Correlates of Lung/Heart Ratio of Thallium-201 in Coronary Artery Disease

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We studied 306 patients with chest pain (262 with coronary artery disease and 44 with no coronary artery disease) to determine which of 23 clinical, exercise, thallium, and angiographic variables best discriminate between patients with increased lung/heart ratios of thallium versus those with normal ratios. Normal lung/heart ratio values were defined using an additional 45 subjects with <1% probability of coronary artery disease. The number of diseased vessels was the best discriminator between patients with increased ratios versus those with normal ratios. Double product at peak exercise, number of segments with abnormal wall motion, patient gender, and duration of exercise were also significant discriminators. Using discriminant function analysis these variables could correctly identify 81% of cases with increased lung/heart ratios and 72% of cases with normal ratios. These results indicate that an increased lung/heart ratio of thallium reflects exercise-induced left ventricular dysfunction and affords a better understanding of why this thallium parameter is a powerful prognostic indicator in patients with chest pain.

Increased lung thallium activity in coronary artery disease (CAD) was initially reported from our laboratory (*1*). Since then, we have found that this phenomenon correlates with exercise-induced elevations in pulmonary capillary wedge pressure, extent and severity of CAD, number of initial defects on thallium images, level of exercise achieved prior to injection of thallium, and propranolol use (*1–6*). Other investigators have also reported the occurrence of this phenomenon in patients with multivessel disease (*7,8*) and with pulmonary venous hypertension (mitral valve disease) in the absence of CAD (*9*). More recently, in a long-term follow-up study of patients with CAD, we found lung/heart ratio to be the most important thallium predictor of future cardiac events (*10*). Although the above variables have been separately correlated with lung/heart ratio of thallium, we performed this study to examine which variable(s) best correlate with this phenomenon and which discriminate between patients with increased

ratios versus those with normal ratios. This is the first study in which computer analyzed thallium parameters are correlated with lung/heart ratio of thallium.

MATERIALS AND METHODS

Patient Population

Three hundred and fifty-one subjects form the basis of this report. Forty-five subjects had <1% probability of CAD (Group I). They were <45 yr of age (mean age ± 1 s.d. = 38 ± 5 yr, 87% male), asymptomatic, had normal physical examination, and normal rest and exercise electrocardiograms. These patients did not undergo cardiac catheterization. Group II consisted of 306 patients (53 ± 10 yr of age, 82% male) who underwent cardiac catheterization and exercise thallium imaging for evaluation of chest pain. Of these, 44 had no CAD, 87 had one vessel, 85 had two vessel, and 90 had three-vessel disease.

Exercise Testing

All patients underwent maximal treadmill exercise testing using the Bruce protocol. Medications were not stopped prior to the exercise test (*11*). Baseline electrocardiogram (EKG), heart rate (HR), and blood pressure (BP) were recorded at rest and at each minute of exercise. Exercise was terminated when fatigue, angina, dyspnea, hypotension, or severe ventricular arrhythmias occurred. An abnormal exercise EKG was defined as one that exhibited a normal baseline ST segment and

demonstrated significant ST segment depression on exercise (12). Exercise EKGs were considered nondiagnostic if: (1) the EKG was normal but the patient had not achieved ≥85% of maximal predicted heart rate (13); (2) if baseline ST segment depression, left ventricular hypertrophy, or left bundle branch block were present (14); or, (3) if the patient's medical regimen included a digitalis preparation at the time of the study (15). An exercise BP response was considered abnormal if the systolic BP fell or failed to increase at peak exercise.

Thallium Imaging

At peak exercise, 2.0 mCi of thallium-201 (^{201}Tl)* was injected intravenously and the patient was encouraged to exercise an additional 30–60 sec. Initial and delayed images were acquired in the anterior, 50 degree left anterior oblique (LAO), and 70 degree LAO projections using previously reported methods (16). Computer analysis of thallium images was performed on a VAX 11/780† interfaced to a frame buffer.‡ The method has been described in detail previously (16). In brief, the observer places a region of interest around the left ventricle following which registration, background subtraction, and determination of average segmental thallium activity in each view as a percentage of the hottest 9-pixel region in that view, are performed automatically. From these data, presence or absence of defects, redistribution, and abnormal clearance are derived, based on data obtained from normal group I subjects with <1% probability of CAD (16). In our method, redistribution and abnormal clearance are not similar. For determining the presence or absence of redistribution, the computer utilizes an algorithm that simulates the visual assessment of redistribution (16), whereas, clearance is determined as the half-life of thallium (in hours) in the myocardium and considered abnormal if it is slower by 98% or more compared with the fastest clearing segment in the same heart (17). The lung thallium activity was measured using a region of interest method, and expressed as a fraction of the activity in the hottest myocardial segment in the initial image (lung/heart ratio), as previously reported and illustrated in Figure 1 (2).

