Effects of Exercise on Kinetics and Distribution of K-43 and Tl-201 in Isolated Myocardium: Concise Communication

Josep G. Llaurado, George A. Smith, and Jane A. Madden

Wood Veterans Administration Medical Center, Marquette University, and The Medical College of Wisconsin, Milwaukee, Wisconsin

Kinetics and distribution of K-43 and Tl-201 were studied in isolated myocardial tissue from rats to assess the effects of exercise. The experimental design was as follows. Rats in some groups were forced to swim for 2 hr; immediately after swimming, they were injected with 0.2 mCi of ^{43}KCl or ^{201}TlCl; at 0.5 or 3 hr after injection they were killed and a myocardial segment was obtained and subjected to washout with nonradioactive Krebs fluid in a special chamber. The radioactivity remaining in the tissue was recorded continuously for 1 hr. In control groups ("rested") the exercise was omitted. Altogether there were four groups of ten animals each for both K-43 and Tl-201. A three-compartment model (extracellular, main intracellular, and subcellular) was used; transport rate constants and relative compartment sizes were determined. The most striking finding was the unchangeability of K-43 parameters with regard to experimental condition (rest compared with exercise) and sampling time (0.5 compared with 3 hr after radionuclide injection). On the other hand, Tl-201 parameters were modified by exercise and sampling time. Notable differences between K-43 and Tl-201 kinetics were found. The hypothesis that alterations at the cellular level may affect regional myocardial distribution of a radionuclide is discussed.

J Nucl Med 22: 441–446, 1981

The physiological similarity between radiothallium and radiopotassium has been emphasized repeatedly. Some reports, however, have noted certain differences (*1–4*). It is noteworthy that radiopotassium continues to be used in some experimental (*5,6*) and clinical (*7*) situations. Distribution of mineral radionuclides in myocardium is related to (a) regional blood flow and (b) efficiency of extraction by myocardial cells (*8–12*). In previous work (*13,14*) we established that a three-compartment model (extracellular, intracellular, and subcellular) describes adequately the kinetics and distribution of Tl-201 in the myocardium. In clinical myocardial perfusion scintigraphy it is currently customary to compare images obtained after exercise with those at rest. Here we examine possible differences between potassium- and thallous-ion kinetics in the myocardium of *exercised* animals by comparing the kinetics and distribution of K-43 with Tl-201 in isolated myocardium of rats injected at rest and after 2 hr of strenuous swimming.

Received Nov. 6, 1980; revision accepted Dec. 23, 1980.

For reprints contact: J. G. Llaurado, Nuclear Medicine Service (115), Wood VAMC, Milwaukee, WI 53193.

MATERIALS AND METHODS

Male white rats (Sprague–Dawley), about 300 g each, were acclimated to our animal quarters for at least 10 days before the beginning of the experiment. Animals were divided into two major groups: (a) those not stressed, hereafter called *rested*, and (b) those stressed by being forced to swim in water at room temperature for 2 hr, hereafter called *exercised*. Immediately after

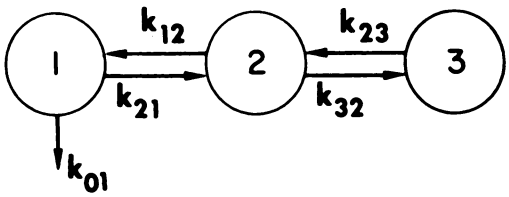

FIG. 1. Model of radionuclide cation distribution in myocardium consisting of three compartments: (1) extracellular, (2) intracellular, and (3) subcellular. Intercompartmental transport rate constants are symbolized by the k_{ij}.

swimming, the exercised and rested rats were anesthetized with pentobarbital sodium (50 mg/kg) intraperitoneally and injected intrajugularly with 0.2 mCi of carrier-free ^{43}KCl* or of $^{201}TlCl$,† of specific activity greater than 200 mCi/mg, in 0.2 ml of 0.9% NaCl. In the rested groups, only the exercise was omitted. Each group of animals, rested and exercised, was further subdivided into two subgroups according to time of tissue sampling, 0.5 or 3 hr after the chosen radionuclide injection.

