Comparison of Myocardial Thallium-201 Clearance after Maximal and Submaximal Exercise: Implications for Diagnosis of Coronary Disease: Concise Communication

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Recently the quantitation of regional thallium-201 clearance has been shown to increase the sensitivity of the scintigraphic detection of coronary disease. Although Tl-201 clearance rates might be expected to vary with the degree of exercise, this relationship has not been explored. We therefore evaluated the rate of decrease in myocardial Tl-201 activity following maximal and submaximal stress in seven normal subjects and 21 patients with chest pain, using the seven-pinhole tomographic reconstruction technique. In normals, the mean Tl-201 clearance rate declined from 41% ± 7 over a 3-hr period with maximal exercise to 25% ± 5 after 3 hr at a submaximal level (p <0.001). Similar differences in clearance rates were found in the normally perfused regions of the left ventricle in patients with chest pain, depending on whether or not a maximal end point (defined as either the appearance of ischemia or reaching 85% of age-predicted heart rate) was achieved. In five patients who did not reach these end points, 3-hr clearance rates in uninvolved regions averaged 25% ± 2, in contrast to a mean of 38% ± 5 for such regions in 15 patients who exercised to ischemia or an adequate heart rate. These findings indicate that clearance criteria derived from normals can be applied to patients who are stressed maximally, even if the duration of exercise is limited, but that caution must be used in interpreting clearance rates in those who do not exercise to an accepted end point.

J Nucl Med 23: 381–385, 1982

Recently several groups have evaluated the rate of thallium-201 clearance—or "washout" over time—following exercise scintigraphy and have concluded that slow clearance is indicative of coronary artery disease (*1–3*). Based upon a group of subjects with a low likelihood of coronary artery disease, Garcia and co-workers (*1*) have established normal limits for the percent washout between the initial postexercise scintigram and the four-hour "redistribution" study. These workers did not evaluate the relationship between the clearance rate and the amount of exercise performed.

Thallium-201 is taken up by the myocardium in proportion to blood flow, and the level of exercise is an important determinant of coronary flow (*4–6*). The clearance of Tl-201 from myocardium is in part determined by the relative concentrations of Tl-201 in myocardium and blood (*7*). Therefore, the level of exercise might be an important determinant not only of the initial Tl-201 uptake but also of the kinetics of its subsequent clearance. Conceivably, patients who perform only a low level of exercise might have reduced washout rates unrelated to their coronary anatomy. Indeed, Watson and co-workers (*2,3*) noted a modest correlation between the

Received Nov. 2, 1981; revision accepted Jan. 11, 1982.

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initial postexercise myocardial Tl-201 concentration and washout rate. This group chose to consider only an increase in Tl-201 over time as indicative of disease, rather than to develop normal limits for washout.

To gain a better understanding of this problem, we quantitated Tl-201 washout in normal subjects following both maximal and submaximal exercise. We then examined the effect of the level of stress on Tl-201 washout rates in nondiseased regions in patients with chest pain, the majority of whom had angiographically proven coronary disease.

METHODS

Study subjects. The normal group consisted of seven middle-aged male volunteers (mean age 47, range 40–53) who were felt to be free of clinically significant coronary disease. All had negative histories and normal physical examinations, serum cholesterol levels, resting electrocardiograms, treadmill exercise tests (in which they exercised to or above age-predicted aerobic capacity) (*8*), resting blood-pool scintigrams, and supine exercise wall-motion studies (including a rise in ejection fraction of at least 10% with exercise).

The second group consisted of 21 male patients drawn from a series of 70 consecutive patients who underwent coronary arteriography and Tl-201 scintigraphy for evaluation of chest pain and who were chosen because they had identifiable cardiac regions that were clearly perfused by unobstructed vessels. Six of these had no significant coronary disease (as defined by a stenosis of >50% of luminal cross sectional area), nine had one-vessel disease, and six had two-vessel disease. Relevant clinical information on these patients is shown in Table 1.

