Diagnosis of Extensive Coronary Artery Disease: Intrinsic Value of Increased Lung ^{201}T1 Uptake with Exercise SPECT

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Exercise lung ^{201}Tl uptake calculated with planar imaging has an important diagnostic and prognostic value in patients with coronary artery disease (CAD). However, its value with SPECT imaging raises methodological concerns and is controversial. We studied its value for the discrimination between extensive (E) and limited (L) angiographic CAD with exercise SPECT. **Methods:** Four methods of lung-to-heart ratio quantification were calculated in patients with a low likelihood (< 5%) of CAD (n = 62). Their dependent variables were defined, and corresponding correction equations were derived. Receiver operating characteristic (ROC) analysis was performed in a pilot group (L-CAD, n = 49; E-CAD, n = 126) to define the optimal method of calculation of the lung-to-heart ratio. Its best threshold providing the best sensitivity for a specificity of 90% was defined. After correction for dependent variables, the 4 methods were also compared by ROC analysis and the optimal corrected method was compared with the optimal uncorrected method using ROC analysis and the best threshold. The consistency of these results in the validation group (L-CAD, n = 41; E-CAD, n = 122) and of the results of visual analysis of lung ^{201}Tl uptake were then verified. **Results:** On ROC analysis in the pilot group, the optimal method of calculation of the lung-to-heart ratio was the mean activity in a region of interest drawn at the base of the lungs to the mean activity over the heart (L_b/H). For the best threshold, L_b/H presented a sensitivity of 34%. Corrected L_b/H still remained the best method of calculation on ROC analysis compared with the other corrected methods. On ROC analysis, there was no difference between corrected and uncorrected L_b/H. For the best threshold, corrected L_b/H presented a similar sensitivity of 37% compared with uncorrected L_b/H. When applied to the validation group (L-CAD, n = 41; E-CAD, n = 122), the best-defined threshold in the pilot group for corrected L_b/H presented a diagnostic value similar to that in the pilot group (sensitivity, 41%; specificity, 90%), but uncorrected L_b/H presented a higher sensitivity (47%; $P < 0.04$) and a slightly lower specificity (80%). Results of lung ^{201}Tl uptake visual analysis were inconsistent between pilot and validation groups (42% versus 58% sensitivity, $P = 0.012$; 86% versus 66% specificity, $P = 0.023$). **Conclusion:** For evaluation of E-CAD versus L-CAD, quantification of the exercise lung-to-heart ^{201}Tl uptake ratio with SPECT is feasible, reproducible, more discriminate than simple visual analysis, and best calculated as L_b/H. It presents an intrinsic diagnostic value even after correction for other clinically valuable dependent variables.

Key Words: ^{201}Tl; SPECT; exercise; coronary artery disease; radionuclide

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Exercise myocardial perfusion scintigraphy is a well-established method for diagnosis as well as risk stratification of patients with coronary artery disease (CAD). This is based primarily on the extent of the scintigraphic perfusion defect (*1–4*). After a stress test, the presence of multiple vascular myocardial perfusion defects suggests multivessel CAD.

However, in patients with multivessel CAD, perfusion defects are frequently limited to the culprit coronary artery stenosis. In fact, the appearance of clinical or electrocardiographic positivity may motivate interruption of the exercise stress test, allowing visualization of the most ischemic zone but masking the potential presence of ischemia in other coronary arteries with significant coronary artery stenosis. Then, the defect visualized after a stress test is related to the most severe coronary artery stenosis but may not fully reflect the extent of the CAD (number of vessels involved). This is considered as a major drawback of the method, because it is patients with extensive CAD (E-CAD) (multivessel, proximal left anterior descending artery [LAD]) who benefit most from revascularization in terms of survival (*5–9*).

To improve performance of the scintigraphic method for detection of E-CAD and risk stratification, the use of other indirect scintigraphic signs besides multiple vascular myocardial perfusion defects has been reported and validated, i.e., ^{201}Tl lung uptake (*10,11*), ^{201}Tl lung washout (*12*), transient ischemic left ventricular dilatation (*13*), and myocardial ^{201}Tl washout (*14*).

