell partition of Tl-201, we undertook to compare the in vitro kinetics and distribution of Tl-201 in myocardium of rats injected at rest and after 2 hr of strenuous swimming.

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MATERIALS AND METHODS

Male Sprague-Dawley rats, 250–300 g each, were used. They were acclimatized in our animal quarters for approximately 10 days before the study. They were divided into two groups: (a) those not stressed, hereafter named *rested,* and (b) those stressed by forcing them to swim in water at room temperature for 2 hr, hereafter named *exercised.* Immediately after swimming, or at an equivalent time for the rested animals, rats were anesthetized with sodium pentobarbital (35 mg/kg) intraperitoneally. The jugular vein was exposed surgically and injected with about 0.2 mCi of ^{201}TlCl (specific activity greater than 200 mCi/mg) in 0.2 ml of 0.9% NaCl. Nylon sutures were applied to close the skin incision. Each group of animals, rested and exercised, was further subdivided into two according to time of tissue sampling, $^1/_2$ hr or 3 hr after Tl-201 injection; this gave four groups of ten animals each.

At the selected times rats were guillotined and bled. The thoracic cavity was quickly opened and the left ventricle excised. With the anterior coronary artery as a guide, an attempt was made to sample consistently the

same region of the left ventricle in all animals. Segments of the outer layer of the left ventricle, 0.5 mm in thickness, were cut with a Stadie-Riggs microtome. Each thin segment (about 10 × 8 mm) was subjected to continuous outflow of Tl-201. The procedure consists basically of suspending the tissue segment in a tube where it is washed continuously with Krebs solution (gassed with 95% O_2 + 5% CO_2) in an apparatus specially constructed in the laboratory (*6*) which assures constant temperature (37.5°C) and flow (15 ml/sec). Radioactivity in the myocardial segment was recorded with a spectrometer and printer before starting the washout (t_0) and every 10 sec thereafter for 1 hr. Although counts were obtained every 10 sec, the following times were chosen for the processing of data in the computer input; 0, 10, 20, 30, 60, 90, and 120 sec; every minute from 2 to 14 min; and every 2 min to the end of the record. This point selection provides a greater statistical weight on the initial part of the outflow curve. This is desirable for two reasons: (a) the higher radioactivity counts are more accurate; (b) since the curve declines faster at the beginning, important information might otherwise be missed.

A compartmental analysis model with *transport rate constants* (k_{ij}) as primary parameters was used to describe thallous-ion kinetics in the myocardium. To solve the compartmental system we employed the SAAM (Simulation, Analysis And Modeling) computer program (*7*). The model considers thallium as partitioned into an extracellular (EC), an intracellular (IC), and a subcellular (SC) space (Fig. 1). The computer output for thallous ion outflow from the tissue yields a double curve composed of: (a) a theoretically calculated curve that is compared point by point with (b) the experimentally obtained curve. The computer program modifies the initial estimates of k_{ij} iteratively to seek the best fit between the two curves. For further details see reference (*8*). The overall fractional deviation between experimental and theoretical values for each point in time was about 2%. The SAAM program output also provides an internal estimate of the uncertainties associated with the parameters under study. The overall value of these uncertainties was about 10%. This indicated that the model is consistent with the experimental data. From numerical values for the transport rate

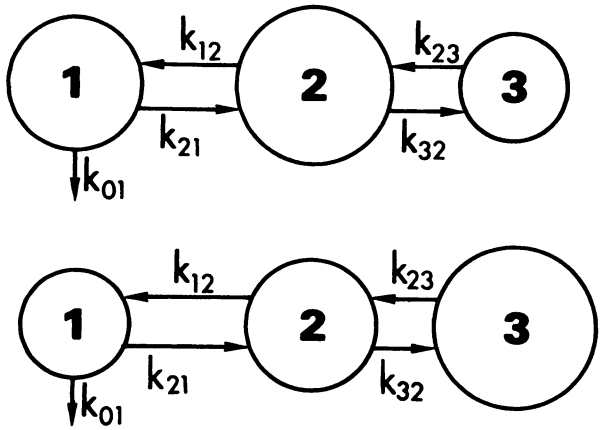

FIG. 1. Three-compartment model of Tl-201 distribution in myocardial wall of rested rats (top) and exercised rats (bottom) showing initial relative sizes of: (1) extracellular, (2) main intracellular, and (3) subcellular compartments at ½ hr after injection of Tl-201. Intercompartmental transport rate constants are symbolized by k_{ij}. Note shrinkage of Compartments 1 and 2, and enlargement of Compartment 3, in exercised animals (bottom drawing), compared with rested ones (top drawing).

