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# Effect of Exercise Position During Stress Testing on Cardiac and Pulmonary Thallium Kinetics and Accuracy in Evaluating Coronary Artery Disease

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We compared the effects of symptom-limited upright and supine exercise on  $^{201}\text{Tl}$  distribution and kinetics in the heart and lungs of 100 consecutive patients. Our analysis was based on data obtained with a digital gamma camera in the  $45^\circ$  left anterior oblique position at 5, 40, 240, and 275 min postadministration of [ $^{201}\text{Tl}$ ]chloride. We found significant differences in the results at the 5- and 40-min intervals; viz, (a) higher cardiac and (b) lower pulmonary thallium activity after upright exercise in 94 subjects at both intervals, and (c) greater variability in total and regional cardiac thallium kinetics after supine exercise. With supine exercise, the relatively low initial cardiac activity, relatively high lung activity, and the greater variability in thallium kinetics combined to make interpretation of quantitative data and cardiac images difficult and less accurate with respect to detection of coronary artery disease. These observations have important implications for the interpreting physician when thallium stress tests are performed in the supine position.

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**W**hile the upright position, either on a treadmill or bicycle, is traditionally used in stress exercise electrocardiography, deviations from this practice to the use of supine exercise on a specially designed table have occurred in nuclear medicine with respect to both ECG-gated radionuclide angiocardiology and thallium-201 ( $^{201}\text{Tl}$ ) stress testing. The relative ease of performing the imaging during, as well as after, the exercise, and the limitations of space for alternative exercise apparatus may have contributed to this practice. Observations that the frequency and magnitude of ECG changes with symptom-limited exercise in patients with coronary artery disease (CAD) are not greatly influenced by patient position (1,2) provide partial justification for this practice.

On the other hand, the pattern of cardiopulmonary circulatory dynamics is influenced significantly by the position of the individual during the exercise. Thus, when upright and supine exercise are compared, differ-

ences have been observed in pulmonary blood volume, interstitial water volume, lung transit time, cardiac stroke volume, filling pressures, maximum heart rate, and systolic blood pressure (3-9). These observations suggest that  $^{201}\text{Tl}$  localization and kinetics might also be significantly affected by exercise position. We therefore sought to compare the effects of supine and upright positions on these parameters in a series of patients referred for study of myocardial perfusion as part of an evaluation for the presence of coronary artery disease.

## MATERIALS AND METHODS

### Subjects

One hundred consecutive unselected patients were referred to the department for myocardial perfusion imaging as a part of a diagnostic evaluation for coronary artery disease. Ninety-four patients were referred because CAD was considered possible based upon clinical history and symptoms, and six patients were referred because they were asymptomatic runners who were concerned about the possibility of having a myocardial infarction while running. Mean age was 58 yr with a standard deviation of 10 yr.

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## Protocol

All patients were studied by both treadmill thallium testing (T) and supine bicycle ergometer testing (SB) in random sequence with an interstudy interval averaging 9 days (range 5–32). When possible, therapy with beta adrenergic antagonists was stopped 48 hr prior to the examination. Because of the necessity for treatment, nine patients were on beta-blocker therapy for both examinations and four patients began beta-blocker therapy between the examinations. For the treadmill testing, the patients were exercised following a standard or modified Bruce protocol; the modification consisted of allowing patients who had difficulty walking rapidly to perform an initial 3 min at Stage 0 (10). For the supine exercise, the patients began with a workload of 200 kpm, which was increased by 100–200 kpm every 3 min. The patients exercised until they reached an endpoint of severe fatigue, chest pain, or shortness of breath. A 12-lead ECG was recorded before exercise, at every level of exercise, and after exercise. Maximum heart rates (HR) and rate-pressure products (RPP) were also recorded. One minute prior to termination of exercise 1.5–2.2 mCi of [<sup>201</sup>Tl]chloride was injected intravenously. Imaging was begun 5 min after exercise for 10 min in each projection: 45° left anterior oblique (LAO), anterior, and 70° LAO (patient lying on right side) using a digital gamma camera. A repeat 45° LAO projection image was then obtained beginning at 40 min postexercise. A similar sequence of images was obtained beginning 4 hr after the tracer administration. All images were stored in the camera's computer using a 256 × 256 × 8 matrix.