Visual and quantitative evaluation of ^{201}Tl lung uptake with planar imaging has been proposed and widely validated

TABLE 1
Clinical Patient Characteristics

Characteristic	Group 1 (healthy) (n = 62)	Group 2 (pilot) L-CAD (n = 49)	Group 2 (pilot) E-CAD (n = 126)	P	Group 3 (validation) L-CAD (n = 41)	Group 3 (validation) E-CAD (n = 122)	P
Age (y)	55 ± 9	56 ± 10	61 ± 10	0.05	59 ± 11	60 ± 10	NS
Females (n)	37 (59)	7 (14)	11 (9)	NS	12 (29)	11 (9)	0.002
Weight (kg)	67 ± 12	76 ± 11	74 ± 11	NS	73 ± 12	76 ± 11	NS
Previous MI	0 (0)	20 (41)	85 (67)	0.001	19 (46)	79 (65)	0.03
Anterior MI	0 (0)	3 (6)	36 (29)	0.001	4 (10)	33 (27)	NS
Medication*	7 (11)	20 (41)†	84 (67)	0.002	26 (63)†	85 (70)	NS
β-Blockers	1 (2)	13 (27)	62 (49)	0.007	17 (41)	60 (49)	NS
Exercise HR‡ (bpm)	153 ± 18	134 ± 23	123 ± 22	0.012	131 ± 23	120 ± 23	0.02
Work level‡ (watt)	120 ± 38	129 ± 34§	117 ± 35	0.05	105 ± 32§	110 ± 31	NS

*Antiangina medication.
†$P = 0.033$ between groups.
‡Mean ± SD.
§$P = 0.002$ between groups.
NS = not significant; MI = myocardial infarction; HR = heart rate; work level = exercise work level.
Values in parentheses are percentages.

as a diagnostic and prognostic indicator in CAD. However, its value when calculated with exercise SPECT imaging is controversial and raises methodological concerns (*15–19*). Moreover, in patients with CAD, its correlation with other well-established important diagnostic and prognostic clinical variables, particularly heart rate and exercise work level, was largely documented (*15,17,20*), and its correlation with patient's weight was also reported (*21*). But, the intrinsic clinical value of ^{201}Tl lung uptake after its correction for these clinical and exercise variables was not defined. Therefore, we conducted this study to compare with SPECT imaging the accuracy of visual versus quantitative determination of lung ^{201}Tl uptake, to determine the optimal method for its quantification, to define its relationship to the different clinical and exercise variables, and, finally, to define its intrinsic diagnostic value as a marker of E-CAD after correction for these dependent variables.

MATERIALS AND METHODS

Population

The population included patients referred to our department at Bichat University Hospital for exercise ^{201}Tl imaging. These patients were classified into 3 groups. The clinical characteristics of the 3 groups are summarized in Tables 1 and 2.

Group 1. This group was evaluated to determine the variables affecting the lung-to-heart ratio variance and provide corresponding correction equations for these significant variables, which would define a corresponding calculated, corrected lung-to-heart ratio. It included 62 patients with a low likelihood (<5%) of CAD according to age, sex, symptom classification, and results of exercise electrocardiography (*22*). This method of defining healthy subjects allows selection of a group with closer clinical characteristics to the patients with CAD than do the normal angiographic criteria (*23*).

Group 2 (Pilot Group). This group was evaluated to determine the optimal normal thresholds (optimal number of SDs) for detecting increased lung-to-heart ratio for the uncorrected and corrected ratios after the application of the correction equations defined in group 1. This group included 175 consecutive patients who had undergone coronary angiography within 3 mo of the exercise ^{201}Tl SPECT study without a supervening clinical cardiac event. Group 2 was subclassified according to the coronary angiographic findings into limited CAD (L-CAD) and E-CAD. L-CAD included patients with normal coronary angiograms (<50% diameter stenosis) and patients with 1-vessel CAD other than the proximal LAD. E-CAD included patients with proximal LAD CAD and patients with 2-vessel, 3-vessel, or left main CAD.

Group 3 (Validation Group). The optimal thresholds for detecting increased lung-to-heart ratio defined in group 2 (optimal number of SDs for corrected and uncorrected ratios) were then prospectively validated in an additional group of 163 consecutive patients who had also undergone coronary angiography within a 3-mo period before or after the exercise ^{201}Tl SPECT study without

TABLE 2
Angiographic Patient Characteristics

Coronary angiogram	Group 2 (pilot) L-CAD (n = 49)	Group 2 (pilot) E-CAD (n = 126)	Group 3 (validation) L-CAD (n = 41)	Group 3 (validation) E-CAD (n = 122)	P
0 vessel	14	—	9	—	NS
1 vessel					
Proximal LAD	—	20	—	17	NS
Other	35	—	32	—	NS
2 vessel	—	42	—	46	NS
3 vessel	—	64	—	59	NS

NS = not significant.
Values represent number of patients.

a supervening clinical cardiac event. This group was also subclassified according to coronary angiographic findings into L-CAD and E-CAD as in group 2.

Exclusion criteria included exercise combined with any pharmacologic test, severe hypertension, valvular heart disease, cardiomyopathy, complete left bundle branch block, atrial fibrillation, pacemaker, advanced chronic bronchopulmonary disease, prior coronary artery bypass surgery or coronary angioplasty, patients on dialysis, and patients with contraindications to exercise.

