Influence of Peak Exercise Heart Rate on Normal Thallium-201 Myocardial Clearance

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Measurement of myocardial clearance rates between initial and delayed images is a major justification for adding computer quantification to the interpretation of exercise ^{201}Tl images. To clarify the range of normal thallium clearance and its relationship to the level of exercise achieved, exercise thallium images in 89 normal subjects were analyzed: 45 asymptomatic subjects with <1% probability of coronary artery disease (CAD) (Group I), and 44 patients with chest pain found to have no significant CAD on angiography (Group II). Mean initial regional thallium uptake was similar in the two groups, but myocardial thallium clearance (mean ± 1 s.d.) was slower in Group II, expressed as a longer half-life in the myocardium (8.2 ± 7.6 hr compared with 3.4 ± 0.7 hr p <0.001). Analysis of variance using ten clinical and exercise variables as covariates showed that the slower clearance in Group II was related to a lower peak exercise heart rate (HR) (154 ± 27 compared with 183 ± 11, respectively, p <0.001). By linear regression analysis, a decrease in peak HR of 1 beat/min was associated with a slower thallium clearance (longer half-life) of 0.05 hr. Using this formula, the clearance value in each patient was then corrected for peak exercise heart rate by decreasing measured clearance by 0.05 hr multiplied by the amount peak exercise heart rate which was below 183 (the mean value in Group I). There were no differences in the "corrected" clearance between the two groups. We conclude that thallium myocardial clearance after exercise is related in part to factors other than the presence of CAD, being slower when peak exercise HR is lower. Therefore, thallium clearance rates alone uncorrected for peak exercise heart rate should be used with caution when diagnosing CAD.

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Exercise injected thallium-201 (^{201}Tl) imaging is widely used to identify patients with angiographically significant coronary artery disease (CAD) (*1–14*). The classic hallmark of CAD on an exercise thallium image is reduced initial myocardial uptake indicating a regional perfusion abnormality. Recently, slow thallium myocardial clearance has been suggested as a second imaging marker of CAD (*15,16*), although others have suggested that factors unrelated to coronary perfusion affect clearance rate (*13*). If initial uptake and clearance are useful variables in identifying CAD, their range in normals should be narrow.

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Although patients with no CAD by angiography have been used to define the normal exercise thallium scan, the selection bias in choosing which patients should undergo coronary angiography results in some of these patients having abnormal thallium perfusion images reflecting either false-positive scans or true abnormalities of coronary perfusion or coronary reserve which are not appreciated on the coronary angiogram (*9,10,17–19*). Clinically normal subjects with low probability of CAD are an alternative group from which to define the normal range (*20*). These subjects seldom undergo coronary angiography and their normality is inferred from their clinical status, not from their coronary anatomy. Nevertheless, patients from both groups constitute the normal population in comparison to patients with significant CAD, especially in terms of patient management and prognosis (*11*). The present

study analyzed both quantitative thallium uptake and clearance imaging variables in a large number of normal subjects with either <1% probability of CAD or no significant CAD by coronary angiography. The hypothesis to be tested is that these two "normal" populations have similar coronary perfusion so that any differences between them can be related in part to demographic differences, such as age, sex, medications, or the level of exercise achieved.

MATERIALS AND METHODS

Eighty-nine "normal" subjects who underwent maximal exercise testing in conjunction with thallium imaging were included in this study. They were divided into two groups: Group I was clinically normal and Group II was angiographically normal. Group I consisted of 45 subjects below age 45 referred for exercise evaluation and who had <1% likelihood of CAD before the thallium test (*20*). There were 39 males, six females, mean ± 1 s.d., age 38 ± 5 yr. All had a normal rest and exercise electrocardiogram and achieved at least 85% of their maximal predicted heart rate (220 minus age).

