Myocardial Kinetics of Thallium and Potassium in Man

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SUMMARY Myocardial and blood kinetics of thallium-201 (201Tl) and potassium-42 (42K) were studied in five patients with normal coronary angiography. A mixture of 400 μCi of 201Tl, 400 μCi of 42K, 50 μCi of iodine-125 radioiodinated human serum albumin as intravascular indicator, and 400 μCi of tritiated water (THO) as extravascular indicator was injected as a bolus into the pulmonary artery, and blood time-concentration curves were obtained from the aortic root and coronary sinus. These curves were numerically deconvoluted to obtain the frequency function of transit times (FFTT) of the four isotopes through the coronary system.

Initial maximal myocardial extraction of the two tracers were similar. The net maximal myocardial uptake of 201Tl per 100 g of tissue ranged from 1.0–2.7% of the injected dose and was positively related to myocardial blood flow (MBF) calculated from THO and to the ratio MBF/cardiac output (CO), while net uptake of 42K ranged from 1.4–2.4%, but was not correlated with MBF nor with MBF/CO.

The analysis of the FFTT indicates that 42K, but not 201Tl, is washed out from the myocardium more rapidly when MBF and the heart rate are higher. Thus, thallium appears to be a much more suitable agent than potassium isotopes for myocardial perfusion studies.

ISOTOPES OF POTASSIUM (42K, 42K and 38K in particular), potassium analogs such as rubidium-86, rubidium-84 and rubidium-81, and, lately, thallium-201 (201Tl) and other cationic tracers such as NH4+ are currently used for noninvasive assessment of regional myocardial perfusion in man. Their use is based on the fractionation principle described by Sapirstein,1 2 according to which the indicator that is totally or nearly totally extracted during the first pass can be used to estimate regional perfusion as a fraction of the cardiac output (CO). However, the information on the kinetics of these indicators and their behavior as a function of the ratio of myocardial blood flow (MBF) to CO is scarcely known. Animal studies indicate that thallium appears to be only partially extracted by the myocardium and to approximately the same extent as potassium.3 4 By contrast, the myocardial thallium content 10 minutes after the peripheral injection appears to be approximately twice as large as that of potassium.3 In man, thallium kinetics have been investigated by serial scintigraphy,6 7 which can provide only an integrated information on the compounded kinetics of the tracer in blood, pericardiac tissues and myocardium. These kinetics may have different time-courses and thus contribute to different extents to scintigrams obtained after the injection of the tracer.

This study in man was undertaken to derive information on 201Tl and 42K myocardial kinetics, as related to MBF and CO, from their frequency function of coronary transit times obtained by the indicator-dilution method.

Materials and Methods

Patients

Five male patients (ages 29–48 years) with atypical chest pain and no angiographic evidence of cardiovascular disease who were candidates for coronary sinus lactate determination during pacing were selected. The patients were studied after informed consent was obtained. The 201Tl kinetics study was performed in all patients, and the 42K kinetics study in four patients.

Experimental Protocol

All studies were performed under resting conditions about 30 minutes after completion of the diagnostic procedure. In one patient, the study was repeated during supine exercise (cycloergometer).

A mixture of the indicators (400 μCi of 201Tl* 400 μCi of tritiated water (THO†), 50 μCi of radioiodinated human serum albumin (125I RHSA‡) and 400 μCi of 42K§) was injected as a bolus through a polyethylene tube into the pulmonary artery. Concentration curves were obtained by intermittent sampling from the aortic root and the coronary sinus through two USCI 7.5 Sones catheters (80 cm in length, 1-ml internal volume) introduced percutaneously. In the resting studies, paired samples were obtained at 1.5-second intervals for up to 70 seconds by an automatic collector§ and manually at progressively longer intervals up to 30 minutes. In the exercise study, the injection was performed 5 minutes after the beginning of exercise (60 minutes after the control injection), and sampling was continued for 15 minutes during exercise.