Exercise Stress Test Procedure

Exercise consisted of an ergometer stress test. Exercise began at a workload of 30 W and increased by 30 W every 3 min. ^{201}Tl was injected 1 min before the end of a symptom-limited exercise at a dose of 111 MBq with dose variation based on patient's weight. Patients had their antiangina medication status dictated in concert with their referring cardiologists.

Imaging Procedure and Acquisition or Processing Protocol

SPECT imaging was begun in <6–7 min after ^{201}Tl injection at stress and at 15 min at rest after reinjection of 56 MBq ^{201}Tl. All SPECT studies were acquired on a 1-head γ camera (Elscint Ltd., Haifa, Israel) equipped with low-energy, high-resolution collimators. Images were acquired using a step-and-shoot circular orbit over a 180° arc, starting at the 45° right anterior oblique projection and ending at the 45° left posterior oblique projection, for a total of 30 projections at 30 s/projection. One energy window was used consisting of a 20% window centered on the 70-keV peak. All projection images were acquired into 64 × 64 image matrices, corrected for nonuniformity and center of rotation and quality controlled for patient or organ movement.

Analysis of ^{201}Tl Lung Uptake in SPECT Imaging

An experienced observer who was unaware of patient grouping evaluated ^{201}Tl lung uptake visually and quantitatively.

Visual Evaluation of Lung ^{201}Tl Uptake. The anterior projection of the normalized stress SPECT acquisition was used for visual assessment of lung ^{201}Tl uptake. Accordingly, patients were classified as having increased or normal visual lung uptake.

Quantitative Measurement of Lung ^{201}Tl Uptake. The anterior projection of the normalized stress SPECT acquisition was used for quantification of the lung-to-heart ratio. Circular regions of interest (ROIs) consisting of 41 pixels were drawn over the lung and the heart (Fig. 1).

For the lung, mean lung activity was calculated: first, with a circular ROI drawn on the maximum activity region at the base of the right or left lung (L_b) avoiding the hepatic and cardiac activities; and second, with a circular ROI drawn on the maximum activity region at the apex of the right or left lung (L), avoiding the mediastinum.

For the heart, mean activity (H) and maximal (H_{max}) activity were calculated by drawing a circular ROI over the heart. This allowed the calculation of 4 different lung-to-heart ratios: L_b/H, L_b/H_{max}, L/H, and L/H_{max}.

Data Analysis

The different lung-to-heart ratios in group 1 patients (low likelihood of CAD) were expressed as mean ± SD for each method of calculation (L_b/H, L_b/H_{max}, L/H, and L/H_{max}).

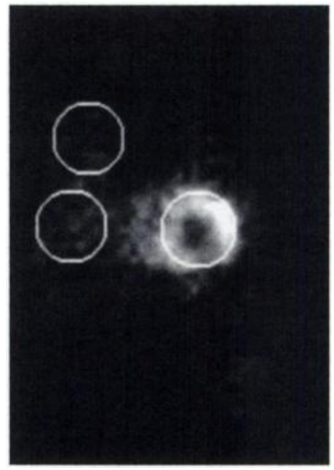

FIGURE 1. Circular ROI drawn over maximum activity region at base and apex of lung and over heart.

Univariate and stepwise regression analyses were performed with the StatView program (version 5.0; SAS Institute, Inc., Cary, NC), and regression equations were derived for correction of dependent variables and root-mean-square residuals. Variables reported to affect the lung-to-heart ratio were studied (*15,17,20,21*). Only those with $P < 0.2$ on univariate analysis were included in the stepwise regression analysis model. $P < 0.05$ on the stepwise regression analysis was considered significant.

Receiver operating characteristic (ROC) analysis was performed with the CLABROC program (version 1.2 0.1; University of Chicago, Chicago, IL) for continuous data and the CORROC2 program (version 1.2 0.1; University of Chicago) for categoric data. Briefly, for each method of calculation, this consisted of establishing varying threshold criteria for abnormality by varying the number of SDs (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 SDs) from its corresponding normal mean lung-to-heart ratio defined in group 1 for the uncorrected ratio and the fitted values for the corrected ratio. Then, for each defined threshold, the calculated quantitative lung-to-heart ratio values were related to the angiographic presence or absence of extensive CAD in the 126 patients of group 2 (pilot group).

The best threshold between normal versus abnormal values was defined as the cutoff (i.e., number of SDs from the mean) that, by ROC analysis, resulted in the best sensitivity for detection of E-CAD with an associated specificity > 0.9.

For this purpose, the sensitivity for detection of extensive CAD was defined in the pilot group as the percentage of patients with extensive CAD who had lung-to-heart ratios exceeding the normality threshold and specificity as 1 minus the percentage of patients with limited CAD who had lung-to-heart ratios exceeding the defined normality threshold.

