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Relevance of Increased Lung Thallium Uptake on Stress Imaging in Patients With Unstable Angina and Non-Q Wave Myocardial Infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI)-IIIB Study

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Objectives. **This study sought to determine the significance of abnormal thallium-201 (Tl-201) lung uptake on stress imaging in the absence of perfusion abnormalities.**

Background. **Abnormal Tl-201 lung uptake, represented by an increased lung/heart ratio (LHR), on stress imaging is a marker of stress-induced left ventricular dysfunction and poor prognosis in patients with coronary artery disease.**

Methods. **We evaluated 1,271 patients from the Thrombolysis in Myocardial Infarction (TIMI)-IIIB trial (86% of TIMI-IIIB cohort) with unstable angina or non-Q wave myocardial infarction, who underwent predischarge exercise (92%) or dipyridamole stress (8%) Tl-201 imaging. An increased LHR (≥0.50) was related to perfusion abnormalities and adverse cardiac events at 1 year.**

Results. **Of 1,271 patients, there were 762 (60%) with and 509 (40%) without perfusion abnormalities. An increased LHR was seen in 227 patients (18%) (173 [23%] with, 54 [11%] without perfusion abnormalities). Patients with an increased LHR had a lower left ventricular ejection fraction, higher body weight, lower exercise capacity and a higher prevalence of angina on exercise than patients with a normal LHR. In the two groups with increased LHR, there was no difference in age, hypertension, previous myocardial infarction, total exercise time, frequency of angina and ST segment depression on exercise. However, the group with an increased LHR and normal myocardial perfusion had a preponderance of women (65% vs. 30%, $p < 0.001$). At 1-year follow-up, patients with an increased LHR had a higher cardiac event rate than those with a normal LHR (18% vs. 10%, respectively, $p = 0.001$) despite a higher revascularization rate (28% vs. 15%, $p < 0.001$). An increased LHR was associated with increased adverse cardiac events, irrespective of the presence or absence of perfusion abnormalities.**

Conclusions. **An increased LHR continues to be associated with higher adverse cardiac events in the current era of aggressive interventional management of coronary artery disease. An increased LHR in the absence of myocardial perfusion abnormality is seen mostly in women and overweight patients. However, despite the apparent absence of perfusion abnormalities, an increased LHR in this group is also associated with a higher rate of adverse cardiac events.**

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Exercise stress myocardial perfusion imaging provides important information about the extent of myocardial ischemia and scar in patients with coronary artery disease (1–3). This technique is used routinely for the clinical evaluation and risk stratification of patients with coronary artery disease. With thallium-201 (Tl-201) imaging, an increased lung/heart ratio (LHR) provides additional relevant diagnostic and prognostic information (4–8). Several studies have shown abnormal lung Tl-201 uptake also to be associated with greater segmental myocardial perfusion abnormality, increased severity and extent of coronary artery disease and impaired left ventricular function (5,8–10). Follow-up studies have shown (11–13) abnormal lung Tl-201 uptake to be the most important predictor of subsequent adverse cardiac events. Abnormal lung Tl-201 uptake during pharmacologic stress imaging has similar clinical significance to that noted during exercise (14,15).

Most studies evaluating increased LHR were carried out before the widespread use of thrombolytic agents or aggressive interventional treatment of patients with coronary artery disease. Consequently, the clinical and prognostic significance of this finding in the context of current management of patients with coronary artery disease is not well defined. Moreover, abnormal lung Tl-201 uptake is occasionally seen in patients without any myocardial perfusion abnormality. The significance of abnormal lung Tl-201 uptake in this circumstance is also not known. To address these issues, we analyzed the data base of the Thrombolysis in Myocardial Infarction (TIMI)-

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
ECG = electrocardiogram, electrocardiographic
LHR = lung/heart ratio
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis in Myocardial Infarction
Tl-201 = thallium-201
t-PA = tissue-type plasminogen activator

IIIB study, which included a large cohort of well characterized patients presenting with acute coronary syndromes who also underwent stress Tl-201 imaging.