Cardiac Catheterization

Coronary artery disease during coronary arteriography was defined as a 50% or greater luminal narrowing of one or more major coronary arteries or their major branches, based on the average score of two experienced, independent observers. The major branches included the major diagonal branch of the left anterior descending coronary artery, the obtuse marginal branch of the left circumflex coronary artery, and the posterior descending branch of the right coronary artery in a right dominant system, or left circumflex coronary artery in a left dominant system. In 14 patients, a ramus intermedius artery was present and was considered equivalent to the major diagonal branch of the left anterior descending coronary artery. Left-ventricular ejection fraction (LVEF) was calculated from the right anterior oblique (RAO) view of the left ventricular angiogram using the modified Dodge equation (18). For analysis of wall motion, two independent blinded observers divided the left ventricle in the RAO view into three segments (anterolateral, apical, and inferoposterior) (19). Wall motion was subjectively scored as: 0 = normal, 1 = hypokinetic, 2 = akinetic, 3 = dyskinetic. For this study, abnormal wall motion
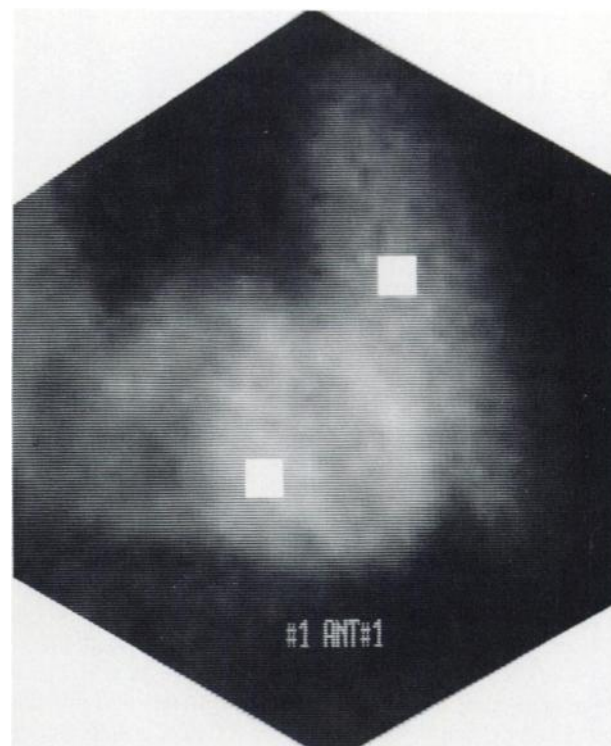
FIGURE 1
This figure illustrates the method of defining the region of interest over the lung and the left-ventricular myocardium to determine lung/heart ratio of thallium. In this example of a patient with multivessel disease, the ratio is increased to 0.69. The right ventricle also appears to be prominent, which suggests right-ventricular hypertrophy secondary to pulmonary hypertension, resulting from episodic exercise-induced pulmonary edema.

was defined in a segment with a score of 1–3; differences in opinion were settled by consensus.

Data Analysis

We analyzed the relationship between lung/heart ratio of thallium and various variables in Group II patients in two steps. First, we performed a multiple, all possible subset regression analysis based on the Furnival–Wilson algorithm to determine which variables correlated with lung/heart ratio of thallium (20). This analysis estimates regression equations for best variables where best variables are defined by their r^2 values. Twenty-three clinical, exercise, thallium, and angiographic variables were correlated with lung/heart ratio of thallium (Table 1).