Categoric data were reported as percentages, and continuous data were reported as mean ± SD. For categoric data comparisons, the χ^2 test, McNemar test, and binomial test were used as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Visual Determination of Lung ^{201}Tl Uptake in Detection of Patients with E-CAD Versus L-CAD

In the pilot group, increased visual lung ^{201}Tl uptake was observed more frequently in patients with E-CAD than in

TABLE 3
Comparative Value of Different Methods of Evaluation of ^{201}Tl Lung Uptake

Group	Sensitivity	Specificity	PPV	NPV	OR
Pilot					
Corrected L_b/H	37	90	90	35	5 (1.9, 13.7)
Uncorrected L_b/H	34*	90	90	35	5 (1.7, 12.3)
Visual lung uptake	42†	86‡	88	37	3 (1.3, 5.6)
Validation					
Corrected L_b/H	41	90	93	34	6 (2.2, 19.2)
Uncorrected L_b/H	47*	80	88	34	4 (1.5, 8.5)
Visual lung uptake	58†	66‡	84	35	3 (1.3, 5.6)

*$P < 0.04$ between groups.
†$P = 0.012$ between groups.
‡$P = 0.02$ between groups.
PPV = positive predictive value; NPV = negative predictive value; OR = odds ratio.

patients with L-CAD (42% versus 14%; $P = 0.002$). This was also verified in the validation group (58% versus 34%; $P = 0.01$) (Table 3).

However, despite similar angiographic characteristics, the performances of visual analysis were inconsistent between the pilot and validation groups. Sensitivity increased from 42% to 58% ($P = 0.012$), whereas specificity decreased from 86% to 66% ($P = 0.02$), respectively (Table 3).

Quantitative Measurement of Lung ^{201}Tl Uptake

Reproducibility of Quantitative Lung-to-Heart Ratio Measurement. Inter- and intraobserver reproducibilities were measured in 26 patients randomly chosen from group 1. Results are reported in Table 4.

Variables Affecting Lung-to-Heart Ratio Variance in Group 1 (<5% CAD). Univariate and stepwise regression analysis results for each method of lung-to-heart ratio calculation are presented in Table 5. The stepwise regression equations providing the basis for the calculation of corrected lung-to-heart ratios are presented in Table 6.

Comparison of Different Uncorrected and Corrected Lung-to-Heart Ratio Methods and Definition of Corresponding Appropriate Normal Thresholds in Pilot Group. On ROC analysis, the uncorrected L_b/H ratio is the best discriminate factor compared with the respective uncorrected L_b/H_{max} ($P = 0.025$), uncorrected L/H_{max} ($P = 0.001$), and uncorrected L/H ($P = 0.05$). The uncorrected L/H_{max} is the least discriminate factor compared with the respective uncorrected L_b/H ($P = 0.001$), uncorrected L/H ($P = 0.001$), and uncorrected L_b/H_{max} ($P = 0.05$) (Fig. 2). Subsequently, only uncorrected L_b/H was considered in the following detailed analysis. The best threshold for uncorrected L_b/H ratio was 0.525 (mean ± 3.5 SD). It provided a sensitivity of 34% (confidence interval [CI]: 26, 43) and a specificity of 90% (CI: 78, 97).

TABLE 4
Intra- and Interobserver Reproducibility of Lung-to-Heart Ratios

Ratio	Intraobserver r	Intraobserver P	Intraobserver SEE	Interobserver r	Interobserver P	Interobserver SEE
L_b/H	0.90	0.0001	0.029	0.88	0.0001	0.029
L_bH_{max}	0.88	0.0001	0.024	0.87	0.0001	0.021
L/H	0.96	0.0001	0.017	0.86	0.0001	0.029
L/H_{max}	0.96	0.0001	0.012	0.88	0.0001	0.019

On ROC analysis, the corrected L_b/H ratio is a more discriminate factor than the respective corrected L/H_{max} ($P = 0.0004$), corrected L/H ($P = 0.007$), and corrected L_b/H_{max} ($P = 0.0125$). Also, the corrected L/H is a more discriminate factor than the corrected L/H_{max} ($P = 0.006$). No significant difference was noted between the corrected L/H and corrected L_b/H_{max} (Fig. 3). Subsequently, only corrected L_b/H was considered in the following detailed analysis. The best threshold for the increased corrected L_b/H ratio was the mean ± 3 SD. It provided a sensitivity of 37% (CI: 29, 46) and a specificity of 90% (CI: 78, 97).

On ROC analysis, no significant difference was found between the uncorrected L_b/H, L_b/H_{max}, L/H, and L/H_{max} and respective corresponding corrected lung-to-heart ratios for detection of E-CAD (Fig. 4).

Accuracy of Defined Uncorrected L_b/H and Corrected L_b/H Best Thresholds in Detection of Patients with E-CAD Versus L-CAD in Validation Group. For the uncorrected L_b/H in the validation group, overall sensitivity and specificity were 47% (versus 34% in the pilot group; $P < 0.04$) and 80% (versus 90% in the pilot group; P was not significant), respectively (Table 3).