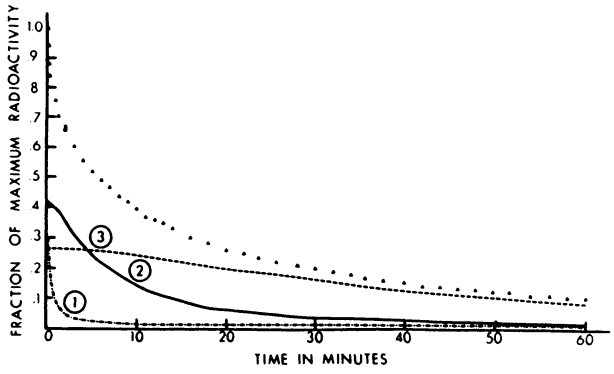

FIG. 2. Kinetics and distribution of Tl-201 in myocardial segment obtained ½ hr after i.v. injection of radionuclide into *rested* rat. Uppermost tracing plots Tl-201 washout (●, experimental; ■, theoretical; ▲, coincidental points) in total tissue where experimental and theoretically calculated data give appearance of single tracing owing to good agreement between the two sets of data. Three lower curves describing Tl-201 in each compartment are computer-simulated and represent (1) extracellular, (2) main intracellular, and (3) subcellular compartments.

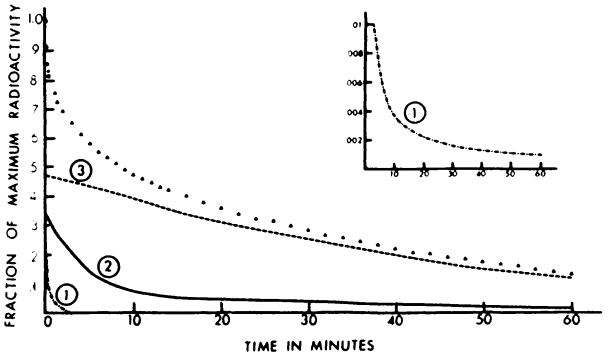

FIG. 3. Kinetics and distribution of Tl-201 in a myocardial segment obtained ½ hr after i.v. injection of this radionuclide into *exercised* rat. Uppermost tracing plots Tl-201 washout (●, experimental; ■, theoretical; ▲, coincidental points) in total tissue where experimental and theoretically calculated data give appearance of single tracing owing to good agreement between the two sets of data. Three lower curves describing Tl-201 in each compartment are computer-simulated and represent (1) extracellular, (2) main intracellular, and (3) subcellular compartments. Curve for extracellular compartment is continued in inset on expanded ordinate scale. Note higher values throughout study for Compartment 3, and rapid decline of Compartment 1, compared with those for rested rats (Fig. 2).

constants it is possible to calculate (*8,9*) relative compartment sizes (q_j/q_T) for the thallous ion at the beginning of the outflow (t_0 time). Calculation of the relative overall transport (r_{01}/q_T) at the beginning of the outflow (t_0) is detailed in the Appendix.

RESULTS

Differences in Tl-201 distribution between exercised and rested animals at ½ hr after injection. Illustrative plots of the outflow data from typical experiments are shown as points in Fig. 2 for a rested rat and in Fig. 3 for an exercised animal. In these and subsequent figures the datum-point plot, which is composed of both theoretically calculated and experimental curves, appears as a single curve made almost exclusively of coincidental points, because, for the great majority of points, adjacent points are indistinguishable within the limits of resolution of the graph. The fraction of Tl-201 in each compartment, as obtained from the computer output, is represented by the three curves labeled 1, 2, and 3. Note the marked preponderance, initially and along the course of time, of Compartment 3 (SC) in the specimen corresponding to the exercised animal (Fig. 3).