Methods

TIMI-IIIB was a prospective, multicenter clinical trial involving 1,473 patients designed to test the efficacy of thrombolytic therapy versus placebo, and early invasive strategy versus early conservative strategy for the management of patients admitted with unstable angina or non-Q wave myocardial infarction (16,17). As part of the study protocol, patients underwent predischarge myocardial perfusion imaging. Patients were enrolled in 25 centers in the United States and 6 in Canada, and the study was supported by six core laboratories and two central units (17). The details of the study design, participants, study cohort and overall study results have been described previously (17).

Patients. Patients presenting with chest pain judged to be ischemic in origin but without any evidence of Q wave myocardial infarction were enrolled. The inclusion and exclusion criteria have been described in detail (17). In brief, patients with chest pain lasting ≥5 min but ≤6 h in the preceding 24 h with objective evidence of ischemic heart disease were entered into the study. The objective evidence of myocardial ischemia included at least one of the following: 1) transient ST segment elevation or new ST segment depression or T wave inversion in at least two contiguous leads; 2) previous history of myocardial infarction; 3) ≥70% lumen narrowing of at least one or more coronary arteries on previous coronary angiography; 4) evidence of ischemia on previous stress Tl-201 imaging. Patients with electrocardiographic (ECG) findings consistent with acute Q wave myocardial infarction were not entered into the study. Additional exclusion criteria included contraindication to thrombolytic therapy or heparin, myocardial infarction in the preceding 21 days, coronary angiography within 30 days, percutaneous transluminal coronary angioplasty (PTCA) within 6 months, coronary artery bypass graft surgery (CABG) in the past, pulmonary edema or hypotension at presentation, left bundle branch block, a coexisting serious ailment, women of child-bearing potential and concurrent treatment with oral anticoagulant agents.

All patients were to be treated with heparin, aspirin and vigorous antianginal therapy. The patients were randomly assigned in double-blind fashion to treatment with tissue-type plasminogen activator (t-PA) versus placebo and to an early invasive strategy (coronary angiography followed by revascularization of suitable coronary anatomy within 18 to 48 h of admission) versus an early conservative strategy (coronary angiography and revascularization only in the event of failure of initial therapy) using a 2 × 2 factorial design (Table 1). Irrespective of the randomization category, all patients were assigned to undergo predischarge stress Tl-201 imaging.

Table 1. Patient Population

	Total Pts Entered Into Study (n = 1,473)	Pts With Predischarge Tl-201 (n = 1,271)	Pts Without Predischarge Tl-201 (n = 202)
Mean age (yr)	59	59	60
Women (%)	34	33	38
Randomization			
t-PA			
Early invasive	367	302	65
Conservative	362	332	30
Placebo			
Early invasive	373	306	67
Conservative	371	331	40

Data presented are number of patients, unless otherwise indicated. Pts = patients; Tl-201 = thallium-201; t-PA = tissue-type plasminogen activator.

Stress Tl-201 imaging. The protocol mandated stress Tl-201 imaging before discharge in all patients. Those capable of exercising underwent treadmill exercise using a modified Bruce protocol. Patients unable to exercise underwent pharmacologic stress with intravenous dipyridamole. End points for treadmill exercise were severe chest pain, severe shortness of breath, fatigue, appearance of serious arrhythmias, hypotension (≥10-mm systolic blood pressure fall) or completion of three stages of exercise. Tl-201 (2.0 to 2.5 mCi) was injected at peak exercise, and the exercise was continued for another 1.5 to 2.0 min. Planar myocardial perfusion imaging was started within 5 to 10 min of injection and was repeated 2.5 to 4 h later. Three standard planar views (anterior, left anterior oblique, left lateral) were acquired. Patients undergoing pharmacologic stress received 0.56 mg/kg body weight of dipyridamole intravenously over 4 min, with continuous monitoring of blood pressure and ECG, and 2.0 to 2.5 mCi of Tl-201 was injected 4 min after completion of the dipyridamole infusion. Planar imaging was started within 5 to 10 min of the injection of Tl-201. Each view was acquired for 8 min. All images were stored on a floppy disk and were transferred to the Yale University Radionuclide Core Laboratory for uniform image processing, quantification and blinded interpretation by one of the two readers (B.L.Z., F.W.).