Heart rate, pulmonary and aortic pressures,

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pulmonary and coronary arteriovenous oxygen (AV O₂) differences were determined immediately before the injection and at the end of sampling in order to check the presence of steady-state hemodynamic conditions.

Sample Processing and Counting

For samples, the injected dose and standard 0.6-ml aliquots were pipetted, made up to 8 ml with alcohol, sealed and counted for gamma radiations on a Nuclear Chicago Well Counter. The isotopes were separated by decay and by their energy level. Counting of 201TI and 125I RIHSA was performed after 42K decay to at least 0.4%. The contribution of 201TI to the 125I channel was 12%. The counting rates of potassium samples were not affected by the activity of adjacent samples despite their high-energy radiation. Beta counting was performed about 1 month later on 1-ml aliquots of the alcoholic fraction using a Hewlett-Packard Tricarb Counter after appropriate standard processing.

Data Processing

The data were corrected for background activity, isotopes decay and overlapping by a computer program. Arterial and venous concentrations of each isotope were expressed as a fraction of the injectate per milliliter of blood.

Analysis of Input and Output Curves

From the dilution curves, the following parameters were obtained:

Cardiac Output

CO was determined from the injected dose of 125I RIHSA and its primary extrapolated arterial dilution curve.

Blood Disappearance Rate of Thallium and Potassium

This was evaluated from the respective arterial curves up to 30 minutes after the injection at rest and up to 15 minutes during exercise.

Maximal Rate of Myocardial Extraction of Thallium and Potassium

This was estimated according to the method of Crone. For each indicator, maximal extraction was calculated on the ascending portion of the primary venous curves of 125I RIHSA, 201TI and 42K. It was expressed as the maximum value of the ratio I/I, where I was the 125I RIHSA concentration and I the 201TI or 42K concentration.

Myocardial Uptake of Thallium and Potassium

The time course of tracer myocardial uptake was estimated as:

\[ \text{MBF} \int_0^\infty (C_A(t) - C_V(t)) \, dt \]

which corresponds to the integrated AV coronary difference of each isotope as a percentage of the injectate, multiplied by the MBF/100 g of tissue estimated from the THO mean transit time (see below). It was expressed as a fraction of the injected dose/100 g of tissue. The time at which the amount of tracer not extracted by the myocardium during the first pass was exactly balanced by recirculating tracer was taken when

\[ \int_0^\infty (C_A(t) - C_V(t)) \, dt = \frac{1}{A_1} \]

where A₁ is the integral of the primary dilution curve extrapolated to infinity. Measurements of MBF by the fractionation principle should be taken at this time.

Calculation and Analysis of Frequency Function of Transit Times

The frequency function of transit times (FFTT) corresponds to the outlet response to a delta function input of each indicator at the coronary inlet in the absence of recirculation. FFTT was obtained from input and output curves that were linearly interpolated at 1.5-second intervals after the initial 47 samples, collected automatically. As expected, the numerical deconvolution of the input curve into the output curve resulted in large oscillations of the FFTT. These oscillations were smoothed by an iterative procedure until convolution of the smoothed function into the input curve produced a function adequately fitting the experimental output curve. Adequacy of the fitting was judged according to two arbitrary criteria: 1) a deviation of individual computed values from the experimental points smaller than ±5% for no more than five consecutive points, 2) a chi-square value not exceeding 7.

Tracer Recovery

Tracer recovery was calculated as

\[ \int_0^\infty h(t) \, dt \]

where h(t) is the value of FFTT at each time t. For 201TI and 42K recovery was calculated by extrapolation to infinity of the final slope calculated by the least-squares method, between 10 and 25 minutes at rest and between 8 and 15 minutes during exercise.