At the selected times, rats were decapitated with a guillotine and bled. The thoracic cavity was quickly opened and the heart excised. The anterior coronary artery was used as a guide to sample consistently the same region of left ventricle in all animals. Segments of left ventricle, 0.5 mm in thickness, were cut with a Stadie-Riggs microtome. Each thin segment (about 10 by 8 mm) was continuously bathed with nonradioactive Krebs fluid in an apparatus specially constructed in the laboratory (*15*). With a well scintillation detector attached to a spectrometer and printer, radioactivity in the myocardial segment was recorded before starting the washout (time t_0) and every 10 sec thereafter for 1 hr (*14*). A compartmental analysis model with *transport rate constants* (k_{ij}) as primary parameters was used to describe the kinetics of the radionuclide cations in the myocardium. To solve the compartmental system we used the SAAM (Simulation, Analysis And Modeling) computer program (*16*). The model (Fig. 1) considers the cations as partitioned into an extracullular (EC), an intracellular (IC), and a subcellular (SC) space (*17*). From numerical values for the transport rate constants it is possible to calculate (*17*) relative compartment sizes (q_j/q_T) for the cations at the beginning of the outflow (t_0).

RESULTS

Typical examples of plots of outflow data, obtained from animals sampled 0.5 hr after radionuclide injection, are shown as points for a rested rat injected with K-43 (Fig. 2) or Tl-201 (Fig. 3), and for an exercised animal injected with K-43 (Fig. 4) or Tl-201 (Fig. 5). In these figures the datum-point plot, which is composed of both experimental and theoretically calculated curves, appears as a single curve made almost exclusively of coincidental points, because corresponding points are nearly always indistinguishable within the limits of resolution of the graph. The fraction of radionuclide in each compartment, as obtained from the computer output, is represented in Figs. 2–5 by the three curves labeled 1, 2, and 3. Graphs obtained from animals sampled 3 hr after radionuclide injection were visually similar to those shown in Figs. 2–5, and for the sake of space economy are not shown herein.

In Table 1 the values for transport rate constants and relative compartment sizes are compared. Those corresponding to Tl-201 are placed in *italics* immediately below the K-43 values. Note that for each radionuclide there are four subgroups of animals: (a) those tissue-sampled 0.5 hr after injection following the rest schedule; (b) tissue-sampled 0.5 hr after injection following exercise; (c) tissue-sampled 3 hr after injection following the rest schedule; and (d) tissue-sampled 3 hr after injection following exercise.

Transport rate constants. In myocardial segments from animals studied 0.5 hr after radionuclide injection, there were statistically significant differences between

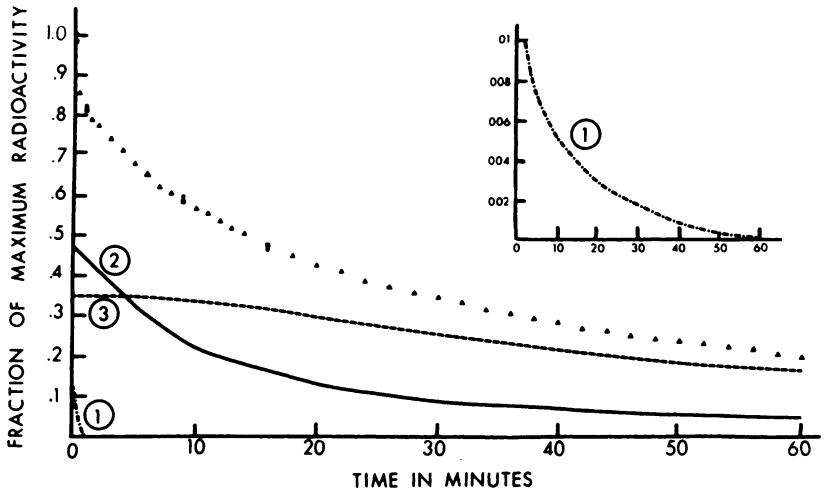

FIG. 2. Kinetics and distribution of K-43 in myocardial segment obtained 0.5 hr after i.v. injection of this radionuclide into a *rested* rat. Uppermost tracing is plot of K-43 washout (●, experimental; ■, theoretical; ▲, coincidental points) in total tissue where experimental and theoretically calculated curves appear as single curve owing to good agreement of the two sets of data. The three lower curves describing K-43 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 an expanded ordinate scale.