## Image Processing

Circular regions of interest (ROIs) were drawn around the left ventricle (LV) in all views. A thin ring of background activity was then sampled outside of the LV with care being taken to exclude right ventricular myocardial activity. The background activity per pixel was approximated by a hyperbolic function using a best-fit algorithm:

$$\text{Background} = aX + bY + cXY + d,$$

where X and Y are spatial coordinates referenced to the center of the LV, and a, b, c, and d are best-fit constants derived by the computer.

The background was then subtracted from the left ventricular region. Circumferential thallium activity profiles were generated by computing the average thallium activity per pixel along radians from the LV center every 5°. Smoothed profiles from the immediate and delayed images were displayed on the same scale for interpretation of the examination.

Regions of interest were drawn over the mid-portion of the left lung (L) in the 5-min, 40-min, 240-min, and 275-min, 45° LAO views and thallium activity per pixel

was calculated. Total thallium activity in the LV after background subtraction was also calculated for the 45° LAO views. The lung and left ventricular data was then normalized to the dose of thallium administered.

## Evaluation for Coronary Artery Disease

The original images were viewed in gray scale and several color scales and compared with the processed images and activity profiles. In the activity profile interpretation, the regional changes in thallium activity between the immediate and delayed views were compared using the profiles. Areas, representing 1/8 or more of the myocardium, having a net reduction in activity per pixel between the early and delayed images which was <2/3 that of areas which appeared normal in the gray scale images were considered abnormal. If one or more such areas also appeared to have relatively increasing activity between the immediate and delayed images in the gray scale and color representations of the unprocessed images, the examination was considered positive for stress-induced hypoperfusion (Fig. 3).

EKGs were interpreted as positive if exercise induced ST segment depression >1 mm occurred.

Of the 100 total patients, 75 had independent evaluation for CAD. These consisted of seven patients who had <5% probability of CAD based upon age, clinical history, and stress ECGs (11) and 70 patients who had subsequent coronary arteriography. The arteriography was considered positive if stenotic lesions were present which reduced luminal diameter by >50%. Ten of the patients with CAD had infarcts in areas associated with narrowed coronary arteries. Because of reported variability in thallium kinetics in infarcts, they were excluded from analysis leaving a total of 65 patients for comparison of clinical accuracy of treadmill and supine exercise.

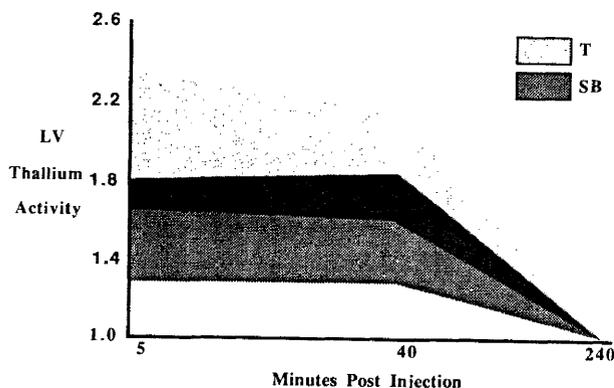
## RESULTS

### Cardiac Work

Data on maximum heart rates (HR) and rate-pressure products (RPP) for supine and upright exercise for the 96 patients who did not begin beta-blocker therapy between the two examinations is presented in Table 1. HR was significantly higher with treadmill exercise (92 of 96 patients had higher HR with T). RPP was also significantly higher with treadmill exercise, but the magnitude of the difference was less than that of HR because over half of the patients developed higher systolic blood pressures in the supine position.