In Table 1 values for the transport rate constants are compared. All except k_{23} were shown statistically to be significantly augmented. Of particular importance is the fourfold increase in transport rate constant k_{32} describing Tl-201 movement from IC to SC compartment.

Relative compartment sizes at t_0 are tabulated in the lower half of Table 1. Specimens from exercised animals as compared with rested ones exhibited: (a) a significantly smaller Compartment 1 (EC), 0.20 against 0.33; (b) a significantly smaller Compartment 2 (IC), 0.31 against 0.46; and (c) a significantly much larger Compartment 3 (SC), 0.49 against 0.21. Changes in compartment size at t_0, between specimens from rested and exercised animals, are shown graphically in Fig. 1.

The relative overall transport, r_{01}/q_T, from tissue to outside at t_0 was significantly increased in exercised animals as compared with rested ones (Table 1).

Differences in Tl-201 distribution between exercised and rested animals at 3 hr after injection. Plots of outflow data from typical experiments are shown in Fig. 4 for a rested rat and in Fig. 5 for an exercised animal. Comparison of values for the transport rate constants (Table 1) reveals the same direction of changes as in the ½-hr specimens, but with less quantitative difference to the extent that only k_{01} and k_{32} were significantly higher in exercised as compared with rested animals.

Relative compartment sizes at t_0, for specimens from exercised rats as compared with rested ones, were as follows: (a) Compartment 1 (EC) was significantly smaller, 0.24 against 0.33; (b) Compartment 2 (IC) was statistically unchanged, 0.40 against 0.44; and (c) Compartment 3 (SC) was significantly enlarged, 0.36 against 0.23, though not as much as in the ½-hr specimens.

The relative overall transport, r_{01}/q_T, from tissue to outside at t_0 was also significantly increased in exercised

TABLE 1. VALUES OF TRANSPORT RATE CONSTANTS*, k_{ij} (sec^{-1}), RELATIVE COMPARTMENT SIZES† (q_j/q_T), AND RELATIVE OVERALL TRANSPORTS‡, r_{01}/q_T (sec^{-1}), FOR Tl-201 IN MYOCARDIAL SEGMENTS OF RESTED AND EXERCISED RATS‖

Parameter of interest	½ hr after Tl-201 injection					3 hr after Tl-201 injection				
	rested	(N = 10)	exercised	(N = 10)	P<§	rested	(N = 10)	exercised	(N = 10)	P<§
10^3k_{01}	24.4	±1.51	78.2	±8.78	0.001	27.0	±4.82	57.3	±8.24	0.01
10^3k_{12}	2.20	±0.085	3.97	±0.57	0.01	2.06	±0.13	2.33	±0.33	N.S.
10^3k_{21}	3.24	±0.23	6.53	±1.24	0.02	3.03	±0.37	4.02	±0.57	N.S.
10^3k_{23}	0.60	±0.044	0.62	±0.043	N.S.	0.48	±0.030	0.47	±0.038	N.S.
10^3k_{32}	0.25	±0.018	1.03	±0.13	0.001	0.25	±0.022	0.53	±0.12	0.05
q_1/q_T	0.33	±0.025	0.20	±0.010	0.001	0.33	±0.024	0.24	±0.022	0.02
q_2/q_T	0.46	±0.013	0.31	±0.017	0.001	0.44	±0.014	0.40	±0.034	N.S.
q_3/q_T	0.21	±0.022	0.49	±0.024	0.001	0.23	±0.020	0.36	±0.049	0.05
$10^3r_{01}/q_T$	7.76	±0.44	14.9	±1.06	0.001	7.90	±0.89	12.2	±1.14	0.01

* Transport rate constant (k_{ij}) is the fraction of Tl-201 in Compartment j (2nd subscript) that enters Compartment i (1st subscript) in unit time (see Fig. 1). Values of k_{ij}, which have the dimension sec^{-1}, are multiplied by 10^3 to facilitate comparison.

† Relative compartment sizes are calculated as ratios between appropriate values of k_{ij} (*8,9*). Each q_j symbolizes the quantity (activity) of Tl-201 in its compartment, and q_T the total quantity in the tissue at the beginning of the outflow (t_0).