Residual Function

This function indicates the course of the permanence times of the indicator in the myocardium and coronary blood and was calculated as

\[ 1 - \int_0^\infty h(t) \, dt \]

where I is the amount of the tracer delivered to the
Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>BSA (m²)</th>
<th>HR (beats/min)</th>
<th>CO (l/min)</th>
<th>MBF (ml/min/100 g)</th>
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<tr>
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<td>48</td>
<td>1.80</td>
<td>103</td>
<td>12.4</td>
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<tr>
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<td>8.7</td>
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<tr>
<td>5 ex</td>
<td></td>
<td>156</td>
<td>15.6</td>
<td></td>
<td>260</td>
</tr>
</tbody>
</table>

Abbreviations: BSA = body surface area; HR = heart rate; CO = cardiac output; MBF = myocardial blood flow; ex = protocol repeated during supine exercise.

Figure 1. Time-concentration curves of iodine-125 radiiodinated human serum albumin (125I RIHSA), potassium-42 (42K), thallium-201 (201Tl) and tritiated water (THO) of patient 2: (A) in the aorta, and (B) in the coronary sinus. The concentration (C) is expressed as a fraction of the injectate (D). The arterial concentration of 125I RIHSA, 42K and 201Tl are similar during the first pass, while that of THO is more dispersed. Obvious differences are also present during the first minute in the coronary sinus, indicating wide differences in the accessible space.
coronary inlet as a delta function and the integral is the amount recovered at the outlet up to time \( t \). This function was computed because, being cumulative, it was scarcely influenced by possible residual oscillation of FFfT, and because it provided immediate information on the rate tracer washout from the myocardium.

**Myocardial Blood Flow**

The MBF/100 g of tissue was calculated from the mean transit time of THO as 0.88/t, assuming a blood/tissue partition coefficient equal to 0.88.

**Results**

**Hemodynamic Data**

None of the patients developed pain or significant changes in coronary AV lactate difference during the diagnostic pacing test.

The principal hemodynamic data for the five patients are presented in table 1. The hemodynamic measurements performed before and after each sampling period were remarkably constant, suggesting the presence of steady-state hemodynamic conditions.

The values of MBF/100 g of myocardium at rest was, on the average, 1.2% of CO, which would correspond to 3.6% of CO, assuming a left ventricular weight of 300 g, and showed a strong positive correlation with CO \(( r = 0.85; p < 0.02)\), with MBF/CO \(( r = 0.88; p < 0.02)\) and with heart rate \(( r = 0.97; p < 0.001)\). In turn, CO correlated well with heart rate \(( r = 0.80; p < 0.05)\).

**Coronary Input and Output Dilution Curves**

Illustrative curves of \(^{125}\text{I} \text{RIHSA, }^{42}\text{K, }^{201}\text{TI and THO from patient 2 are shown in figure 1; the standard errors of the peak venous samples were } 0.4-0.3\% \text{ for } ^{125}\text{I RHI}_{	ext{SA, 1.3-0.7\% for } ^{201}\text{TI, 1.3-0.8\% for } ^{42}\text{K and 1.0-0.5\% for THO. The standard errors for the last five arterial and venous samples, which had the lowest count rates, were } 0.9-0.7\% \text{ for } ^{125}\text{I RHI}_{	ext{SA, 13-3.7\% for } ^{201}\text{TI, 9.5-4.0\% for } ^{42}\text{K and 2.0-1.1\% for THO curves. Small but consistent differences were present in the arterial concentration of the four isotopes during the first passage, resulting from their different space of distribution in the lungs. Immediately after their primary dilution curves, } ^{201}\text{TI and } ^{42}\text{K concentrations showed a progressive and rapid fall relative to the reference tracers, indicating a retention in extravascular body space. } ^{201}\text{TI and } ^{42}\text{K activity in the arterial blood averaged, respectively, } 2.5\% \text{ and } 2.5\% \text{ of the injected dose per liter of blood at 2 minutes, } 0.8\% \text{ and } 0.7\% \text{ at 10 minutes, and } 0.4\% \text{ and } 0.3\% \text{ at 30 minutes. The time course of the arterial curves of } ^{201}\text{TI and } ^{42}\text{K was similar in all patients, but only during the first minute; after this time it showed individual variability, indicating individual differences in the relative total body extraction of the two indicators. Maximal Rate of Myocardial Extraction**