### Thallium Kinetics

The left ventricular activity at 5 min (LV<sub>5</sub>) was compared with activity at 40 min (LV<sub>40</sub>), and the activity at 240 min (LV<sub>240</sub>) was compared with activity at 275 min (LV<sub>275</sub>) for each study. Mean LV<sub>240</sub> was not significantly



**FIGURE 1**  
Illustration of differences in early left ventricular thallium activity between supine and treadmill exercise. Shaded areas represent the mean  $\pm$  s.d. of LV thallium activity for both forms of exercise. Values are normalized to delayed activity. Treadmill exercise produced higher LV thallium activity at both 5 and 40 min postexercise. Early LV thallium activity was more variable after supine exercise, with several patients having large increases between 5 and 40 min

different than  $LV_{275}$  for both SB and T and is therefore referred to as delayed left ventricular activity,  $LV_d$ . The 5–40 min comparisons were more variable. Seven patients with treadmill exercise had  $LV_{40}$  values which were  $>105\%$  of the corresponding  $LV_5$  values (range 108–120%). All of these patients had severe CAD. With supine exercise, 16 patients had  $LV_{40}$  values which were  $>105\%$  of the  $LV_5$  values (range 107–160%). Of the 11 of these patients who had catheterization, eight had CAD, two had aortic stenosis, and one had cardiomyopathy.

Average  $LV_5$ ,  $LV_{40}$ , and  $LV_d$  values with treadmill exercise were compared with those of supine exercise. There was no significant difference for the  $LV_d$  values, but a very significant difference for the 5- and 40-min values ( $p < .001$ ) (Table 1 and Fig. 1). Compared with supine exercise, 93% of the patients had either higher  $LV_5$  or  $LV_{40}$  values with treadmill exercise.

Percent thallium myocardial washout (%MW) was defined following convention (17) and determined by comparing the total left ventricular activity measured

in the 5- and 40-min images with  $LV_d$  activity.

$$\%MW_5 = (LV_5 - LV_d)/LV_5 \times 100,$$

$$\%MW_{40} = (LV_{40} - LV_d)/LV_{40} \times 100,$$

$\%MW_m$  was defined as the maximum of the  $\%MW_5$  and  $\%MW_{40}$  values for each test. Data on  $\%MW$  for the 96 patients who did not begin beta-blocker therapy between the upright and supine tests is presented in Table 1. The differences in  $\%MW_5$  and  $\%MW_{40}$  between treadmill and supine exercise paralleled the differences in  $LV_5$  and  $LV_{40}$ . Of the 96 patients, 91 therefore had higher  $\%MW_m$  with treadmill exercise. The differences in  $\%MW_5$ ,  $\%MW_{40}$ , and  $\%MW_m$  between treadmill and supine exercise were correlated with various parameters including HR, RPP, maximum work load achieved, and maximum blood pressure. Difference in  $\%MW_m$  as compared with difference in maximum heart rate was found to have the best correlation. Figure 1 shows the relationship between differences in HR and differences in  $\%MW$  between treadmill and supine exercise. A best fit linear regression was found to be:

$$y = 0.47x + 1.6, \text{ where}$$

$$y = \%MW_m(T) - \%MW_m(SB),$$

$$x = 100 \times (HR_T - HR_{SB})/HR_{SB}, \text{ and}$$

$$R = 0.81.$$

The regression line passes near the origin, indicating that initial LV thallium activity, and thus  $\%MW$ , is related to HR rather than to the type of exercise. If patients were able to achieve the same HR for supine as upright exercise, they would therefore be expected to have similar values of  $\%MW$ .

Thallium activity in the pulmonary ROIs ( $L_5$ ,  $L_{40}$ ,  $L_{240}$ , and  $L_{275}$ ) was compared for the upright and supine exercise. Irrespective of the type of exercise, mean  $L_{240}$  and  $L_{275}$  values were not significantly different and are therefore referred to as delayed lung activity,  $L_d$ . Mean  $L_5$  and  $L_{40}$  values differed within T ( $p < 0.001$ ) and within SB ( $p < 0.001$ ), and  $L_5$  and  $L_{40}$  differed between ( $p < 0.01$ ) T and SB examinations.  $L_5$  values were higher than  $L_{40}$  values for all patients within each test; 80 patients had lower  $L_5$  values with upright exercise, and