‡ Relative overall transport (r_{01}/q_T) represents the quantity of Tl-201 transferred from Compartment 1 into Compartment 0 (outside) per unit time divided by the total quantity in the tissue, q_T, at the beginning of the outflow (t_0). Values of r_{01}/q_T, which have the dimension reciprocal of time, are multiplied by 10^3 to facilitate comparison.

‖ Mean ± s.e.m.

§ By Student's t-test.

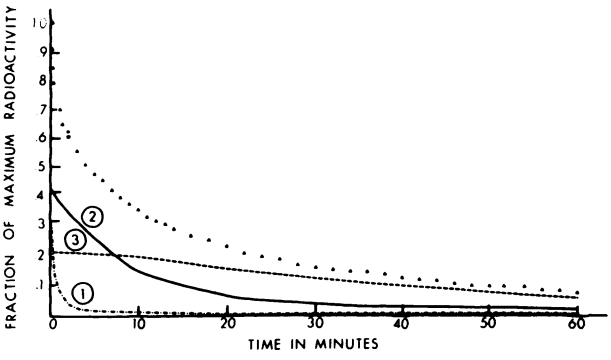

FIG. 4. Curves obtained as in Fig. 2 (*rested* rat), except that sample of heart muscle was excised *3 hr* after i.v. injection of Tl-201.

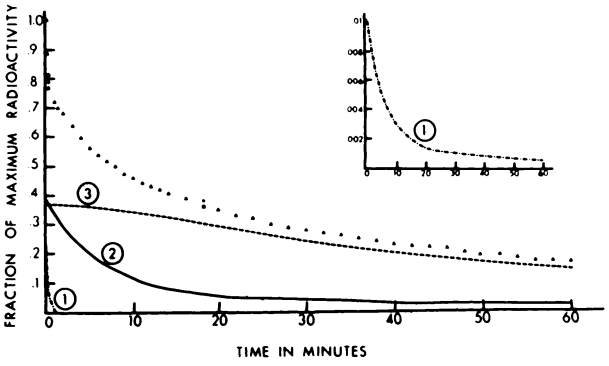

FIG. 5. Curves obtained as in Fig. 3 (*exercised* rat), except that sample of heart muscle was excised *3 hr* after i.v. injection of Tl-201. Curve for extracellular compartment is redrawn in inset, with expanded range. Note higher values throughout study for Compartment 3, and rapid discharge of Compartment 1, compared with those for rested rats (Fig. 4).

animals as compared with rested ones (Table 1).

Temporal differences in Tl-201 distribution within rested and exercised animals. All parameter values (except k_{23}) were statistically indistinguishable between ½-hr and 3-hr specimens in rested animals. All parameter values (except k_{23}) for the specimens obtained 3 hr after injection into exercised animals were between values for specimens from rested animals and specimens obtained ½ hr after injection into exercised animals. This is particularly clear for the relative distribution of Tl-201 between Compartments 2 and 3 and for the relative overall transport (Table 1, cf., ½-hr exercised group with 3-hr exercised group). In a preliminary communication (*5*) the subtler parameter differences between ½-hr and 3-hr specimens were reduced, probably owing to the inclusion of fewer data points for the mathematical analysis of the washout curves.

DISCUSSION

Results of the present study on Tl-201 partition in myocardial segments (Table 1) indicate that from 67% (rested animals) to 80% (exercised animals) of the thallium is intracellular. That the thallous ion is predominantly intracellular was suggested by Lund (*10*) and inferred by Gehring and Hammond (*11*), but no attempt had hitherto been made to quantitate its subcellular partition. The values of 67 to 80% obtained from the analysis of the washout data probably underestimate the original in vivo intracellular Tl-201, because measurements of in vitro outflow in myocardial segments may not be directly translatable to the in vivo conditions where the tissue might be less permeable to the loss of Tl-201.

The finding of a significantly increased relative transport, r_{01}/q_T, from tissue to outside indicates an augmented Tl-201 outflow in myocardial segments of exercised as compared with rested animals. Since there is evidence that maximum myocardial concentration of Tl-201 is achieved by 5-15 min after injection (*12-14*) and that the plasma level—after the first 20 min—is almost constant in time (*12*), the collection of specimens at ½ and 3 hr in the present study most likely corresponds to a phase of radionuclide dynamic equilibrium between myocardium and plasma.