Tl-201 image interpretation. Images were interpreted using quantitative previously described methods (18). In brief, paired unprocessed stress–redistribution images were displayed for initial visual interpretation. Circumferential count

Table 2. Clinical Characteristics of Study Patients According to Presence or Absence of Increased Lung Thallium-201 Uptake

	Increased Lung Tl-201 Uptake (n = 227 [18%])	Normal Lung Tl-201 Uptake (n = 1,044 [82%])	p Value
Mean age (yr)	58	59	0.77
Women (%)	38	32	0.06
Hypertension (%)	47	41	0.14
Height (cm)	168	168	0.5
Weight (kg)	85	78	< 0.001
Unstable angina (%)	66	69	0.44
Prior MI (%)	45	39	0.11
>60% occlusion on cor angio (%)*			
0 vessel	15	21	
1 vessel	43	39	
≥2 vessels	43	40	0.4
LVEF (%)*	54	60	< 0.0005
Abnormal perfusion (%)	76	56	< 0.0001
LHR	0.7	0.4	< 0.0005
Early invasive strategy (%)	36	50	< 0.001
t-PA treatment (%)	55	49	0.12
Total ex time (s)†	434	495	< 0.0001
Peak HR (beats/min)	107	119	< 0.0001
Peak SBP (mm Hg)	164	160	< 0.52
Angina on ex (%)	22	15	0.006
ST dep ≥1 mm on ex (%)	27	22	0.074

*Available only in patients randomized to early invasive strategy: 82 patients with increased lung thallium-201 (Tl-201) uptake, 516 with normal lung Tl-201 uptake. †Available for 209 patients with increased lung Tl-201 uptake, 957 with normal Tl-201 uptake. Data presented are percent of patients, unless otherwise indicated. cor angio = coronary angiogram; ex = exercise; HR = heart rate; LHR = lung/heart ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure; ST dep = ST segment depression; t-PA = tissue-type plasminogen activator.

Table 3. Characteristics of Groups I and III (groups with increased lung thallium-201 uptake)

	Group I (perfusion abnormalities) (n = 173)	Group III (no perfusion abnormalities) (n = 54)	p Value
Mean age (yr)	59	58	0.65
Women (%)	30	65	< 0.001
Hypertension (%)	43	57	0.07
Height (cm)	169	166	0.04
Weight (kg)	85	84	0.68
Unstable angina (%)	62	80	0.02
Prior MI (%)	47	35	0.12
>60% occlusion on cor angio (%)*			
0 vessel	7	32	
1 vessel	46	36	
≥2 vessels	47	32	0.01
LVEF (%)*	52	60	0.016
LHR	0.68	0.73	0.76
Early invasive strategy (%)	33	46	0.07
t-PA treatment (%)	53	59	0.43
Total ex time (s)†	444	407	0.23
Peak HR (beats/min)	107	104	0.38
Peak SBP (mm Hg)	163	167	0.87
Angina on ex (%)	25	15	0.1
ST dep ≥1 mm on ex (%)	30	19	0.13

*Available only in patients randomized to early invasive strategy: 57 patients in thallium-201 (Tl-201) defect group, 25 in no Tl-201 defect group. †Available in 161 Group I patients and 48 Group III patients. Data presented are percent of patients, unless otherwise indicated. Abbreviations as in Table 2.

distribution profiles were generated after background subtraction and smoothing. These were compared to the normal database profiles obtained from a cohort of normal subjects with a low likelihood of coronary artery disease. Segments <2 SD of the averaged normal profile were considered abnormal. Left ventricular myocardium in each view was divided into five segments, and each segment was scored as normal, scar, ischemia or mixed (scar and ischemia).

Lung Tl-201 activity was assessed from the quantitative LHR obtained from the unprocessed left anterior oblique images (the first view acquired after tracer injection) by obtaining a ratio of average counts/pixel in the left ventricular myocardium and the left lung. This was done automatically by placing a 3 × 3-pixel region of interest over the left ventricular myocardium with highest counts and a similar-sized region of interest over the left upper lung field. A ratio ≥0.5 was considered indicative of abnormal lung Tl-201 uptake. High risk studies were predefined as those with 1) multiple areas of reversible perfusion abnormalities in more than one vascular territory; 2) a single large area of reversible perfusion abnormality; or 3) reversible perfusion abnormality with an increased LHR. According to the TIMI-IIIB protocol, the presence of high risk Tl-201 images was an indication for coronary angiography and consideration for revascularization if appropriate. An increased LHR in the absence of a reversible perfusion abnormality was predefined not to be an indication for cardiac catheterization.