Once the variables with significant correlations were identified, they were analyzed using stepwise discriminant function analysis to determine: (a) which of the significant variables actually discriminated between patients with increased lung/heart ratios of thallium compared with those with normal ratios; and, (b) how well these variables discriminated between increased and normal lung/heart ratios of thallium (21). For this analysis, lung/heart ratio was expressed as either increased or normal. Normal values of lung/heart ratio of thallium was derived from Group I asymptomatic subjects with <1% probability of CAD. Lung/heart ratio was considered to be abnor-

TABLE 1
Variables Analyzed for Correlation with Lung/Heart Ratio of ^{201}Tl

Clinical
   Age
   Patient gender
   Previous myocardial infarction
   Use of beta blockers
   Presence of clinical heart failure
   Use of digitalis and/or diuretics
   Smoking
Exercise
   Mean ST segment depression on the electrocardiogram
   Peak exercise heart rate
   Change in HR from rest to peak exercise
   Peak exercise systolic BP
   Change in systolic BP from rest to exercise
   Abnormal BP response (fall or failure to rise)
   Peak exercise double product
   Change in double product from rest to exercise
   Duration of exercise
   Angina during exercise
Thallium
   Number of segments demonstrating initial defects
   Number of segments demonstrating redistribution
   Number of segments demonstrating abnormal clearance
Angiographic
   Number of vessels showing significant coronary stenosis
   Left-ventricular ejection fraction at rest
   Number of segments demonstrating abnormal wall motion
   (right anterior oblique projection)

TABLE 3
Results of Stepwise Discriminant Function Analysis

Variable entered	F Value	p Value
Number of diseased vessels	47.99	<0.001
Peak double product	19.34	<0.001
Number of segments with abnormal wall motion	8.80	<0.01
Patient gender	7.19	<0.01
Duration of exercise	5.77	<0.01

mal if it was greater than mean ± 2 s.d. of the value in this normal group.

RESULTS

Group I Subjects

The lung/heart ratio of thallium in asymptomatic normal subjects (Group I) was 0.37 ± 0.07. Based on these data, lung/heart ratio in Group II patients was considered abnormal if it was >0.51.

Group II Subjects

The multiple all subset regression analysis demonstrated that nine of the 23 variables had significant correlations with lung/heart ratio of thallium. The significant variables with the individual regression coefficients, standard errors of the estimate, p value, and contribution to the multiple correlation are shown in Table 2. The contribution to the multiple correlation is the amount by which r^2 would be reduced if the variable were removed from the regression equation. The multiple correlation using all these variables was significant ($r = 0.65$, $p < 0.0001$, s.e.e. $= 0.11$).

As can be seen in Table 2, female sex, peak double product, LVEF at rest, and duration of exercise correlated inversely with lung/heart ratio of thallium, whereas, the number of segments demonstrating abnormal wall motion, number of segments demonstrating redistribution, presence of a previous myocardial infarct, the number of diseased vessels, and presence of clinical heart failure correlated positively with lung/heart ratio of thallium.

When these nine variables were analyzed using stepwise discriminant function analysis, only five discriminated between patients with increased lung/heart ratios and those with normal ratios. The most important discriminator was the number of diseased vessels, followed by the peak double product. The other three variables were the number of segments demonstrating abnormal wall motion at rest, patient gender, and duration of exercise. Together, these variables were able to correctly discriminate between 157 patients with increased lung/heart ratios and 149 patients with normal lung/heart ratios in 76% cases. Patients with increased lung/heart ratios were correctly identified in 81% cases, whereas, those with normal ratios were

TABLE 2
Results of All Possible Subsets Multiple Regression Analysis

Variable	Regression coefficient	s.e.e.	p Value	Contribution to r^2
Patient gender	−0.071	0.019	0.000	0.032
Number of segments with abnormal wall motion	0.025	0.007	0.001	0.027
Peak double product	−0.411 e^{-5}	0.134 e^{-5}	0.002	0.022
Left-ventricular ejection fraction	−0.001	0.000	0.008	0.016
Old myocardial infarct	0.042	0.016	0.010	0.015
Number of segments with redistribution	0.015	0.007	0.025	0.011
Number of diseased vessels	0.017	0.008	0.032	0.010
Duration of exercise	−0.006	0.003	0.037	0.010
Presence of clinical heart failure	0.098	0.050	0.052	0.009

correctly identified in 72% cases. The variables selected and F value for entering the model are shown in Table 3.

DISCUSSION

Increased lung activity of thallium is related to increased transudation of interstitial fluid into the lung at the time of injection of thallium. Thus, in the context of CAD, it would imply that during exercise, lung water content increases probably as a result of increased pulmonary capillary pressure resulting from ischemic left ventricular dysfunction. We have previously shown that lung thallium activity increases in dogs in whom left atrial pressure is increased (3). We have also demonstrated that increased lung thallium activity is seen in patients with CAD who increase their pulmonary capillary wedge pressure during supine exercise (2). We have reported in separate studies that lung/heart ratio of thallium is related to several rest and exercise variables in patients with CAD (1-6). The present study was performed to determine which rest and exercise variables had the best correlation with lung/heart ratio of thallium and which variables best discriminated between patients with increased and normal lung/heart ratios. In addition, this study was performed using computer-analyzed thallium variables.