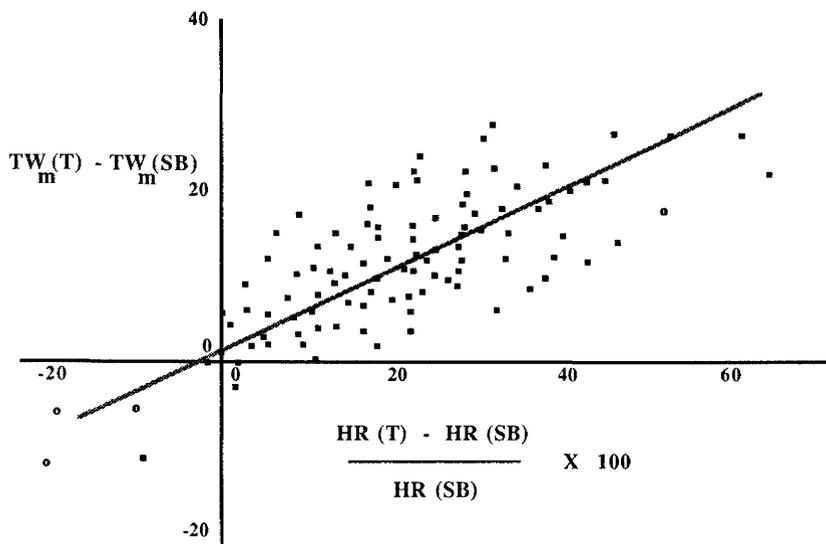
**TABLE 1**  
Maximum Heart Rates and Rate-Pressure Products for Supine (SB) and Upright (T) Exercise for 96 Patients Without Beta-Blocker Therapy

	HR	RPP	$LV_5$	$\%MW_5$	$LV_{40}$	$\%MW_{40}$	$L_5$	$\%PW_5$	$L_{40}$	$\%PW_{40}$
T	132	207	1.89	47	1.78	44	1.48	32	1.14	12
SB	108	178	1.48	33	1.49	34	1.67	40	1.28	22
Significance	.	†	.	.	.	.	†	†	†	†

•  $p < 0.001$  (paired t test).

†  $p < .01$ .

LV values are normalized to  $LV_d$ , L values are normalized to  $L_d$ .



**FIGURE 2**  
Relationship of differences in maximum heart rate to differences in %MW<sub>m</sub> observed between treadmill and supine exercise. Difference between %MW<sub>m</sub> for T and SB is plotted against % increase in HR of T referenced to that of SB. Open circles represent patients who began beta-blocker therapy between two examinations

78 patients had lower L<sub>40</sub> values with upright exercise, compared with supine exercise.

Values of percent pulmonary thallium washout (%PW) were computed from the thallium activity in the ROIs over the lungs and comparisons were made between 5- and 40-min values (Table 1).

$$\%PW_5 = (L_5 - L_d)/L_5 \times 100,$$

$$\%PW_{40} = (L_{40} - L_d)/L_{40} \times 100.$$

Because of its lower mean L<sub>5</sub> and L<sub>40</sub> values, treadmill exercise had correspondingly lower mean values of %PW<sub>5</sub> and %PW<sub>40</sub>. The decline in pulmonary thallium activity over time is essentially exponential (Fig. 3).

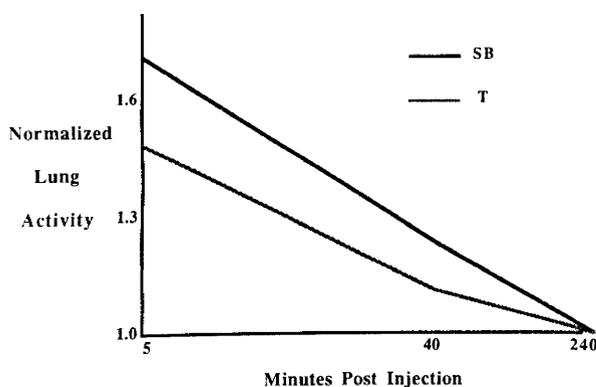
#### Accuracy in Evaluation of CAD

Of the 65 independently evaluated patients, 46 had and 19 did not have CAD. Forty-six treadmill scans were interpreted as positive for CAD, while 40 supine exercise scans were positive. Discordant scans results with respect to interpretation for CAD between tread-

mill and supine exercise occurred in 16 of the 65 patients. In 11 patients, areas of myocardium suggesting stress induced hypoperfusion were present in the treadmill examination but not in the supine examination, while the opposite occurred in five patients. Table 2 contains the results of the determination of CAD by the treadmill exercise and supine exercise compared for all patients who had independent evaluation. As can be seen, treadmill testing was significantly more accurate in evaluation of CAD, having statistically higher sensitivity and higher, though nonsignificantly so, specificity. ECG sensitivity was similar for upright and supine exercise. No false-positive ECG's occurred.