Group II consisted of 44 patients who had undergone cardiac catheterization and exercise thallium imaging within 2 wk of each other. There were 23 males, 21 females, age 52 ± 13 yr. Twenty of these patients were on cardiac medications, which were not discontinued for the exercise test. Thirty-one (70%) had ST segment depression at rest or exercise. All had no or <25% stenoses as judged by two independent observers. All patients had normal left ventricular wall motion and ejection fraction on biplane contrast ventriculography and a left ventricular end-diastolic pressure at rest of less than 13 mmHg.

All subjects underwent maximal treadmill exercise based on the Bruce protocol (*21*). During the procedure, heart rate, blood pressure, and the electrocardiogram were monitored by a cardiologist. At peak exercise, all patients were injected with 2.0 mCi of ^{201}Tl intravenously and encouraged to exercise for an additional 45 to 60 sec. The thallium imaging methods have been previously reported (*8,14*). Initial (5 min postexercise) and delayed (3 to 4 hr postexercise) images were collected in each of the three views, anterior, 50° left anterior oblique (LAO), and 70° LAO.

The computer method of quantifying thallium images has been described previously (*22-24*). Briefly, images were transferred to a minicomputer* by way of magnetic tape, which is interfaced with an image display system.† An elliptical region of interest (ROI) is placed around the left ventricle and the region corresponding to the valve planes is excluded. Subsequent steps of registration, background subtraction, and determination of regional thallium activity in the initial and delayed images are automatic. From these data, initial thallium uptake and clearance in five segments in each image are derived. The initial uptake is in relative units (100% = hottest 9-pixel region) and not in absolute counts. Myocardial thallium clearance rates are expressed as the tracer half-life presuming monoexponential washout from the myocardium (*25*).

Statistical Analysis

Differences between the mean segmental values in Group I compared with Group II variables were considered significant at $p < 0.01$ using a Neuman-Keuls multicomparison test. If a significant difference was found, then analysis of variance with covariates was performed to explain any possible reason for the difference. The covariates included age, sex, rest, and exercise heart rate and blood pressure, use of beta blockers, and duration of exercise. If a covariate correlated with the difference in a particular variable between the two groups, then linear regression was performed between the covariate and that variable. Then, a normal range was established based on the 2 s.d. range of values in Group I (clinically normal subjects). Those Group II (catheterized patients) outside this range were identified before and after correcting for the effect of covariates. Statistical software was used for analysis.‡

RESULTS

There was no significant difference in mean relative initial thallium uptake in any of the 15 segments between the two groups of patients (Table 1). In both

TABLE 1
Initial Regional Thallium Distribution (%)*

Item	Group I (n = 45)	Group II (n = 44)	p Value
Anterior view			
Segment 1	70 ± 8	70 ± 10	N.S.
Segment 2	91 ± 4	90 ± 6	N.S.
Segment 3	89 ± 5	87 ± 10	N.S.
Segment 4	87 ± 6	85 ± 11	N.S.
Segment 5	62 ± 8	62 ± 11	N.S.
50° LAO view			
Segment 1	73 ± 8	75 ± 12	N.S.
Segment 2	92 ± 4	92 ± 5	N.S.
Segment 3	87 ± 5	84 ± 9	N.S.
Segment 4	80 ± 5	79 ± 10	N.S.
Segment 5	65 ± 9	67 ± 15	N.S.
70° LAO view			
Segment 1	71 ± 6	74 ± 9	N.S.
Segment 2	90 ± 4	88 ± 9	N.S.
Segment 3	86 ± 6	83 ± 9	N.S.
Segment 4	90 ± 5	87 ± 9	N.S.
Segment 5	72 ± 9	76 ± 11	N.S.

* Values are mean ± 1 s.d.