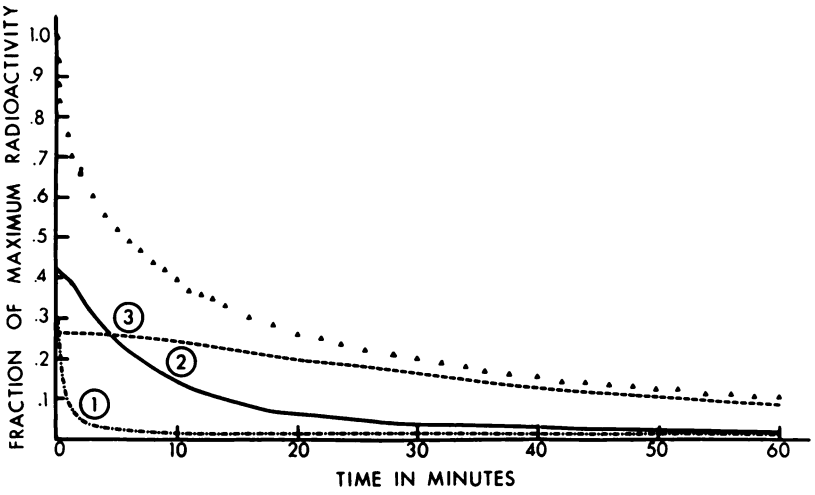

FIG. 3. Kinetics and distribution of Tl-201 in a myocardial segment obtained 0.5 hr after intravenous injection of this radionuclide into a *rested* rat. Symbols and arrangement are analogous to those for K-43 in Fig. 2.

K-43 and Tl-201 in all five values of k_{ij} for rested animals and in four out of five values of k_{ij} for exercised animals. In specimens from animals studied 3 hr after radionuclide injection, there were statistically significant differences between K-43 and Tl-201 in three values of k_{ij} for rested animals, but only in k_{12} for the exercised ones.

Whereas k_{ij} for Tl-201 often revealed a significant increase as a consequence of exercise, for K-43 no such effect was observed; in fact, the corresponding k_{ij} values were statistically indistinguishable from each other regardless of sampling time (0.5 compared with 3 hr after K-43 injection) or experimental condition (rest compared with exercise).

Relative compartment sizes. In specimens from rested animals at both 0.5 and 3 hr after radionuclide injection, Compartment 1 (EC) was statistically markedly diminished for K-43 compared with Tl-201, Compartment 2 (IC) was unchanged, and Compartment 3 (SC) was statistically augmented for K-43 compared with Tl-201 (Table 1, lower half).

For Tl-201 there were significant changes induced by exercise at both 0.5 and 3 hr, but for K-43 the corresponding relative compartment sizes were statistically unchanged regardless of sampling time (0.5 compared with 3 hr after K-43 injection) or experimental condition (rest compared with exercise).

DISCUSSION

The most striking feature of this investigation was the unchangeability of K-43 parameters with regard to sampling time (0.5 compared with 3 hr after radionuclide injection) and experimental condition of the animal (rest compared with exercise). On the other hand, Tl-201 parameters were influenced by exercise, the most consistent effects at 0.5 hr sampling being: (a) an increase of k_{01}, the transport rate constant concerned with extruding ion from the EC organ space into the organ exterior; (b) an increase of k_{32}, the transport rate constant representing Tl-201 movement from IC to SC compartment, (c) a shrinkage of Compartment 1 (EC); and (d) an enlargement of Compartment 3 (SC). To the extent that the above changes were less marked in specimens obtained 3 hr after Tl-201 injection, it is clear that Tl-201 kinetics and distribution in myocardium are