Scintigraphic procedure. All subjects underwent treadmill exercise in the postabsorptive state according to the Bruce protocol (*8*). Our usual procedure is to continue exercise to exhaustion, limiting chest pain, serious arrhythmias, or electrocardiographic evidence of severe ischemia, but two patients were forced to stop before these end points because of calf claudication, two quit because of poor motivation, and a fifth exercised for 11 min but did not achieve either his age-predicted heart rate or exercise level (*8*). Approximately one minute before the termination of exercise, a bolus of 2 mCi thallium-201 was injected through an indwelling intravenous infusion line, and scintigraphy was begun within

TABLE 1. CLINICAL, EXERCISE, AND SCINTIGRAPHIC DATA IN PATIENTS WITH CHEST PAIN

Patient	Age	Coronary problem	Exercise duration (min)	% MPHR	HR × BP (× 10^3)	Exercise end point	ECG	Mean % washout
			GROUP I—submaximal exercise					
1	64	OVD	8.0	70	13	fatigue	negative	28
2	58	1VD	6.1	76	34	claud.	negative	23
3	47	1VD	5.2	60	17	claud.	negative	23
4	45	1VD	6.0	52	16	claud.	negative	25
5	31	1VD	11.0	59	17	fatigue	negative	25
			GROUP II—maximal exercise					
1	54	OVD	7.7	83	33	CP	negative	35
2	68	2VD	4.3	94	28	CP	positive	39
3	55	1VD	10.0	65	20	CP	negative	34
4	70	1VD	4.5	51	15	CP	positive	48
5	45	2VD	10.5	85	25	fatigue	positive	32
6	32	1VD	13.0	97	34	fatigue	negative	41
7	41	2VD	5.3	61	17	CP	positive	38
8	53	2VD	8.6	65	14	CP	positive	39
9	58	2VD	9.4	70	19	CP	positive	35
10	30	OVD	14.0	100	35	fatigue	L.B.B.B.	45
11	56	OVD	10.4	87	27	fatigue	positive	39
12	57	2VD	5.6	55	19	CP	positive	32
13	48	1VD	12.0	88	29	fatigue	negative	35
14	59	1VD	4.0	80	22	CP	positive	40
15	59	OVD	8.9	82	26	CP	negative	36
16	32	OVD	12.0	98	32	fatigue	negative	45

Abbreviations: %MPHR = percent maximum predicted heart achieved; HR × BP = product of heart rate and blood pressure; ECG = stress electrocardiogram results (positive or negative for ischemia); VD = vessel disease; claud. = claudication; CP = chest pain.

15 min of the completion of exercise. Normal subjects and patients then returned for "redistribution" scintigraphy. Care was taken to perform the follow-up scintigram as close as possible to 3 hr following the initial study, and in all cases the actual time of imaging did not vary by more than 20 min from the scheduled time. Patients were instructed not to engage in strenuous activity during the interim, but were permitted to have a light snack.

The seven normal volunteers returned after 2–4 wk for repeat studies. The same procedure was followed, but Tl-201 was injected one minute before half of the transpired time of the initial test and exercise was terminated at half the original exercise time.

Scintigrams were performed with a large-field-of-view gamma camera equipped with a seven-pinhole collimator, using methods described by Vogel et al. (*9,10*). Scintigrams were collected for 750,000 counts. Careful attention was paid to reproducing the initial patient and collimator positioning on repeat studies. A reconstruction algorithm similar to that described by Vogel was used (*9*). Twelve slices were reconstructed at 1.25-cm intervals, beginning at 7.5 cm from the collimator. Three slices, reflecting the apical, mid-, and basal left ventricle, were chosen for quantitative analysis. After the center of the left ventricle was manually chosen, circumferential profiles that displayed maximal pixel activity at six-degree intervals were generated for each slice as described by Vogel et al. (*6*). An approach similar to that of Garcia et al. (*1*) was adopted to quantitate Tl-201 clearance. Following normalization for duration of acquisition, the percent change in maximal pixel activity between the initial and delayed scintigrams was determined radian by radian. This change was displayed as percent washout in a similar 60-point circumferential profile for each slice (see Fig. 1). For each of the three ventricular slices, circumferential profiles indicating the 95% confidence limit for our laboratory's lower boundary of normal washout have been generated from a group of 15 normal subjects, including the seven normals discussed in this paper, and these were used in the evaluation of the 21 study patients.

