Effects of Heart Rate on Myocardial Thallium-201 Uptake and Clearance

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The effects of heart rate on the myocardial uptake and clearance of ^{201}Tl were studied prospectively in seven healthy men, mean age 43 ± 7 (s.d.) yr. Initial and delayed (3 hr) thallium images were obtained in three views after three bicycle exercise tests: to maximal, 80% and 60% of predicted maximal heart rate. The mean of three views initial myocardial ^{201}Tl uptake was higher at maximal than at both 80% and 60% of predicted maximal heart rate, being 81% ($p < 0.01$) and 60% ($p < 0.01$) of maximal activity, respectively. The myocardial activity in the delayed images was identical. There was a linear relationship between heart rate and the initial myocardial activity, $r = 0.86$ ($p < 0.001$). The mean (range) ^{201}Tl clearance was 58% (51–65), 47% (34–56), and 34% (22–49) (all differences $p < 0.01$), respectively. Concordance among the three individual views in estimating clearance was best for the highest exercise level. There was a linear relationship between heart rate and clearance, $r = 0.80$ ($p < 0.001$). Clearance was altered by only $1.67 \times 10\%$/heart bpm (0.024 hr/heart beat). Clearance in the liver, spleen and lungs increased at submaximal exercise levels. Thus, a linear relationship between heart rate and clearance is the result of changes in the initial exercise myocardial ^{201}Tl activity. Submaximal exercise may reduce reproducibility of clearance estimation, and the change of myocardial clearance with heart rate seems less than previously suggested.

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The interpretation of planar thallium-201 (^{201}Tl) images (*1–3*) to identify patients with coronary artery disease (CAD) may have a considerable inter- and intraobserver variation (*4*). Computer analysis with quantitation of the ^{201}Tl regional left ventricular clearance (*5,6*) has been shown to have a higher sensitivity and specificity for the detection of significant CAD (*7,8*). The diagnostic use of quantitation of clearance improves when the normal range is narrow. The peak exercise heart rate has been suggested to bear a positive relationship with thallium myocardial clearance (*9,10*). However, the analysis was done in a mixed population of patients on drug therapy and normal subjects, which may confer limitations to its interpretation. Furthermore, there is experimental evidence that a relationship between heart rate and thallium clearance is linked with variations in the initial exercise-related images (*11*), but this has not been quantitated in man.

Thus, we studied the initial ^{201}Tl myocardial uptake and clearance at three different exercise levels in healthy volunteers. The use of such subjects eliminates the influence of possible confounding variables that may be seen in patients, and has the advantage of having the subjects serving as their own controls.

METHODS

Subjects

Seven men were studied, with mean age 43 ± 7 yr, range 36–54 yr. None had evidence of cardiopulmonary disease as determined by history, physical examination, and a normal resting and exercise ECG. None participated actively in sports. Six had never been smokers, one smoked less than ten cigarettes a day. None had other risk factors for CAD. All were normotensive.

The subjects had a light lunch (bread and black coffee) between the initial and delayed images. None were performing any exercise between the initial and delayed registrations, they were mostly sitting or walking quietly about.

Bicycle Exercise

Three exercise tests in the upright position on a manually braked bicycle were performed. The initial work load was 50

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W, with subsequent increases of 50 W every 3 min. Exercise was carried out to exhaustion and maximal heart rate, and to 80% and 60% of predicted maximal heart rate (*12*).

An intravenous cannula was inserted before exercise. At peak exercise (or predetermined endpoint) 2 mCi of ^{201}Tl were injected intravenously, and exercise continued for 1½ min. At the two lowest exercise levels, the brakes were adjusted so as to keep the heart rate constant during the last 1½ min of exercise. The actual activity in the syringe was always controlled before injection to ensure an exact dose of 2 mCi of thallium. The injections were given by the same physician at all three exercise tests, and injected rapidly in one bolus.

Image Acquisition

Images were acquired using a Siemens Scintiview camera with a low-energy, all-purpose, parallel-hole collimator. Within 1–2 min of stopping exercise, imaging always began in the 45° left anterior oblique (LAO) view, thereafter in the 70-degree left lateral and anterior views. Delayed acquisition was done 3 hr later in the same projections. All images were acquired for 5 min.