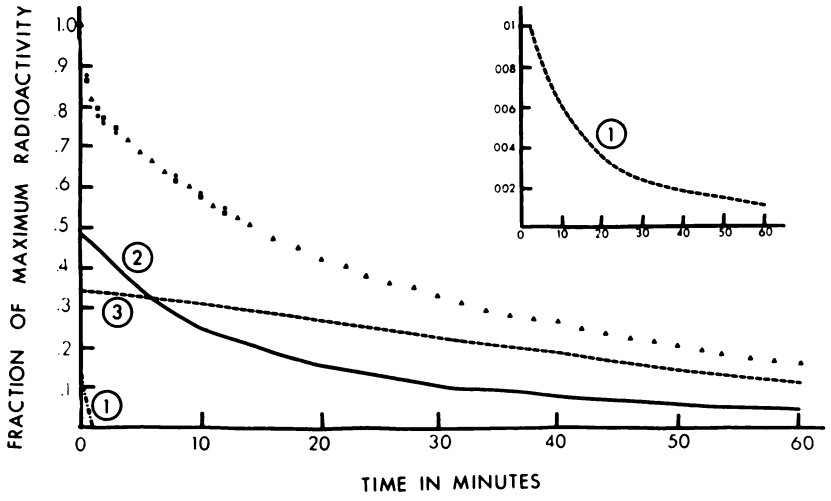

FIG. 4. Kinetics and distribution of K-43 in myocardial segment obtained 0.5 hr after i.v. injection of this radionuclide into *exercised* rat. Symbols and arrangement are analogous to those in Fig. 2.

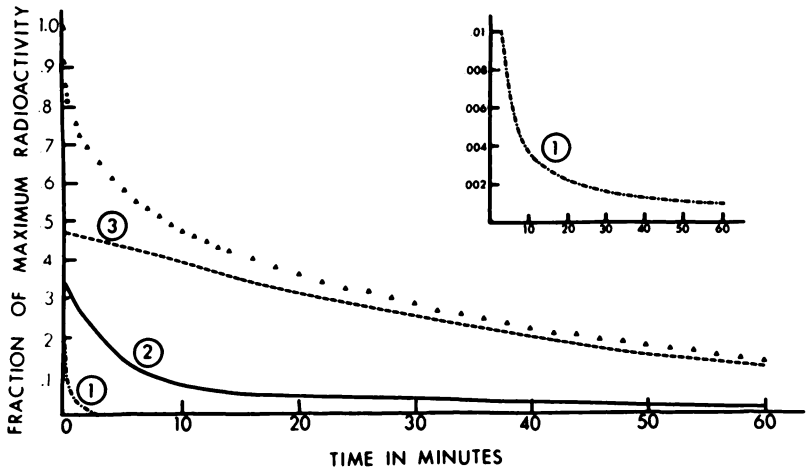

FIG. 5. Kinetics and distribution of Tl-201 in myocardial segment obtained 0.5 hr after i.v. injection of this radionuclide into *exercised* rat. Symbols and arrangement are analogous to those in Fig. 2.

modified by the sampling time (0.5 compared with 3 hr in this study).

The importance of ionic exchange between circulating blood and myocardial cell, in addition to coronary blood flow per se, in explaining the rate at which mineral radionuclides are taken up by the myocardium is well recognized (*8–12*). In this context, there were notable differences between K-43 and Tl-201 myocardial kinetics; first, in rested animals k_{01} was in a highly significant manner much larger for K-43 than for Tl-201; this difference was also present as a trend in exercised animals. This finding provides experimental kinetic evidence (a) for the suggestion (*3,18*) that clearance of Tl-201 from myocardium is relatively slow, and (b) for

TABLE 1. VALUES OF TRANSPORT RATE CONSTANTS* (k_{ij}, sec^{-1}) AND RELATIVE COMPARTMENT SIZES† (q_i/q_T) FOR K-43, AND *Tl-201* IN MYOCARDIAL SEGMENTS OF RESTED AND EXERCISED RATS (mean ± s.e.)