Figure 2 shows the initial myocardial extraction curves for \(^{201}\text{TI and } ^{42}\text{K. The maximal extraction values were } 91-81\% \text{ (mean } 87\%\text{) and } 90-77\% \text{ (mean } 85\%\text{), respectively, without consistent differences between the two tracers; these values did not correlate with the values of MBF. The rate of decrease of the } ^{201}\text{TI extraction values was smaller than that of the } ^{42}\text{K values, indicating that the } ^{201}\text{TI backflow from the extravascular space was smaller than that of } ^{42}\text{K during the initial 15 seconds.}
Myocardial Uptake

The net myocardial uptake of $^{201}$TI per 100 g of tissue (expressed as a fraction of the injected dose) tended to reach a plateau; that of $^{42}$K peaked earlier and then tended to decrease rapidly in all cases except the one with the lowest flow (fig. 3). The maximal uptake of $^{201}$TI ranged from 1.0–2.7% of the injected dose per 100 g of tissue and that of $^{42}$K from 1.4–2.4%. The values of myocardial uptake of $^{201}$TI at 2, 10 and 25 minutes after the injection correlated positively with MBF ($r = 0.87; p < 0.001$) and with MBF/CO ($r = 0.73; p < 0.001$), but, these correlations were not observed for $^{42}$K (fig. 4).

The amount of tracer not extracted during the first pass at rest was exactly balanced by recirculation at variable times after the injection (from 30–135 seconds for $^{201}$TI and from 75–240 seconds for $^{42}$K). This equality was never attained for $^{42}$K during exertion (figs. 3B and 3C). Maximum potassium uptake relative to the amount entered with the first pass was maximum at low flow (1.7 times) and lower at high flow (0.7 times) and showed a weak negative correlation with MBF and MBF/CO. Maximum uptake of thallium was 1.47–1.12 times greater than the amount that entered with the first pass, and did not correlate with MBF or MBF/CO.

Frequency Function of Transit Times

An example of the FFTT of the four indicators obtained from deconvolution of the input and output curves of figure 1 is given in figure 5. The peaks of the $^{201}$TI and $^{42}$K functions were intermediate between those of $^{125}$I RIHSA (the highest) and THO (the lowest). Only the downslopes of the $^{125}$I RIHSA and THO curves could be fitted by a single monoeponential shortly after the peak.

Tracer Recovery

The tracer recovery of the indicators was close to unity for $^{125}$I RIHSA (0.98 ± 0.038), THO (1.02 ±
Discussion

The information on thallium and potassium kinetics derived from the analysis of their coronary input and output curves was integrated by a more sophisticated approach based on the calculation and analysis of their myocardial FFTTs. The information derived from these two approaches will be discussed separately.

Coronary AV Curves

The arterial blood disappearance rate of thallium and potassium is very rapid and shows a remarkably similar time course, which is in agreement with previous observations.3, 5, 15, 16

The values of initial maximal extraction of thallium and potassium are similar to those obtained in animals.
Figure 6. Residual functions of potassium-42 ($^{42}$K) (upper panel) and thallium-201 ($^{201}$Tl) (lower panel). These curves represent the course of the permanence times of the indicator in the myocardium and coronary blood after a delta input in the absence of recirculation. Myocardial uptake of the indicators results from the convolution of the input at all successive times over this function. The two tracers are cleared from the coronary system in a similar fashion: a rapid initial rate followed by a slower one. However, both initial and final removal rates of $^{42}$K are consistently faster than those of $^{201}$Tl.