The same collimator and gamma-ray equipment were used for all studies. The subjects were always strictly supine on a movable bench. The left ventricle was positioned in the center of the registration field using persistance mode before the imaging begun. Positioning was always carried out by the same two observers. The subjects were informed not to move during imaging, and were observed during the whole imaging period.

Image Analysis

Standard software computer programs commercially available from Siemens were used. Alignment of the initial and delayed images were carried out by the computer after manual region of interest (ROI) definition of the left ventricle. Thereafter a new ROI was carefully placed around the whole heart, avoiding its borders; especially the right ventricle, liver, and spleen; with subsequent automatic background subtraction, the major part of this being activity from the lungs. From these images, the outline of the left ventricle was again manually drawn in the initial image and exactly copied by the computer in the delayed, and the left ventricular activity and clearance derived. Clearance (%) was calculated as the initial minus delayed activity divided by the initial activity, multiplied by 100. All analyses were always done after background subtraction.

Activity in the liver and spleen were assessed only in the anterior view at the three exercise levels, since background subtraction was not used. Our use of the upper parts of the liver and spleen would be expected to result in different lung background activity in each particular view. Regions of interests were placed in a small area of the visible part of these organs, and copied from the initial to the delayed view. Lung activity was assessed in the same way in a peripheral lung field in the anterior view. Clearance was calculated at each exercise level.

Statistical Methods

Differences between means were tested using one-way analysis of variance. Coefficients of variation (%) between measurements were calculated as follows: the squared sum of the actual differences divided by the number of measurements gives the standard deviation for repeated measurements. This figure was divided by the mean of the measurements, and multiplied by 100. Simple linear regression analysis by the least squares method was used to assess correlations. p-Values < 0.05 were considered significant.

RESULTS

Reproducibility of Data

The calculations were done for clearance, since this measurement embraces both initial and delayed images. The coefficient of variation for determination of clearance from different views was generally acceptable, but was lowest for maximal exercise and increased to the views at 80% and further at 60% of maximal exercise (Table 1).

Exercise Level

The mean predicted maximal heart rate (range) was 177 ± 7 (166–184) bpm, and the maximal attained heart rate 183 ± 7 (range 170–190) (103% of predicted maximal). None of the subjects reached less than predicted maximal heart rate. The mean heart rate at 80% and 60% of predicted maximal was 142 ± 3 (140–145) and 106 ± 3 (102–110), respectively. The resting heart rate was 70 ± 4 (65–74) (40% of predicted maximal).

Myocardial ^{201}Tl Uptake

The mean initial myocardial activity for all three views in percent of the activity at maximal exercise was 81% ($p < 0.01$) and 61% ($p < 0.01$) at 80% and 60% of maximal exercise, respectively. The activity in the delayed images was 43% and 40%, respectively (N.S.), and 42% at maximal exercise (NS). The counts per pixel for the individual views were about similar at each level of exercise both in the initial and delayed images (Fig. 1). When the activity in the delayed views was expressed as a percentage of the initial view at each exercise level, this apparently increased from maximal to 80% and to 60% of maximal exercise (Fig. 1). However, this was solely because of the decrease in the initial counts.

TABLE 1
Reproducibility of Myocardial Thallium-201 Clearance

	Maximal exercise CV* %	80% of predicted maximal exercise CV %	60% of predicted maximal exercise CV %
LAO†/LLT‡	4.4	4.8	7.0
LLT/Ant.§	3.5	4.9	5.7
LAO/Ant.	5.2	5.8	8.5

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* Coefficient of variation.
† Left anterior oblique.
‡ Left lateral (70°) view.
§ Anterior view.