Sensitivity and specificity of the corrected L_b/H were similar in the pilot and validation groups (37% versus 41% and 90% versus 90%, respectively) (Table 3).

Comparative Value of Uncorrected L_b/H and Corrected L_b/H in Detection of Patients with E-CAD Versus L-CAD in Pilot and Validation Groups. Overall, the discordance between the two methods was observed in 28 of 338 patients (8%). In patients with E-CAD, discordance was observed in 22 of 248 patients (9%); 13 of 22 patients presented an increased uncorrected L_b/H and a normal corrected L_b/H, whereas 9 of 22 patients presented the opposite findings. The former 13 patients compared with the latter 9 patients presented a lower peak exercise heart rate (102 ± 15 versus 145 ± 18; $P = 0.00001$), a lower work level (102 ± 15 versus 124 ± 29; $P = 0.051$), and a higher weight (81 ± 8 versus 63 ± 9; $P = 0.0001$).

In patients with L-CAD, only 6 of 90 patients (7%) presented a discordance between the 2 methods; 1 of 6 patients presented an increased uncorrected L_b/H and a normal corrected L_b/H, whereas 5 of 6 patients presented the opposite findings.

In the overall population, the uncorrected L_b/H ratio compared with the corrected L_b/H ratio presented a specific-

TABLE 5
Variables Affecting Lung-to-Heart Ratios in Group 1 Patients*

	Univariate				Stepwise regression			
Variable	L_b/H	L_b/H_{max}	L/H	L/H_{max}	L_b/H	L_b/H_{max}	L/H	L/H_{max}
Peak HR	0.004	0.01	NS	NS	0.0008	0.0004	NS	NS
Work level	0.10	0.05	0.05	0.03	0.001	0.0001	0.001	0.001
Weight	0.06	0.05	0.04	NS	0.0007	0.0001	0.04	0.023
Age	NS	NS	NS	NS	0.04	0.005	NS	NS
Peak SBP	NS	NS	NS	NS	NS	NS	NS	NS
^{201}Tl dose	NS	0.08	0.10	0.05	NS	NS	NS	NS
Sex	NS	NS	NS	NS	NS	NS	NS	NS

*Low likelihood of CAD (<5%).
HR = heart rate; NS = not significant; SBP = systolic blood pressure.
Probability values are given for univariate and stepwise regression analyses.

ity of 86% versus 90% (*P* was not significant), respectively, and a sensitivity of 40% versus 39% (*P* was not significant), respectively. Moreover, corrected and uncorrected L_b/H ratios presented odds ratios (ORs) of 6 (2.7, 11.8) and of 4 (2.1, 7.6), respectively.

Comparative Value of Visual Versus Quantitative Analysis of ^{201}Tl Lung Uptake in Detection of Patients with E-CAD Versus L-CAD in Pilot and Validation Groups

Compared with visual analysis, the corrected L_b/H ratio was increased in 96 of 248 patients (39%) (versus 50% with visual analysis; $P = 0.0004$) and 9 of 90 patients (10%) (versus 23% with visual analysis; $P = 0.006$). Thus, visual analysis provided an increase in sensitivity but at the expense of a loss in specificity for detection of E-CAD versus L-CAD; 14 of 90 patients with L-CAD had increased lung uptake on visual analysis and normal lung uptake on the quantitative corrected L_b/H ratio, whereas only 2 of 90 patients had normal lung uptake on visual analysis and increased uptake on the quantitative corrected L_b/H ratio.

TABLE 6
Variables Affecting Lung-to-Heart Ratios in Group 1 Patients and Corresponding Stepwise Regression Equations*

Stepwise regression equation	*P*	*r*	RMS
Corrected $L_b/H = (615 - 1.45 \times HR_{ex} + 1.94 \times Weight_{kg} - 0.62 \times Work_W - 1.74 \times Age_y)/0.001$	0.0001	0.6	0.043
Corrected $L_b/H_{max} = (510 - 1.15 \times HR_{ex} + 1.68 \times Weight_{kg} - 0.59 \times Work_W - 1.81 \times Age_y)/0.001$	0.0001	0.65	0.032
Corrected $L/H = (240 + 2.30 \times Weight_{kg} - 0.73 \times Work_W)/0.001$	0.0001	0.54	0.043
Corrected $L/H_{max} = (184 + 1.96 \times Weight_{kg} - 0.64 \times Work_W)/0.001$	0.001	0.56	0.034

*Group 1 patients have low likelihood of CAD (<5%).
RMS = root mean square; HR_{ex} (bpm) = exercise peak heart rate; $Work_W$ = exercise work level.