Variables that Correlate with Lung/Heart Ratio of Thallium

Our results demonstrate that several variables correlate positively with lung/heart ratio of thallium. Of these, the number of diseased vessels is the best discriminator between patients with increased ratios versus those with normal ratios. Another independent discriminator that correlates positively with lung/heart ratio of thallium is the number of segments demonstrating abnormal wall motion at rest. The variables that have significant positive correlations with lung/heart ratio of thallium but are not independent discriminators between increased and normal ratios are the number of segments demonstrating redistribution, the presence of a previous myocardial infarction, and the presence of clinical heart failure. Most probably, once the number of diseased vessels was incorporated into the model, these other variables were suppressed because they are weaker identifiers of the same phenomenon. The variables that did not demonstrate any relationship with lung/heart ratio in this study include the number of segments demonstrating initial defects, the number of segments demonstrating abnormal clearance, presence of angina or ST segment depression on exercise, abnormal BP response on exercise, beta blocker therapy, digitalis and/or diuretic therapy, and smoking.

The variables that have a negative correlation with lung/heart ratio of thallium and that discriminated between increased and normal lung/heart ratio were the double product at peak exercise, duration of exercise, and female sex. Although abnormal LVEF at rest also had a negative correlation with lung/heart ratio of thallium, it did not discriminate between normal and increased ratios.

These data are in agreement with the concept that increased lung/heart ratio of thallium reflects exercise-induced left-ventricular dysfunction. Double product at peak exercise and duration of exercise, which in the present study were independent discriminators between patients with normal and increased lung/heart ratios of thallium, are indirect indicators of exercise-induced left-ventricular dysfunction (22). It has also been demonstrated that exercise-induced left-ventricular dysfunction is seen more often in patients with multivessel disease compared with single vessel disease (23). Therefore, it is not surprising that the number of diseased vessels was the best discriminator between patients with normal and increased lung/heart ratios of thallium. Presence of prior myocardial infarction, number of myocardial segments demonstrating abnormal motion at rest, abnormal rest LVEF, and presence of clinical heart failure also correlate with increased lung/heart ratio of thallium, indicating that this phenomenon may also be seen in patients with poor left-ventricular function at rest. The number of segments demonstrating redistribution also showed a positive correlation with lung/heart ratio of thallium, implying that the extent of global left-ventricular dysfunction on exercise is probably related to the quantum of myocardium demonstrating ischemia during exercise.

Variables that Do Not Correlate with Lung/Heart Ratio of Thallium

Although the HR and systolic BP at peak exercise did not independently correlate with lung/heart ratio of thallium, double product at peak exercise did, suggesting that the combination of HR and systolic BP reflects exercise-induced left-ventricular dysfunction, rather than either alone. Although the presence of ST segment depression, angina during exercise, and number of segments demonstrating abnormal clearance did not correlate with lung/heart ratio of thallium, the number of segments demonstrating redistribution did, suggesting that redistribution is perhaps a better marker of ischemia than these other variables (24). In addition, although the number of segments demonstrating initial defects did not correlate with lung/heart ratio of thallium, presence of a prior myocardial infarction, number of segments demonstrating abnormal wall motion at rest, and LVEF at rest did, implying that these latter parameters may better reflect left-ventricular function at rest.

The only other parameter previously shown to correlate with lung/heart ratio not found to correlate with this phenomenon in the present study was the use of

beta blockers (6). In that study, however, only normal subjects were evaluated. It is probable that in patients with CAD other variables are stronger correlates of lung/heart ratio of thallium. We have previously been unable to demonstrate a correlation between the sex of the patient and lung/heart ratio of thallium (6). In the present study, however, we found a negative correlation between female sex and lung/heart ratio, probably related to attenuation of thallium in the lung caused by overlying breast tissue. In conclusion, we feel that these data afford a better understanding of the value of measuring lung/heart ratio during exercise thallium imaging, especially when it has been demonstrated to be the single best thallium predictor of cardiac events in patients with chest pain (10).

NOTES

ACKNOWLEDGMENTS

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