Figure 7. Exponential peeling of the residual functions shown in figure 6. Subtraction of the monoexponential fitting the final slope from the residual function resulted in a monoexponential curve for all potassium-42 ($^{42}$K) curves but one, suggesting that the kinetics of this tracer can be approximated by a two-compartment system. By contrast, peeling of thallium-201 ($^{201}$Tl) curves never results in a monoexponential course, suggesting a multicompartmental distribution of this indicator.
at rest. However, initial extraction of thallium does not appear to be influenced by the level of MBF, in contrast to the results in animals. This discrepancy may result from an increase in MBF in animals by vasodilation beyond, rather than in proportion to CO and/or to the oxygen demand, and partly from an inaccurate estimate of initial extraction at high flow rates because the sampling interval used was much larger than the coronary mean transit time.

In spite of the similarity of the values of their initial extraction and their arterial concentration, myocardial uptake of thallium and potassium was remarkably different, with a consistently lower uptake of potassium in all cases except the one with the lowest value of MBF. Further, while thallium showed a strong positive correlation with MBF and with MBF/CO, potassium uptake did not correlate with MBF. The correlation between MBF and myocardial thallium uptake is linear over the range explored, but the increase in thallium uptake is only about 40% of the increase in MBF and of the increase in MBF/CO. Because the values of MBF in our studies correlated strongly with those of CO, HR and MBF/CO, it is not possible to draw conclusions on the relative effect of these variables of myocardial uptake.

Information Derived from FFTT

We have analyzed the FFTT of potassium and thallium in terms of the residual function that provides direct, cumulative information on the way the tracer entering the coronary arteries at any given time is washed out. We found a considerably faster washout for potassium than for thallium, and a significant, positive correlation with the level of MBF. Thus, in the presence of similar arterial concentrations and initial extraction, the faster removal of potassium, particularly at high MBF values, accounts for the insignificant increase in potassium uptake with increasing MBF within the range explored (fig. 4). Because HR correlated strongly with the values of MBF, it is not possible to ascertain the relative role of MBF and the frequency of electrical activation of myocardial fibers in potassium release.

The difference between the two tracers appears to be related to a tissue trapping of thallium: although the residual function of potassium could be reasonably fitted by the sum of two exponential functions in all cases but one, the residual function of thallium always appeared to be multiexponential (fig. 7). Further, the incomplete recovery of thallium suggests that the final slope of its FFTT should be even less steep than that computed from the available experimental data.

Practical Implications

Measurement of MBF

The use of cationic tracers for the measurement of MBF as a fraction of CO requires that the fraction of indicator in the myocardium at the moment of the measurement should be proportional to the fraction of CO perfusing the organ. While this condition is met at any time for microspheres injected into the left side of the heart, for potassium and thallium it is met only at the time when the amount not extracted during the first pass is exactly balanced by the amount reentering the myocardium with the recirculation. Our findings indicate that this time is quite variable for both tracers
and that this equality is not maintained at rest and, for potassium, is not reached during exercise. Further, since this time occurs early after the injection, the intracardiac content of the tracer is still sizable\textsuperscript{10, 22, 23} and should be subtracted from external counting. Measurements taken at later times, when blood concentration is negligible, lead to an underdetermined, variable overestimate of the fraction of CO perfusing the myocardium at rest, while it may result in an underestimation during exercise when potassium is used.

**Regional Myocardial Perfusion Studies**

The aim of these studies is generally confined to the evaluation of differences of regional myocardial perfusion in different walls of the heart without an assessment of the absolute regional flow values.

The scintigraphic image can be considered as a result of the fraction of CO perfusing the myocardium relative to the fraction perfusing surrounding organs. In turn, myocardial uptake at any given time will result from the convolution of the arterial input curve (normalized for the ratio) MBF/CO, and the residual function.