The ORs of the corrected L_b/H ratio and visual lung uptake analysis criteria were 6 (2.7, 11.8) and 3 (1.9, 5.7), respectively.

Visual and Quantitative Analysis of ^{201}Tl Lung Uptake in Detection of Patients with E-CAD Versus L-CAD in Pilot and Validation Groups

These results were also valid when applied to patients with and without a previously known myocardial infarction (Table 7).

DISCUSSION

The independent prognostic impact of multivessel CAD, proximal LAD disease, and left ventricular dysfunction and their synergistic interaction in patients with CAD have been

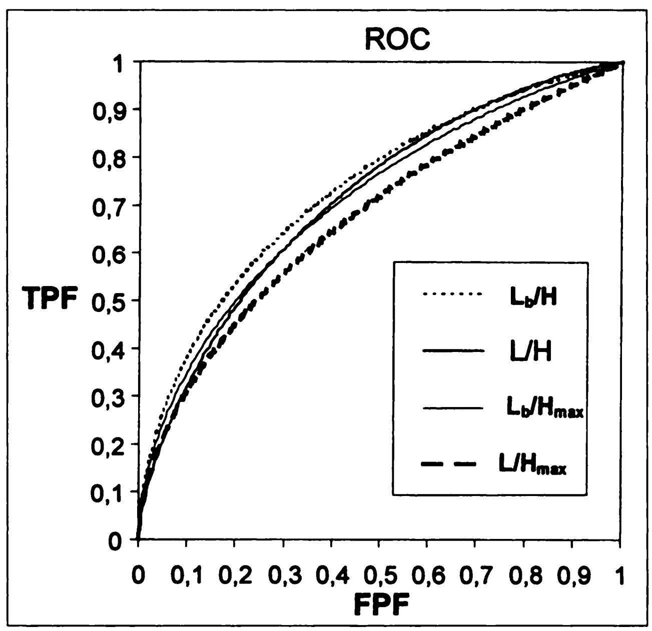

FIGURE 2. ROC curves for each method of calculation of uncorrected lung-to-heart ratio. TPF = true-positive fraction; FPF = false-positive fraction.

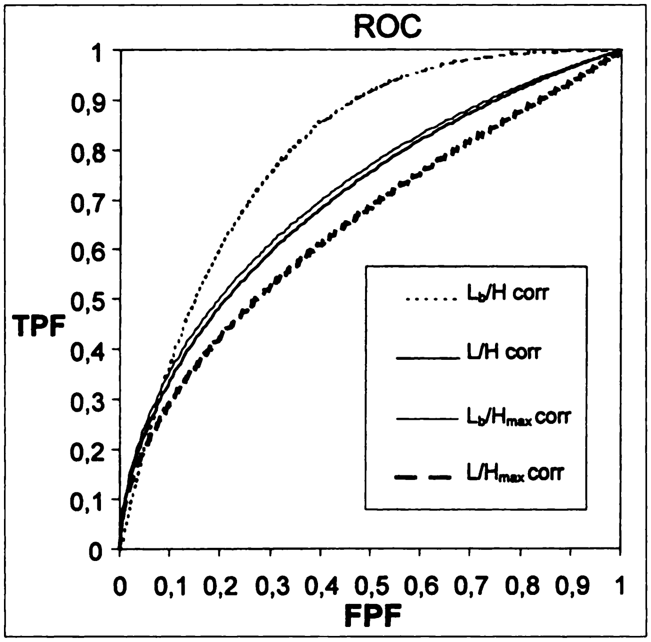

FIGURE 3. ROC curves for each method of calculation of corrected lung-to-heart ratio. TPF = true-positive fraction; FPF = false-positive fraction.

well documented (*24,25*). Detection of patients with these high-risk factors is clinically important because revascularization may improve their prognosis (*7,24,26*).

Therefore, it would be useful clinically to have a noninvasive test capable of detecting these high-risk patients with E-CAD, i.e., discriminating between L-CAD and E-CAD. Exercise ^{201}Tl SPECT is a widely used noninvasive method for diagnosis of CAD and for risk stratification of patients