#### DISCUSSION

The present study shows an important difference between treadmill and supine bicycle ergometer exercise with respect to LV thallium activity in the early imaging period (5 to 40 min postexercise). LV thallium activity was consistently lower with supine exercise, especially at the 5-min interval. The average difference between maximum postexercise left ventricular thallium activity and left ventricular activity at 4 hr with treadmill exercise was 69% greater than the difference for supine exercise. Not surprisingly, therefore, the mean myocardial thallium washout, %MW<sub>m</sub>, with treadmill exercise (48%) was higher than with supine exercise (34%). We found that the thallium activity in the delayed images was the same for both modes of exercise. Lack of influence by type of exercise on delayed activity is expected and is consistent with the concept that such activity is influenced solely by the mass of viable myocardium and plasma concentration of thallium (12-14). The observation that maximum heart rates (HR) were significantly higher for treadmill exercise is in agreement with the results of previous studies (7-9). In fact, HR appears to be the major determinant of the



**FIGURE 3**  
Pulmonary thallium kinetics during supine and treadmill exercise. Lung activity in regions of interest from 5- and 40-min 45° LAO images, normalized to delayed values, is plotted against postinjection interval on logarithmic scale

**TABLE 2**  
**Determination of CAD by Treadmill (T) and Supine (SB) Exercise Compared for All Patients with Independent Evaluation**

	Sensitivity	Specificity	Accuracy	ECG Sensitivity
T	44/46 (95%)	17/19 (89%)	61/65 (94%)	26/46 (57%)
SB	36/46 (78%)	15/19 (79%)	51/65 (78%)	25/46 (55%)
Significance*	p < 0.05	N.S.	p < 0.02	N.S.

\* Chi-square with Yates correction for continuity.

difference in initial LV thallium activity between treadmill and supine exercise. Rate-pressure product differences correlated with %MW differences only because of the heart rate component. Other parameters such as total work performed did not correlate well with differences in maximum myocardial thallium activity or average myocardial thallium washout.

The exact cause of the observed correlation between differences in HR and differences in %MW is uncertain. Initial normal myocardial thallium activity is determined by the fraction of the cardiac output which passes through the coronary circulation, the amount of thallium which is temporarily retained by the lungs, and the amount which passes the noncoronary circulation and recirculates.

Those patients with high pulmonary washout during the 5- to 40-min interval showed increasing left ventricular thallium activity during that interval. This phenomenon was observed more frequently with supine (16 patients) than treadmill (seven patients) exercise. Catheterization studies showed that this was caused by CAD, cardiomyopathy, or aortic stenosis in supine exercise, and CAD in treadmill exercise. This is in agreement with previous studies which have shown that high values of pulmonary washout with supine exercise are associated with multiple vessel CAD (5), although our data indicates other cardiac abnormalities may cause this phenomenon. High values of %PW have also been shown to reflect CAD with treadmill exercise (15,16), and transient early increase in LV thallium activity during upright exercise has been reported as a rare occurrence which is highly specific for CAD (17). The presumed mechanism is exercise induced left ventricular failure with increased left atrial pressure, prolonged pulmonary transit time, and increased lung thallium extraction. During the early minutes following exercise, a portion of the thallium which is initially contained in the lungs could enter the myocardium. While we found that this lung activity interfered with the diagnosis of the presence and location of CAD, it might provide information on important functional parameters such as left atrial pressure.