RESULTS

Clearance rates in normal subjects at maximal and submaximal exercise. The duration of the initial exercise test was 12.5 ± 1.3 min. The maximum heart rate achieved was 95% ± 5 of the age-predicted 175 ± 11 b.p.m. All normal volunteers achieved at least 85% of age-predicted maximal heart rate, and 100% of predicted exercise duration, before discontinuing exercise due to fatigue. All had normal stress electrocardiograms. The mean and standard deviation for thallium clearance over 3 hr in this group are shown in the circumferential profile format in Fig. 1. Following maximum exercise, washout over the 3-hr period between images averaged 42% ±6 in the apical slice, 41% ± 7 in the midventricular slice, and 40% ± 7 in the basal slice, although there were minor regional variations.

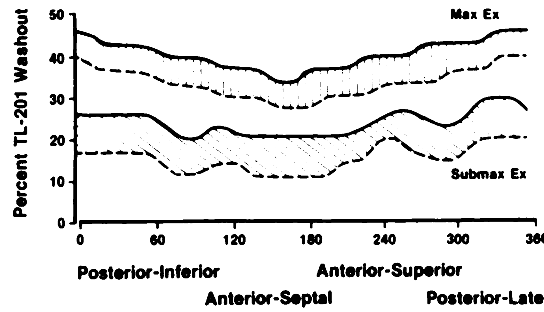

FIG. 1. Circumferential profiles, derived from a representative midventricular slice, showing mean myocardial Tl-201 clearance over 3 hr in seven normal subjects. Upper profile indicates clearance following maximal exercise: lower line the same following half-maximal exercise. Shaded areas below each profile represent one standard deviation below the mean.

The submaximal tests in normals were terminated after an average of 6.2 min. Clearance rates following submaximal exercise are also shown in Fig. 1. Each subject exhibited a reduced 3-hr washout at the lower exercise level, with means of 25% ± 8 for apical and midventricular slices and 24% ± 8 for the basal slice. These washout rates after submaximal exercise were significantly lower than those after maximal exercise ($p < 0.001$ by the paired t-test).

Clearance rates in patients with chest pain. Exercise measurements and clearance rates for the 21 studied patients are shown in Table 1. The mean 3-hr washout rate in anatomically uninvolved regions varied from 23% to 48%. No relationships were apparent between the washout rates in these apparently normally perfused regions and the duration of exercise, percent of predicted maximum heart rate achieved, or product of heart rate and blood pressure (linear regression correlation coefficients all below 0.10).

As noted previously, in five patients exercise was limited by claudication, motivational factors, or conditioning. They did not exercise to an ischemic end point (chest pain or positive stress electrocardiogram) or achieve 85% of their age-predicted maximum heart rate. Mean 3-hr clearance rates in apparently normally perfused regions in these individuals were lower than in any of the 16 patients who displayed an ischemic end point or achieved nearly maximal heart-rate response (25% ± 2 versus 38% ± 5, $p < 0.001$). All five of these patients exhibited washout profiles that fell below the 95% confidence limits of normal in regions that were uninvolved. In contrast, normally perfused regions in the patients who exercised maximally exhibited 3-hr washout rates that were not significantly different from those of normals (38% ± 5 versus 41% ± 7).