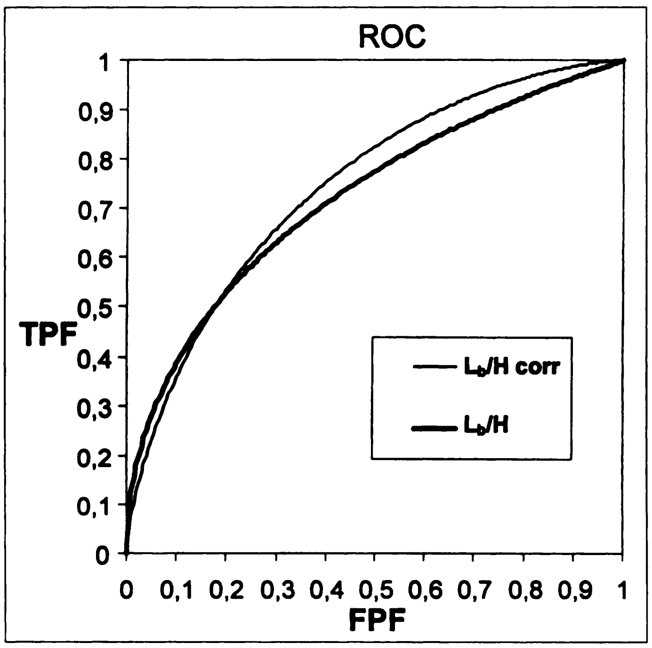

FIGURE 4. ROC curves for uncorrected L_b/H and corrected L_b/H. TPF = true-positive fraction; FPF = false-positive fraction.

TABLE 7
Accuracy of Different Methods of ^{201}Tl Lung Uptake Evaluation in Patients With or Without Previously Known MI (Pilot and Validation Groups)

Group	Sensitivity	Specificity	PPV	NPV	OR
No previous MI					
Corrected L_b/H	21	94	86	42	4 (1.2, 15.7)
Uncorrected L_b/H	25	92	84	43	4 (1.3, 12.2)
Visual lung uptake	39	80	77	45	3 (1.2, 6)
With previous MI					
Corrected L_b/H	48	85	93	28	5 (2, 12.5)
Uncorrected L_b/H	48	77	90	26	3 (1.4, 6.9)
Visual lung uptake	55	72	89	28	3 (1.5, 6.8)

MI = myocardial infarction; PPV = positive predictive value; NPV = negative predicted value.

with known CAD. This is based primarily on the extent of the scintigraphic perfusion defect abnormality (*1–4*) and also on the presence of a stress transient ischemic left ventricular dilatation (*13*) and increased stress lung ^{201}Tl uptake, which is the subject of this study.

It is well established that pulmonary ^{201}Tl uptake increases in the presence of a prolonged transit time through the lungs—i.e., a decrease in cardiac index and an increase in pulmonary capillary wedge pressure (*20,27*). These findings suggest that increased lung ^{201}Tl activity is a nonspecific indicator of impaired left ventricular function rather than a specific sign of CAD. Clinically, it has been shown that increased exercise ^{201}Tl lung uptake is associated with decreased left ventricular function, the presence of multivessel CAD, and poor patient prognosis (*12,28,29*). It has been reported to be the most important predictor of future cardiac events among electrocardiographic, scintigraphic, and angiographic variables in ambulatory symptomatic patients with CAD (*30*).

Visual and quantitative evaluations of ^{201}Tl lung uptake with planar imaging were proposed and widely validated as a diagnostic and prognostic indicator in CAD. However, there is a substantial difference between the planar and SPECT imaging methods for lung ^{201}Tl uptake assessment. The count density is much higher and the imaging is acquired slightly earlier with the planar technique compared with SPECT. These differences dictate the necessity of clinical validation of lung ^{201}Tl uptake assessment with SPECT.

Although the feasibility and reproducibility of lung-to-heart ratio quantitative measurement with the anterior projection of exercise ^{201}Tl SPECT acquisition have been widely validated (*16,17,30*), its value in the diagnosis of E-CAD is debatable (*15–19*). Kahn et al. (*16*) reported that quantitative measurement of lung ^{201}Tl uptake may not provide supplementary information regarding the extent of myocardial ischemia or ventricular dysfunction. Similarly, Ilmer et al. (*17,19*) concluded that because of large overlaps in the measurement data, it is not a clinically useful parameter for the detection and extent of CAD or left ventricular dysfunction in the individual patient. In contrast, Kurata et al. (*15*) found that lung-to-heart ratio measurement may provide information regarding the severity of CAD or left ventricular dysfunction. They reported its weak but significant correlation with peak exercise heart rate, but they did not study its independent value from the latter. Similarly, Aksut et al. (*18*) reported that visually increased lung ^{201}Tl uptake during exercise SPECT identifies patients with more E-CAD by angiography and more left ventricular dilatation, but they also did not study its intrinsic diagnostic value.

The important findings of this study for evaluation of E-CAD versus L-CAD are as follows:

First, visual analysis of lung ^{201}Tl uptake is less accurate than quantitative analysis. The qualitative visual assessment is the most common method used in practice and is based on visual comparison of tracer uptake in the lungs in relation to uptake in the myocardium and mediastinum. Visual analysis compared with quantitative analysis provides a significantly higher sensitivity but at the expense of a significant decrease in specificity with an overall OR of 3 versus 6, respectively. Moreover, whereas the performances of the corrected L_b/H were similar between the pilot and validation groups, this was not the case for the visual analysis, wherein performances were inconsistent despite similar angiographic characteristics. Sensitivity and specificity were significantly different between the pilot and validation groups. It is noteworthy that lung ^{201}Tl uptake assessment was visual in the Aksut et al. (*18*) study and quantitative in the Kahn et al. (*16*) and Kurata et al. (*15*) studies.