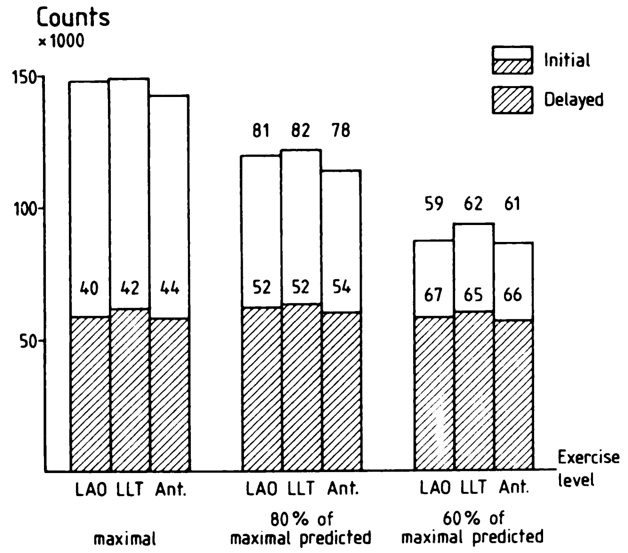

FIGURE 1

Left ventricular ^{201}Tl activity. Figures above columns: % of maximal exercise. Figures in columns: delayed in % of initial view. The initial activity is represented by the whole columns. LAO: left anterior oblique (45°) view. LLT: left lateral (70°) view. Ant.: anterior view.

There was a linear relationship between heart rate and the mean of three views initial left ventricular ^{201}Tl activity (counts per pixel), the correlation coefficient when all three exercise levels were pooled was $r = 0.86$.

The total myocardial activity before background subtraction was at the 80% and 60% exercise levels 93% and 86% of the activity at maximal exercise. The total delayed activity was identical at the three exercise levels.

Myocardial Clearance and Heart Rate

The mean myocardial clearance for all three views was 58%, 47%, and 34% at maximal, 80% and 60% of predicted maximal exercise respectively. The clearance rates for the individual views were not significantly different (Fig. 2).

There was a linear relationship between heart rate and the myocardial ^{201}Tl clearance, $r = 0.80$, $y = 3.30 X + 0.30$. Clearance changed 0.30% for each heart beat below the predicted maximal heart rate. There was a 180-min interval between the initial and delayed images, thus there was a change in clearance of 1.67 × 10%/heart bpm. Calculated 50% clearance (half-life) was at 2.6 hr, 3.2 hr and 4.4 hr from highest to lowest exercise level. This gives a change in half-life of 0.024 hr/heart beat.

Liver, Spleen, and Lung

The ^{201}Tl clearance in the liver, spleen and lung are shown in Table 2. Overall, the differences were the result of changes in the initial exercise levels, while the delayed were unaffected. All clearances were opposite to those of the myocardium, as they increased significantly at the two lowest exercise levels. Furthermore, lung clearance was higher than liver and spleen clearance at all exercise levels.

DISCUSSION

Initial ^{201}Tl Activity

Only the initial ^{201}Tl activity was influenced by exercise level. Previous clinical studies have been limited by using relative counts (*9,11,13*) instead of absolute counts per pixel as in our study, and therefore have not been able to evaluate the initial myocardial ^{201}Tl activity. In animal experiments, the myocardial ^{201}Tl activity is proportional to myocardial blood flow (*14–16*). The increased initial activity is probably associated with an increased delivery of ^{201}Tl to the myocardium, since the myocardial ^{201}Tl extraction fraction is relatively constant (*17,18*) over a wide range of heart rates. The myocardial blood flow is closely coupled with the myocardial oxygen consumption, which correlates with the product of heart rate and systolic blood pressure (*19*). Our subjects had a normal continuous blood pressure increase during exercise, and the product of systolic pressure and heart rate therefore does not improve the relation between initial ^{201}Tl activity and heart rate alone. Furthermore, noninvasive blood pressure measurements during exercise may be unreliable (*20*).

Delayed ^{201}Tl Activity

The delayed ^{201}Tl activity was independent of the magnitude of the initial activity at exercise levels above ~60% of maximal heart rate. There is experimental evidence that this could be a result of the intrinsic myocardial ^{201}Tl washout rate, which is proportional to the initial blood flow in animal studies (*17*). Therefore, a high initial activity seems to be followed by a proportionally rapid washout of ^{201}Tl.