Figure 2 illustrates the importance of examining the

DIFFERENCES IN TL-201 WASHOUT IN 2 PATIENTS WITH RCA DISEASE

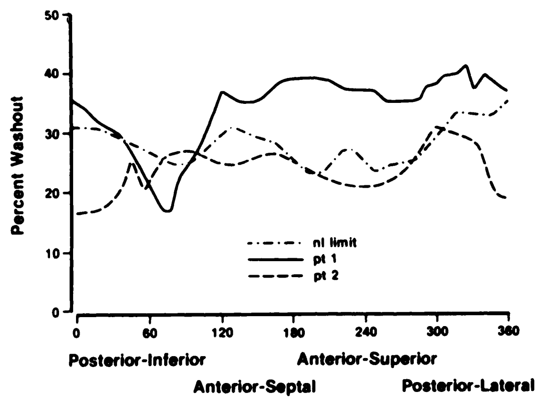

FIG. 2. Profiles from two patients with single-vessel right coronary disease. Patient 1 exercised only 5.3 min, to a heart rate of 116, before developing chest pain. He exhibited normal postexercise clearance in uninvolved regions. In contrast, Patient 2 exercised longer (6.1 min) but stopped because of claudication. His profile fell below our 95% confidence limits in normal subjects in areas clearly supplied by normal vessels.

exercise end point rather than exercise duration in evaluating clearance of thallium-201 from the myocardium. The first patient, who had single-vessel right coronary disease, had normal anterior and posterior wall washout, although he exercised only 5.3 min before stopping due to chest pain at a heart rate of 116 bpm. The second patient exercised 6.1 min but was stopped by claudication with a negative electrocardiogram and a heart rate of 111 bpm (60% of predicted). His washout pattern was abnormal in all regions, although he also had single-vessel right coronary disease.

DISCUSSION

While several groups have pointed out the potential value of thallium-201 regional myocardial clearance rates in the diagnosis of coronary disease (*1-3*), the role of the level of exercise in determining the rate of postexercise washout has not been considered. Thallium-201 is distributed in the left ventricle in proportion to myocardial perfusion (*4-6,11,12*). Blood flow in unobstructed vessels increases progressively with exercise (*6*). Although the rate of Tl-201 clearance from viable heart muscle is determined by multiple factors, it predominantly reflects the minute-by-minute myocardium-to-blood concentration gradient, and thus is also likely to be affected by the level of exercise (*7,13-17*).

Our findings in normals support this line of reasoning. Despite differences in scintigraphic technique, our mean 3-hr clearance rate in normals (41% ± 7) is similar to those reported by Garcia and Watson (*1,2*). Following submaximal exercise, however, this clearance rate is significantly reduced, and is often lower than the mean minus 2 s.d. for maximal exercise.

Our results in patients substantiate the clinical relevance of these findings. Patients who exercised submaximally also had reduced clearance rates in normally perfused regions. In contrast, patients who exercised to ischemia or to near-maximal heart rate, the clinically accepted treadmill end points, displayed normal washout in uninvolved regions. The mechanism for the relatively high clearance rates in these regions, despite sometimes very low levels of exercise, is unclear and, though of great interest, is beyond the scope of this paper. One can only speculate that coronary blood flow in these regions rises disproportionately to the level of exercise.

These findings have important clinical implications. If washout quantitation is to be used diagnostically, it is clear that confidence limits generated from normal subjects following maximal exercise can be applied only to patients who also exercise maximally. On the other hand, such normal limits appear to be applicable even with exercise durations as short as 4-5 min if an adequate exercise end point is achieved.

This study was not designed to compare tomographic and planar imaging or to evaluate the accuracy of quantitative tomographic scintigraphy. Our results do confirm the findings of a preliminary report by Berman et al. (*18*) that evaluation of Tl-201 washout over time can be accomplished with tomographic scintigraphy. It is likely, therefore, that this additional information will improve the sensitivity of the seven-pinhole technique, just as it has with planar imaging (*1,3*).

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