Parameter of interest	0.5 hr after radionuclide injection: rested (N = 10)	0.5 hr after radionuclide injection: exercised (N = 10)	p<‡	3 hr after radionuclide injection: rested (N=10)	3 hr after radionuclide injection: exercised (N = 10)	p<‡
10^3k_{01}	111.0[a] ± 16.6	99.3 ± 17.1		96.1[a] ± 8.52	96.7 ± 17.6	
	24.4 ± 1.51	*78.2 ± 8.78*	*0.001*	*27.0 ± 4.82*	*57.3 ± 8.24*	*0.01*
10^3k_{12}	1.57[b] ± 0.15	1.38[a] ± 0.093		1.51[b] ± 0.069	1.32[c] ± 0.082	
	2.20 ± 0.085	*3.97 ± 0.57*	*0.01*	*2.06 ± 0.13*	*2.33 ± 0.33*	
10^3k_{21}	4.20[b] ± 0.22	3.53[d] ± 0.29		4.05 ± 0.32	3.52 ± 0.32	
	3.24 ± 0.23	*6.53 ± 1.24*	*0.02*	*3.03 ± 0.37*	*4.02 ± 0.57*	
10^3k_{23}	0.37[a] ± 0.024	0.41[b] ± 0.032		0.38[d] ± 0.026	0.39 ± 0.035	
	0.60 ± 0.044	*0.62 ± 0.043*		*0.48 ± 0.030*	*0.47 ± 0.038*	
10^3k_{32}	0.30[d] ± 0.013	0.31[a] ± 0.020		0.29 ± 0.014	0.28 ± 0.041	
	0.25 ± 0.018	*1.03 ± 0.13*	*0.001*	*0.25 ± 0.022*	*0.53 ± 0.12*	*0.05*
q_1/q_T	0.17[a] ± 0.019	0.19 ± *0.022*		0.18[a] ± 0.0095	0.19 ± 0.016	
	0.33 ± 0.025	*0.20 ± 0.010*	*0.001*	*0.33 ± 0.024*	*0.24 ± 0.022*	*0.02*
q_2/q_T	0.45 ± 0.014	0.45[a] ± *0.0083*		0.46 ± 0.015	0.49 ± 0.032	
	0.46 ± 0.013	*0.31 ± 0.017*	*0.001*	*0.44 ± 0.014*	*0.40 ± 0.034*	
q_3/q_T	0.38[a] ± 0.024	0.36[b] ± 0.028		0.36[a] ± 0.015	0.32 ± 0.022	
	0.21 ± 0.022	*0.49 ± 0.024*	*0.001*	*0.23 ± 0.020*	*0.36 ± 0.049*	*0.05*

* Transport rate constant (k_{ij}) is the fraction of radionuclide 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 of appropriate k_{ij} values (*17*). Each q_i symbolizes the quantity (activity) of radionuclide in its compartment and q_T the total quantity in the tissue at the beginning of the outflow (t_0).

‡ By Student's t-test. It refers to the difference between the two *values for Tl-201* read horizontally; that for K-43 was nonsignificant in all cases. Markers (a), (b), (c), and (d) refer to the differences between corresponding values for K-43 and *Tl-201* read vertically: (a) $p < 0.001$; (b) $p < 0.01$; (c) $p < 0.02$; (d) $p < 0.05$.

reports (*1,8,19*) of rapid disappearance of potassium ion from the whole myocardium. On the other hand, transport rate constant k_{12}, governing movement of the ion into EC from IC space, was in all cases significantly smaller for K-43 than for Tl-201. Thus it appears that, in contrast to thallous ion, the movement of potassium ion out of the myocardial cell (as represented by k_{12}) is slower, but potassium ion is washed out much faster (as described by k_{01}) from the EC organ space. This mechanism appears all the more plausible if one considers that in the course of radionuclide outflow from a tissue, the probability of such radionuclide being found free in the EC space is inversely related to the probability of its being bound on macromolecular surfaces bathed by EC fluid (*20*). A firmer binding of thallium than of potassium to macromolecular structures is likely because of the *d* orbitals involved (*21*).