Even in normal patients, supine exercise is likely to be associated with higher pulmonary blood volume and extravascular water volume than with upright exercise (4-6). The higher pulmonary blood volume increases

lung transit time, which has been shown to increase pulmonary thallium extraction in animals (5). The higher extravascular water volume and greater recruitment of capillary bed area (6) during supine exercise would tend to increase interstitial thallium activity compared with erect exercise.

The relatively high initial pulmonary activity, low myocardial activity, and the variability in kinetics associated with supine exercise make interpretation of such studies difficult. The basis for determining the presence of stress-induced myocardial hypoperfusion is detection of changes in the relative distribution of thallium in the heart between the early and delayed images, which must be interpreted in the presence of pulmonary background. The mean heart/lung ratio was 43% higher during the immediate postexercise imaging period with treadmill exercise compared with the ratio during the delayed imaging period. The corresponding ratios were equal for supine exercise.

The lower diagnostic sensitivity with supine exercise probably results from two major factors:

1. The lower initial myocardial thallium activity (probably a result of the lower maximum heart rate achieved) with supine exercise reduces the difference in thallium concentration between normally perfused myocardium and myocardium supplied by stenotic vessels. This makes the latter areas less obvious visually and reduces the magnitude of washout differences between the areas.

2. The higher initial pulmonary thallium activity with supine than with treadmill exercise which leaves the lungs and enters the systemic circulation while the patient rests. A portion of this activity is extracted by the myocardium, and areas of initially low activity in regions of myocardium affected by CAD may become partially or completely filled in from this lung pool as the patient rests. It is also possible that activity from other organs may contribute to this pool but this was not measured in this study. The lower sensitivity of supine exercise is largely responsible for the lower diagnostic accuracy of this exercise mode.

It should be noted that the method of image interpretation in this report differs from previous quantitative methods which usually assume a value of ~50% for %MW to be normal, without considering HR achieved (18,19). We had previously observed that

%MW was related to HR, with the 50% value occurring only when HR approached predicted maximum (22). We therefore identified for each patient regions of myocardium which visually appeared to have normal perfusion and defined calculated values of %MW for these regions as normal. While this helps prevent false-positive diagnoses in patients who achieve low maximum heart rates, it precludes the use of some specific amount of washout to define universally poor thallium uptake as might occur with balanced triple vessel disease. Thus, interpretation of this type of abnormality must be based on observation of a large discrepancy between measured thallium washout and that which is expected based upon maximum heart rate and previous observations. This phenomenon occurred in one patient who achieved a very high maximum heart rate with treadmill exercise (190) and had very low washout throughout the left ventricle with the exception of a small area near the junction of the free walls of the left and right ventricles. His washout after supine exercise was not dramatically different from typical normal values. Catheterization revealed left main disease, which had been predicted from the treadmill examination. Clearly, it would be desirable to develop a nomogram relating maximum heart rate, or some related parameter, to expected washout, but there were not sufficient numbers of patients in this study to do so.

The results of a number of thallium stress studies using supine exercise have been reported (15,20-23). Abnormal pulmonary thallium kinetics associated with CAD (15) and transient thallium defects which disappeared between 2 and 18 min postexercise (23) have been described, but without discussion of the problems likely to be incurred by extrapolating the conclusions to treadmill stress testing. A single case has been reported of a stress abnormality seen only during supine exercise (21). Another group has claimed that their results obtained with supine exercise for CAD evaluation were similar to those of others using upright exercise (15). In our earlier study, in which pulmonary and early cardiac kinetics were not measured, we concluded that treadmill testing was superior to supine exercise for CAD evaluation (22).

The observations in the present study are of particular importance to physicians who interpret images obtained using supine exercise. Supine exercise is not infrequently performed in clinical practice because of the convenience of using a supine exercise ergometer table which can be used for other scanning procedures, and because some patients who are unable to complete treadmill testing may be able to perform supine exercise. The images may be interpreted using criteria developed and validated for treadmill exercise without knowledge of the differences likely to be encountered with supine exercise. Many computer programs for quantitative thallium analysis make use of manufac-

turer-supplied patient data bases, and this study shows that users must consider exercise position and maximum heart rate achieved before applying such data bases to their patients.

## FOOTNOTES

\* Elscint (Apex 415 ECT), Boston, MA.

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