Furthermore, since total tissue ionic inflow and outflow rates must be equal in vivo (*15*), the value of the relative overall transport for outflow, r_{01}/q_T, at t_0 (Table 1) provides an indirect estimate of the tissue uptake of Tl-201 (see Appendix). The exercise-to-rest ratio of this parameter was 1.92 for the ½-hr groups and 1.54 for the 3-hr groups. These values are comparable with Tl-201 exercise-to-rest ratios of 2.5 (at ½ hr) and 2.3 (at 3 hr) found by direct counting of rat's unwashed myocardial segments and to ratios of 1.4 (heart-to-lung at exercise divided by heart-to-lung at rest) and 2.4 (heart-to-liver at exercise divided by heart-to-liver at rest) obtained in man (*16*). An exercise-to-rest ratio of 1.5 after background subtraction in myocardium of normal men has also been reported (*17*).

The more characteristic effect of exercise as against rest was a translocation of the thallous ion into Compartment 3, representing subcellular space. This change was particularly dramatic in the specimens analyzed ½ hr after Tl-201 injection. Although the kinetic approach to compartmental analysis does not provide direct identification of cytological components, independent workers have drawn attention to the heart mitochondria as organelles capable of marked enlargement (*18*) and even structural changes (*19*) with acute exercise, and of considerable thallous-ion uptake (*20*).

Therefore, the finding that Compartment 3 (subcellular) showed even greater thallous-ion accumulation than Compartment 2 (main intracellular) in myocardium of exercised rats killed ½ hr after Tl-201 injection is consistent with the above observations (*18-20*). Note

(Table 1) that in exercised rats killed at 3 hr, the myocardial Compartment 3 revealed a Tl-201 accumulation (0.36) halfway between that seen in exercised rats killed ½ hr after injection (0.49) and that recorded in rested rats (0.21, 0.23). This may be interpreted as a waning from the larger accumulation in myocardial Compartment 3 of exercised rats killed ½ hr after Tl-201 injection. In this context, it is of interest that the extensive mitochondrial damage found in myocardium of rats after 2 hr of swimming was partially reversed by 2 hr of recovery after the swimming, and almost completely so by 24 hr of recovery (*19*). Whether this temporary mitochondrial damage is related to hypoxia or to reduced ATP concentration during exercise remains debatable (*19*).

The question naturally arises as to whether these reversible structural changes in mitochondria, with concomitant changes in experimental Tl-201 uptake, might be related to the well-known observation that in clinical situations the best imaging with Tl-201 is obtained following injection after some kind of stress (increased heart rate through pacemaker, treadmill exercise, etc.). Because of differences in the length of exercise, level of exercise, timing of the Tl-201 injection, and, especially, of the administration of anesthesia before the Tl-201 injection—which by itself may influence the blood-flow distribution—it remains an unsettled matter whether our animal model is strictly applicable to exercise studies in man. The similarity is remarkable, however, between the values for the myocardial Tl-201 exercise-to-rest ratio found in the present animal study and those reported in the literature for human subjects.

APPENDIX

Calculation of relative overall transport of material. In the unified system of nomenclature and symbols for tracer methodology proposed by Brownell et al. (*21*) *transport*, r_{ij}, into compartment i from j is the amount of material transferred from j into i per unit time (dimensions of mass or activity/time). Thus it has the significance of a rate of change in time. (In the older nomenclature this parameter was called "flux.") From the definition of transport, it follows that:

$$r_{ij}(t) = k_{ij}q_j(t) \qquad (1)$$

where: k_{ij} is the transport rate constant (dimension of reciprocal of time)
and q_j the amount of material in compartment j, also referred to as compartment size (dimension of mass or activity).

At a sufficiently long time after introducing the material into the system (*15*):

$$r_{10}(\infty) = r_{01}(\infty), \qquad (2)$$

where the subscripts 1 and 0 refer to compartment 1 and outside, respectively.