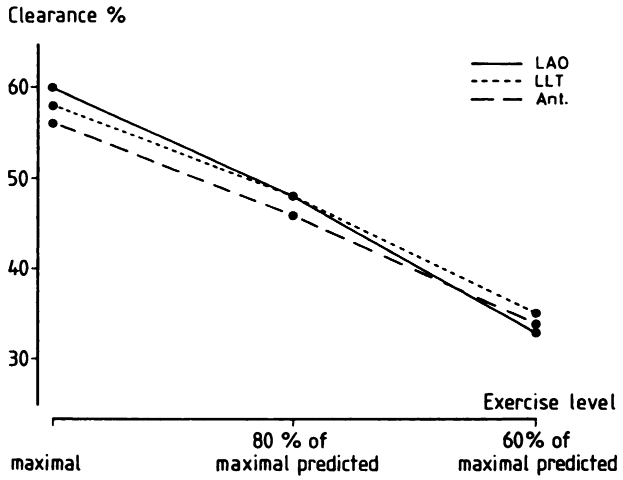

FIGURE 2

Left ventricular ^{201}Tl clearance. Abbreviations as in Figure 1.

TABLE 2
Thallium-201 Clearance (Range) in Lung, Liver, and Spleen

	Maximal exercise %	80% of predicted maximal exercise %	60% of predicted maximal exercise (%)
Lung	11 (3–18)*	24 (12–30)	35 (24–41)†
Liver	2 (−8–6)	10 (2–21)	18 (10–34)
Spleen	3 (−6–10)	9 (1–18)	22 (13–33)

* $p < 0.05$.
† $p < 0.01$ lung compared with liver and spleen.
$p < 0.01$ all differences between exercise levels for each organ.

Thallium-201 Clearance

The linear relation between heart rate and ^{201}Tl clearance is simple, and a correction of clearance based on this relationship easy to use. In our study, predicted maximal heart rate was a quite precise estimate of the true maximal heart rate, maximal being 103% of predicted maximal heart rate. In patients on various cardioactive drug therapy or with a pathological blood pressure response to exercise it may be more imprecise, and the relevance of a correction factor based on heart rate is more uncertain.

Our changes of clearance per heart beat are only about half that of a previous study in patients (*9*). Several factors may have contributed to the different results. The results in volunteers may not apply to subjects with disease, we did not study women who may have a different clearance (*21*), and upright bicycle exercise may not apply directly to treadmill exercise. Furthermore, confounding variables such as cardioactive drugs (*22*) and others that apply to patients were avoided in our study with volunteers serving as their own controls.

Reproducibility

The coefficient of variation for measurement of clearance from different views was lowest at maximal exercise (Table 1), that also had the highest total number of counts per pixel. It has also previously been shown that the reproducibility of the quantitation method improves proportionally with the ^{201}Tl activity (*7,8*). In this way, exercise heart rate influences reproducibility at fixed image acquisition time, or sensitivity (*7,8*) if acquisition time is prolonged. However, since high initial counts do not result in high delayed counts, the delayed activity views reduce reproducibility to a certain extent irrespective of the exercise level or image acquisition time.

Background subtraction is crucial in order to calculate an accurate clearance. We used automatic background subtraction to minimize observer bias, and this was probably of importance for obtaining the very similar clearances and coefficients of variation for the three views at each exercise level.

Lung, Liver, and Spleen

Clearance in these organs was highest at the lowest exercise level. The changes in clearance were caused by changes in the initial uptake. The longer blood transit time at low exercise levels could have been the mechanism behind this, as has been suggested to be important for the extraction of thallium in the lungs (*23*). The decrease in myocardial activity was much less before, than after, background subtraction at submaximal exercise. In view of the relatively modest thallium clearance in the liver and spleen compared with lung, lung activity constituted most likely the largest part of background subtraction at all exercise levels.

Clinical Implications

A correction of clearance based on heart rate is simple since the calculation of predicted maximal heart rate is widely used. However, the usefulness of this factor in patients on cardioactive drugs or with an impaired blood pressure response to exercise is uncertain. Other variables, such as systolic blood pressure, are unlikely to improve the clinical use of a correction because of imprecision in both measurement during exercise and predicted maximal values. Furthermore, the correction seems to be less than previously suggested, this may limit its clinical usefulness in patients in the upper ranges of submaximal heart rates, especially since there also is reduced reproducibility of the quantitation method at submaximal exercise levels. However, correction may be important when used to detect left main stem CAD, where many patients will have submaximal heart rates because of chest discomfort at very low heart rates.

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