Second, as was evident by ROC analysis, the lung-to-heart ratio is best calculated as the ratio of the mean ^{201}Tl activity at the base of the lungs normalized to the mean activity over the heart. In our quantification methods, we measured the mean lung activity at the base and at the apex of the lungs (avoiding mediastinal and abdominal structures) and the mean and maximal activity over the heart. The L_b/H measurement proved to be the most useful. This may be explained by the increased lung ^{201}Tl uptake occurring first at the base of the lungs (before the apical regions) and by the diminished diffuse myocardial perfusion in E-CAD being better reflected by the mean heart ^{201}Tl uptake rather than the maximal heart ^{201}Tl uptake activity. In our departments the time between ^{201}Tl injection and the anterior projection of the SPECT stress acquisition is within approximately 10 min. The delay in commencing imaging after exercise has been reported as decreasing the ability to detect the increased ^{201}Tl lung uptake (*31*). Because the ^{201}Tl lung uptake is ephemeral, with a marked decrease in the first 20 min after injection, the length of time between injection and the SPECT anterior projection acquisition is very important and may explain the discordance between different published studies. For example, Kurata et al. (*15*) and Aksut et al. (*18*) obtained the anterior image projection approximately 13 min and 10 min, respectively, after ^{201}Tl injection, whereas the delay was 17 min for Kahn et al. (*16*) and more than 18 min for Ilmer et al. (*17*). In our departments, the anterior projection is obtained in less than 10 min after stress ^{201}Tl injection. This could explain in part our results being concordant with those of Kurata et al. and Aksut et al., who found that lung ^{201}Tl uptake is valuable, and discordant with those of Khan et al. and Ilmer et al., who found that lung ^{201}Tl uptake is not valuable.

Moreover, Kurata et al. (*15*) used a square ROI of 5×5 pixels (25 pixels) over the most intense left upper lung and the myocardial wall activity. Kahn et al. (*16*) used 55–80 pixels for lung ROI and 6–10 pixels for myocardial ROI, the 2 ROIs being over the most intense activities. Ilmer et al. (*17*) used the mean activity of a square ROI of 4×4 pixels over the myocardial wall and an ROI with a variable size (a minimum of 4×4 pixels) over the left upper lung. Their methods would be closer to our L/H_{max} ratio method of measurement. However, we have shown clearly by ROC analysis that the L_b/H measurement method is the best and should be used instead. Furthermore, in our study, intra- and interobserver reproducibility of the quantitative lung-to-heart ratio is fairly good. The corresponding 2 SD limits are 12% and 17%, respectively.

Third, the L_b/H ratio is correlated positively with the patient's body weight and correlated negatively with peak exercise heart rate, exercise work level, and patient's age. Therefore, the true intrinsic value of the L_b/H ratio should be evaluated after correction for its dependent variables, especially because 1 of the most important prognosticators and diagnostic parameters derived from exercise stress testing is exercise duration or capacity and maximal heart rate (*1,32–37*).

Fourth, the corrected L_b/H ratio for these variables presented a higher diagnostic value than did the uncorrected L_b/H: an OR of 6 (2.7, 11.8) versus 4 (2.1, 6), respectively. It is noteworthy that only an 8% discordance rate was found between the 2 methods. Patients with E-CAD and with increased uncorrected L_b/H and normal corrected L_b/H findings presented a lower peak exercise heart rate, a lower work level, and a higher weight compared with patients with normal uncorrected L_b/H and increased corrected L_b/H findings, thus reflecting the interaction between these variables and the measured lung-to-heart ratio.

This low discordance rate is probably associated with selection bias, because, in our departments, patients judged unable to exercise to a substantial level are subjected to a combined stress test (dipyridamole plus exercise) and therefore excluded from our study. Only 10% of our population exercised to a maximum level of 60 W. This bias would decrease the discordance rate between corrected and uncorrected quantification of L_b/H.

Fifth, these results are also valid when applied to patients with and without previously known myocardial infarction.

CONCLUSION

For the evaluation of extensive versus limited CAD, the quantification of stress lung-to-heart ^{201}Tl uptake ratio with SPECT is feasible and reproducible. Quantification is more discriminate than visual analysis. It is best calculated as the ratio of the mean ^{201}Tl activity at the base of the lungs normalized to the mean activity over the heart. It presents an intrinsic diagnostic value after correction for other clinically valuable dependent variables. This is expected to provide additional diagnostic and prognostic information, but future studies should address specifically this important clinical question.

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