For the case when the tissue was tracer-loaded in vivo but washed out in vitro, the beginning of the washout is equivalent to a "time change" whereby (*6,8*):

$$r_{01}(\infty)\Big|_{\substack{\text{in}\\\text{vivo}}} = r_{01}(0)\Big|_{\substack{\text{in}\\\text{vitro}}}. \qquad (3)$$

Furthermore, by the nature of the washout, $r_{10}(t) \equiv 0$ at the beginning of and throughout the washout, whereas $r_{01}(0)$ momentarily maintains its instantaneous value. Since, by the biologic constraints, all material from the tissue, q_T, must exit through k_{01} (Fig. 1), it follows that the initial rate of change (or initial slope) of the material washout curve is:

$$r_{01}(0) = k_{01}q_1(0) = \frac{dq_T}{dt}\Big|_{t=0}. \qquad (4)$$

This relationship can be expressed relative to q_T to keep in line with the normalized values used for the compartment sizes:

$$\frac{r_{01}(0)}{q_T(0)} = k_{01}\frac{q_1(0)}{q_T(0)} = \frac{dq_T/dt}{q_T}\Big|_{t=0}. \qquad (5)$$

Equation 5 permits the calculation of the relative overall transport, a physiologically meaningful parameter of overall exchange of the material obtainable from washout experiments.

(I) *Calculation through parameters derived from compartmental analysis.* The previous Eq. 5 is rewritten here:

$$\frac{r_{01}(0)}{q_T(0)} = k_{01}\frac{q_1(0)}{q_T(0)}. \qquad (5a)$$

Using the individual values of k_{01} and $q_1(0)/q_T(0)$ from the compartmental model (Table 1), we computed the mean values for the relative overall transport of material that are tabulated in Table 2.

(II) *Calculation through initial-slope method.* This approach is *independent* of any proposed model. It can be obtained simply by division of the initial slope of the washout curve by the initial amount of material (last expression in Eq. 5).

A convenient method for obtaining reliable estimates of the initial slope is based on the fact that in many outflow-recording

TABLE 2. COMPARATIVE VALUES OF RELATIVE OVERALL TRANSPORTS*, r_{01}/q_T (sec^{-1}), AT t_0 BY METHOD I AND METHOD II† (SEE APPENDIX)

$10^3 r_{01}q_1/q_T$ calculated as	½ hr after Tl-201 injection					3 hr after Tl-201 injection				
	rested	(N = 10)	exercised	(N = 10)	p<‡	rested	(N = 10)	exercised	(N = 10)	p<‡
(I) $10^3 k_{01}q_1(0)/q_T(0)$	7.76	±0.44	14.9	±1.06	0.001	7.90	±0.89	12.2	±1.14	0.01
(II) $10^3 \sum_{i=1}^{3} \lambda_i A_i \Big/ \sum_{i=1}^{3} A_i$	7.74	±0.46	14.4	±1.46	0.001	8.41	±1.01	12.8	±1.02	0.01

*Values are multiplied by 10^3 to facilitate comparison.
† Mean ± s.e.m.
‡ By Student's t-test

experiments the temporal curve of disappearance of tracer material from the tissue can be fitted to a sum of exponentials:

$$q_T(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (n = 3 \text{ here}). \tag{6}$$

The absolute value of the initial slope is then given by:

$$\left.\frac{dq_T}{dt}\right|_{t=0} = \sum_{i=1}^{n} \lambda_i A_i, \tag{7}$$

and the relative overall transport as per Eq. 5 will be:

$$\frac{r_{01}(0)}{q_T(0)} = \left.\frac{dq_T/dt}{q_T}\right|_{t=0} = \frac{\sum_{i=1}^{n} \lambda_i A_i}{\sum_{i=1}^{n} A_i} \quad (n = 3 \text{ here}). \tag{8}$$

The values for relative overall transport of material obtained by using Eq. 8 are tabulated in Table 2. Other approaches (less accurate) for estimating the initial slope may be based on drawing a tangent line at the beginning of the curve or on numerically calculating a slope from the first two data points.

Comment. Table 2 exhibits the values of relative overall transport for each group. It is noteworthy that both methods I and II yield very similar results, thus providing indirect evidence of the suitability of a three-compartment model to represent thallous-ion distribution in myocardium.

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