Although it is widely accepted that distribution of thallous ion in mammalian tissue follows, in general lines, that of potassium ion, some workers (*1-4*) have noted important differences. Thus Strauss et al. (*1*) reported, as a significant behavioral difference, the fact that thallium concentration in myocardium is increased in reactive hyperemia whereas potassium concentration is not significantly so (*22*). Furthermore, even under normal circumstances both potassium and thallium are cleared at different rates from myocardium, suggesting that intracellular metabolism of the two is different (*3*). Our results present experimental evidence that compartmental kinetics of these two ions, at least for the first 0.5 hr after injection, are different. Mackay et al. (*4*), by studying simultaneous movements of K-43 and Tl-201, found that exchangeable potassium values obtained by using the so-called Tl-201 space were unreliable. Lameijer and van Zwieten (*2*) reported that the large accumulation of thallium in the renal medulla is unlike that of potassium.

In the present work, the well-known intracellular location of potassium and thallous ions was reconfirmed. The intracellular values of 80% for Tl-201 and 83% for K-43, obtained from analysis of the washout data, may underestimate the original in vivo intracellular cation values, because measurements of in vitro outflow in myocardial segments may not be exactly translatable to in vivo conditions, where the tissue might be less permeable to the loss of mineral ions. Furthermore, an in vivo washout is against a protein-rich extracellular fluid, whereas an in vitro washout is against a Krebs solution. This condition may be more significant in the case of the thallous ion, since this ion is more firmly bound to protein than is potassium (*21*). The histological location of Compartment 3, representing subcellular (SC) space, cannot be determined with absolute certainty by the kinetic approach of compartmental analysis. Note, however, that heart mitochondria have been described as organelles capable of considerable potassium- and thallous-ion uptake (*23*).

More recently, Selwyn et al. (*24*) concluded that it is not yet clear whether regional defects in Tl-201 scintigraphy, as seen following exercise in patients with coronary artery disease, are due to regional alterations of myocardial perfusion or to disturbances of membrane metabolism. Thallium has been shown to substitute for potassium in activating pyruvate kinase and the Na-K ATPase system, and to correlate closely with regional myocardial depletion of creatine phosphokinase (*1,25*). We may speculate that if alterations at the cellular level control regional distribution of the radionuclide—and recent findings with the use of ionophores (*26*) reinforce this hypothesis—then corresponding scintigrams may be even more valuable as measurements of cell viability and/or metabolic status than is perfusion. In this light, kinetic studies in isolated myocardium, such as presented here, may be useful in predicting the behavior of new radionuclides, or that of agents (dipyridamole, ionophores, etc.) modifying existing radionuclides.

FOOTNOTES

* Oak Ridge National Laboratories, Oak Ridge, TN.
† New England Nuclear, North Billerica, MA.

ACKNOWLEDGMENTS

This work was supported by research funds of the Veterans Administration and the American Heart Association/Wisconsin Affiliate. Dr. Jane A. Madden was a Young Investigator with the National Heart, Lung and Blood Institute. We are grateful for the secretarial assistance of Genevieve Wollinka.

REFERENCES

1. STRAUSS HW, HARRISON K, LANGAN JK, et al: Thallium-201 for myocardial imaging.—Relation of thallium-201 to regional myocardial perfusion. *Circulation* 51: 641-645, 1975
2. LAMEIJER W, VAN ZWIETEN PA: Kinetic behavior of thallium in the rat. Accelerated elimination of thallium owing to treatment with potent diuretic agents. *Arch Toxicol* 37: 265-273, 1977
3. GEWIRTZ H, O'KEEFE DD, POHOST GM, et al: The effect of ischemia on thallium-201 clearance from the myocardium. *Circulation* 58:215-219, 1978
4. MACKAY A, DAVIES DL, HORTON PW: Is thallium-201 of use in the measurement of total exchangeable potassium in man? *Eur J Clin Invest* 8:261-262, 1978
5. MARKOV AK, SMITH RO, OGLETHORPE NC, et al: The use of coronary vasodilators in myocardial imaging with ^{43}K. *Eur J Nucl Med* 5:75-84, 1980
6. TILBURY RS, MYERS WG, CHANDRA R, et al: Production of 7.6-minute potassium-38 for medical use. *J Nucl Med* 21:867-871, 1980
7. MARKOV AK, SMITH RO, LEHAN PH, et al: Detection of coronary artery disease with rapid serial rescanning with potassium-43 at rest. *Am J Cardiol* 43:778-786, 1979
8. POE ND: Comparative myocardial uptake and clearance characteristics of potassium and cesium. *J Nucl Med* 13: 557-560, 1972