TABLE 2
Myocardial Thallium Clearance (hr)*

Item	Group I (n = 45)	Group II (n = 44)	p Value
Anterior view			
Segment 1	3.6 ± 0.8	7.2 ± 6.8	<0.001
Segment 2	3.5 ± 0.7	6.4 ± 4.8	<0.001
Segment 3	3.2 ± 0.7	5.1 ± 7.2	<0.001
Segment 4	3.3 ± 0.6	8.1 ± 18.7	<0.001
Segment 5	3.4 ± 0.8	5.9 ± 4.0	<0.001
50° LAO view			
Segment 1	3.6 ± 0.9	6.5 ± 5.1	<0.001
Segment 2	3.3 ± 0.6	5.8 ± 4.6	<0.001
Segment 3	3.2 ± 0.6	6.2 ± 5.2	<0.001
Segment 4	3.4 ± 0.7	6.3 ± 4.8	<0.001
Segment 5	3.7 ± 0.8	10.0 ± 23.3	<0.001
70° LAO view			
Segment 1	3.4 ± 0.7	5.6 ± 3.0	<0.001
Segment 2	3.3 ± 0.5	3.5 ± 12.2	N.S.
Segment 3	3.1 ± 0.6	5.4 ± 2.6	<0.001
Segment 4	3.3 ± 0.6	5.7 ± 3.0	<0.001
Segment 5	3.6 ± 0.8	7.2 ± 9.2	<0.001

* Clearance values are mean ± 1 s.d. and expressed as half-life of thallium in myocardium in hours.

groups, mean activity in the basal segments (1 and 5) in each view was similarly lower compared to segments 2, 3, or 4, ($p < 0.01$), related to attenuation of the basal segments and their proximity to the inflow and outflow tract of the left ventricle. However, mean myocardial thallium clearance (expressed as the half-life of thalium in the myocardium) was slower in 14 of 15 segments in Group II ($p < 0.001$) and this is shown in Table 2. Overall thallium clearance for all segments was 3.4 ± 0.7 hr in Group I and 8.2 ± 7.6 hr in Group II, $p < 0.001$.

Using clinical and exercise parameters as covariates in all 89 subjects, peak exercise heart rate (HR) correlated with clearance (Fig. 1). No other variable improved this correlation and within each group, the correlation was not statistically significant. For a decrease in peak HR of 1 beat/min, clearance slowed (half-life increased) by 0.05 hr. Conversely, for an increase in peak HR of 1 beat/min, clearance was more rapid (half-life decreased) by 0.05 hr. Measured clearance values could then be "corrected" to any HR using the following formula:

$$\text{Corrected clearance} = \text{Measured clearance} - (0.05)(183 - \text{peak exercise HR}).$$

Peak exercise HR was 183 ± 11 in Group I and 154 ± 26 in Group II ($p < 0.001$). The mean peak HR in Group I patients, 183, was chosen arbitrarily as an ideal peak HR. After clearance values in Group II were "corrected" to this HR, there was no longer a significant difference in mean thallium clearance between the two groups. When normal clearance before "correction" was defined by the 2 s.d. range of values in Group I, 39 of 44 Group II patients had abnormal myocardial thallium clearance. After "correction" to a peak HR of 183, only ten Group II patients continued to have abnormal thallium clearance, compared to 39 before "correction."

DISCUSSION

The present study demonstrates that patients with chest pain and no significant CAD by coronary angiography have similar initial thallium uptake compared with clinically normal subjects, but they differ in terms of a slower myocardial thallium clearance. Although a slow thallium clearance has been suggested as a quantitative thallium parameter useful for detecting CAD (*15,16*) these data show that in our patients without CAD it correlated with peak exercise heart rate, a factor unrelated to the presence of CAD. This is similar to a previous study (*13*). This observation is consistent with the hypothesis that with greater levels of exercise and higher heart rates, there is increased flow of blood to the myocardium resulting in a higher initial delivery of thallium to the myocardium and a faster subsequent thallium clearance. Previous experimental data suggest that the clearance of thallium is related to the myocar-