Scintigraphic studies with \( \text{K}^{43} \text{K} \textsuperscript{22, 25} \) and \( \text{Tl}^{201} \text{TI} \textsuperscript{26, 27} \) have shown obvious differences of regional tracer uptake during exercise stress testing above anginal threshold in patients with ischemic heart disease; these findings are interpreted as diagnostic of the location and severity of myocardial ischemia. However, this interpretation of relative scintigraphic differences does not permit differentiation between a regional perfusion deficit due to an inadequate increase in regional myocardial perfusion and that due to an actual reduction of perfusion, as documented during stress testing by the xenon technique\textsuperscript{28, 29} and during spontaneous angina at rest by \( \text{Tl}^{201} \text{TI} \textsuperscript{7} \) thermodilution\textsuperscript{30} and by microspheres.\textsuperscript{31}

On the basis of our findings, an inadequate increase in regional myocardial perfusion during stress testing does not seem to be responsible for large differences in thallium and, especially, in potassium uptake. In fact, while myocardial perfusion increases in proportion to cardiac output, a 100% difference in the level of increase in MBF in two regions of the myocardium would result in no change in their potassium uptake and in about a 40% difference in thallium uptake. Further, a 40% difference of thallium uptake may be barely perceptible because of the likely overlapping of adjacent nonischemic areas. Thus, the massive cold areas occasionally detected in potassium and thallium scintigrams during exercise could be interpreted as the result of an actual severe reduction of perfusion to ischemic areas as demonstrated by the xenon technique,\textsuperscript{28, 29} rather than to an inadequate increase in regional perfusion.

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Pathologic Basis of Thallium-201 Scintigraphic Defects in Patients with Fatal Myocardial Injury

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SUMMARY Using a quantitative, computer-aided circumferential profile technique, we have shown that thallium-201 scintigrams with large defects can identify a group of patients with a high mortality after acute myocardial infarction. To determine whether high-risk thallium scintigrams predict poor survival because of a critical loss of myocardium, we correlated infarct size in 24 autopsied patients with the extent of thallium defect in three views. Of 13 patients with large defects (computer score ≥ 7.0) eight (62%) had > 25% loss of left ventricular (LV) myocardium, but five (38%) had smaller infarcts (4-24% of LV myocardium), suggesting that part of the scintigraphic defect was related to ischemia without necrosis. Eight of nine patients with loss ≥ 25% LV myocardium had large defects. In 10 of 11 patients with small defects (computer score < 7.0), infarcts involved < 20% of LV myocardium. Although scintigrams with large defects predicted a critical loss of myocardium in over 60% of our patients, they included an important second group, in which the scintigraphic defect appeared to reflect a small infarct and a large surrounding area of reversibly ischemic myocardium.

CLINICAL STUDIES have shown the usefulness of thallium-201 scintigraphy for predicting mortality after acute myocardial infarction, and it is generally assumed that this reflects large perfusion defects corresponding to large areas of infarction and therefore a poorer prognosis.1, 2 Although clinicopathologic studies are infrequent, the evidence suggests a high positive correlation between scan defect size and anatomic extent of infarction when the scan is performed within hours of the infarct. As a refinement of the thallium scintigraphic technique, we have applied a quantitative, computer-aided “circumferential profile” method to determine objectively a defect score.3 Using these quantitative scores, we found that initially hemodynamically stable (Killip class I-II) patients can be assigned to groups that are highly predictive of in-hospital and late mortality.2 Defect scores generally range from 0-20, with a score of zero representing no defect and scores above zero reflecting the amount of deviation from normal. Using this method, we have determined that patients can be divided into high-risk (score ≥ 7.0) and low-risk (score < 7.0) groups on the basis of thallium scintigrams obtained within 12 hours of admission, the former carrying a 46% in-hospital mortality and the latter a 3% mortality. The early scintigraphic score is more predictive of outcome than initial functional class, age, sex, history of infarction, location of the acute infarct or peak CK, taken either singly or in combination.6 The prognostic significance of this scoring system for patients with old myocardial infarcts has not yet been examined.

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