9. LEBOWITZ E, GREENE MW, FAIRCHILD R, et al: Thallium-201 for medical use. I. *J Nucl Med* 16:151-155, 1975
10. POHOST GM, ZIR LM, MOORE RH, et al: Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 55: 294-302, 1977
11. WEICH HF, STRAUSS HW, PITT B: The extraction of thallium-201 by the myocardium. *Circulation* 56:188-191, 1977
12. HAMILTON GW, NARAHARA KA, YEE H, et al: Myocardial imaging with thallium-201: effect of cardiac drugs on myocardial images and absolute tissue distribution. *J Nucl Med* 19:10-16, 1978
13. LLAURADO JG, MADDEN JA, MEADE RC, et al: Distribution of thallium-201 injected into rats following stress: imaging, organ to plasma uptake ratios, and myocardial kinetics. *J Nucl Med* 19:172-177, 1978
14. LLAURADO JG, SMITH GA, MADDEN JA, et al: Partition of thallium-201 in isolated myocardial tissue of rats previously injected at rest or after exercise. *J Nucl Med* 20:1136-1141, 1979
15. LLAURADO JG: Digital computer simulation as an aid to the study of arterial wall Na kinetics. *J Appl Physiol* 27:544-550, 1969
16. BERMAN M: Compartmental analysis in kinetics. In *Computers in Biomedical Research*. vol 2, Stacy RW, Waxman BD, Eds. New York, Academic Press, 1965, pp 173-201
17. LLAURADO JG: Relationship between kinetics of inflow and outflow as the basis of a computer simulation for solving compartmental models: example of electrolyte transfers in cardiovascular tissues. In *Dynamic Studies with Radioisotopes in Medicine*. Vienna, International Atomic Energy Agency, 1971, pp 13-26
18. NISHIYAMA H, SODD VJ, ADOLPH RJ, et al: Intercomparison of myocardial imaging agents: ^{201}Tl, ^{129}Cs, ^{43}K, and ^{81}Rb. *J Nucl Med* 17:880-889, 1976
19. L'ABBATE A, BIAGINI A, MICHELASSI C, et al: Myocardial and blood kinetics of thallium-201 and potassium-42 in man at rest. Preliminary report. *J Nucl Med Allied Sci* 21:98-102, 1977
20. WINCHELL HS: Mechanisms for localization of radiopharmaceuticals in neoplasms. *Semin Nucl Med* 6:371-378, 1976
21. HILLE B: The permeability of the sodium channel to metal cations in myelinated nerve. *J Gen Physiol* 59:637-658, 1972
22. PROKOP EK, STRAUSS HW, SHAW J, et al: Comparison of regional myocardial perfusion determined by ionic potassium-43 to that determined by microspheres. *Circulation* 50:978-984, 1974
23. BARRERA H, GÓMEZ-PUYOU A: Characteristics of the movement of K^+ across the mitochondrial membrane and the inhibitory action of Tl^+. *J Biol Chem* 250:5370-5374, 1975
24. SELWYN AP, FOX K, SHILLINGFORD JP: Myocardial imaging with extractable cations and inert tracers: the effects of flow and metabolism. *Clin Cardiol* 1:60-67, 1978
25. ZARET BL, DICOLA VC, DONABEDIAN RK, et al: Dual radionuclide study of myocardial infarction.—Relationships between myocardial uptake of potassium-43, technetium-99m stannous pyrophosphate, regional myocardial blood flow and creatine phosphokinase depletion. *Circulation* 53:422-428, 1976
26. MAUBLANT J, GACHON P, MOINS N, et al: Myocardial imaging in dogs with thallium-201 and the ionophore grisorixin. *J Nucl Med* 21:787-789, 1980