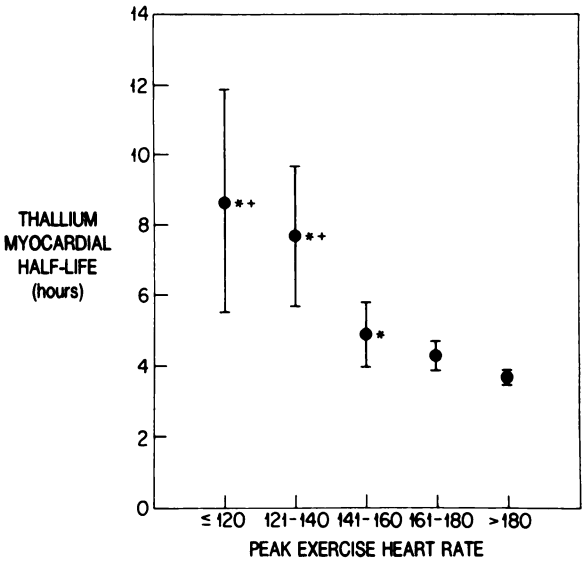

FIGURE 1
Relationship between thallium myocardial clearance (ordinate) compared with heart rate achieved at peak exercise (abscissa) in 89 normal patients. Thallium clearance is expressed as half-life of thallium in myocardium in hours. Values are mean ± s.e.m. (circles and bars). 89 patients are from two populations with two data points on right containing all Group 1 patients and two data points on left containing only Group 2 patients. * $p < 0.05$ compared with >180; † $p < 0.05$ compared with 161–180

dial blood-pool gradient of thallium activity such that delivery of a greater amount of myocardial thallium initially will result in its being cleared faster (*25*). However, our quantitation of thallium activity is in relative not absolute counts and, therefore, this cannot be proven from our data.

Because peak exercise heart rate may vary considerably in the population, we analyzed our data to provide a nomogram so that clearance data may be compared with normal (defined by Group I) even when the stress is not maximal. For each heart rate reduction by 1, normal clearance slows by 0.05 hr in terms of half-life of thallium in the myocardium. Of 44 patients with no CAD, 39 had an abnormal thallium clearance, as defined by Group I patients. However, "correction" of clearance to peak exercise heart rate placed 29/39 (74%) of the no CAD patients, who had lower peak exercise heart rate and who initially appeared to have abnormal myocardial thallium clearance, in a category with those having a normal clearance. Once the clearance in Group II patients was "corrected" for peak exercise heart rate, there was no longer a difference in clearance between Groups I and II. This suggests that peak exercise heart rate is one major variable explaining the differences in clearance observed. Nevertheless, ten (26%) continued to have abnormal "corrected" clearance. This is consistent with the occurrence of abnormalities of coronary perfusion in some of these patients and suggests that other factors present in patients with chest pain and no angiographic CAD may also affect clearance. Clarification of this issue awaits future studies.

Clinical Implications

Patients with chest pain and no significant CAD by angiography are a heterogenous group often showing abnormalities of thallium clearance in comparison to clinically normal subjects with <1% probability of CAD. Because the clearance of thallium to be anticipated in an individual patient depends in part on peak exercise heart rate, "correcting" clearance for peak exercise heart rate will help to determine whether a particular clearance value should be judged as normal or abnormal. Some patients with chest pain and no CAD by angiography, however, may still be abnormal, even after the effect of lower levels of exercise are considered in this manner.

In establishing the range of normal for exercise thallium imaging or possibly any test to detect CAD, the type of normal patient chosen will affect the results. If normal is defined by Group I subjects, the range of normal will be narrow and the sensitivity for detection of CAD will be high. As a result, some patients shown to have no CAD at coronary angiography will appear to be similar to those with CAD, which may produce an apparently poor specificity. Alternatively, if normal is defined by Group II patients, the range of normal will be wider and the specificity of determining CAD defined by coronary angiography will increase, probably at the expense of sensitivity. Therefore, a test for CAD needs to consider both sets of normal patients to define its true diagnostic value.

FOOTNOTES

* VAX 11/780, Digital Equipment Corporation, Maynard, MA.

† DeAnza Systems, Sunnyvale, CA.

‡ University of California at Los Angeles (BMDP, revised 1983), including programs P1D, P1R, and P2V.

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