Cardiac catheterization. Patients randomized to the early invasive strategy underwent cardiac catheterization, left ventricular angiography and coronary arteriography 18 to 48 h after randomization. Coronary angiography was performed in multiple projections using standard techniques, and left ventriculography was performed in the right anterior oblique view. Left ventricular ejection fraction was calculated from the left ventriculogram. Angiograms were reviewed immediately at the local center to ascertain the presence of a culprit lesion and were followed by revascularization, if possible. PTCA was the preferred modality for revascularization and was performed after the initial angiography or as soon as possible thereafter, if the culprit lesion was amenable to angioplasty. In patients with multivessel coronary artery disease, PTCA of major vessels other than the culprit artery was also performed in an attempt to maximally reduce ischemia. CABG was performed in patients with ≥50% narrowing of the left main coronary artery or with three-vessel disease and a depressed left ventricular ejection fraction (≤40%) or in those whose coronary

Table 4. Clinical Characteristics of Groups IV and III (groups with no perfusion abnormalities)

	Group IV (normal LHR) (n = 455)	Group III (inc LHR) (n = 54)	p Value
Mean age (yr)	58	58	0.87
Women (%)	39	65	< 0.0005
Hypertension (%)	39	57	0.01
Height (cm)	167	166	0.59
Weight (kg)	77	84	< 0.001
Unstable angina (%)	75	80	0.46
Prior MI (%)	28	35	0.28
>60% occlusion on cor angio (%)*			
0 vessel	29	32	
1 vessel	42	36	
≥2 vessels	29	32	0.85
LVEF (%)*	63	60	0.09
LHR	0.36	0.73	< 0.001
Early invasive strategy (%)	58	46	0.1
t-PA treatment (%)	48	59	0.11
Total ex time (s)†	516	407	< 0.0001
Peak HR (beats/min)	119	104	< 0.0001
Peak SBP (mm Hg)	160	167	<0.41
Angina on ex (%)	11	15	0.46
ST dep ≥1 mm on ex (%)	14	19	0.35

*Available only in patients randomized to early invasive strategy: 263 patients with normal lung/heart ratio (LHR), normal perfusion group; 25 with increased (inc) lung/heart ratio, no thallium-201 defect group. †Available in 421 Group IV patients and 48 Group III patients. Data presented are percent of patients, unless otherwise indicated. Abbreviations as in Table 2.

Table 5. Frequency of Coronary Angioplasty or Bypass Surgery at 42 Days After Thallium-201 Imaging

	Increased LHR	Normal LHR	p Value
All pts	n = 227	n = 1,044	
PTCA	28 (12%)	94 (9%)	0.12
CABG	37 (16%)	63 (6%)	< 0.001
PTCA/CABG	64 (28%)	152 (15%)	< 0.001
Perf abn	n = 173	n = 589	
PTCA	22 (13%)	69 (12%)	0.73
CABG	34 (20%)	53 (9%)	< 0.001
PTCA/CABG	55 (32%)	118 (20%)	0.002
No perf abn	n = 54	n = 455	
PTCA	6 (11%)	25 (6%)	0.10
CABG	3 (6%)	10 (2%)	0.13
PTCA/CABG	9 (17%)	34 (8%)	0.02

Data presented are number (%) of patients (pts). CABG = coronary artery bypass graft surgery; LHR = lung/heart ratio; Perf abn = perfusion abnormalities; PTCA = percutaneous transluminal coronary angioplasty.

anatomy was not suitable for PTCA. Patients randomized to the early conservative strategy underwent cardiac catheterization only after failure of initial therapy, as indicated by the recurrence of angina, or on the basis of the finding of high risk predischarge stress Tl-201 imaging or ≥20 min of ischemic ST segment depression on 24-h Holter monitoring or if unstable angina recurred after hospital discharge, as previously defined (17). Coronary angiographic and ejection fraction data were available only for patients who were randomized to the early invasive strategy group.

Follow-up. The patient, family or physician were contacted at 1 year (range 365 to 550 days after randomization) and questioned concerning the occurrence of adverse cardiac events defined as death, nonfatal myocardial infarction or spontaneous ischemia requiring hospital admission.

Statistical analysis. The Student unpaired *t* test was used for continuous dependent variables and chi-square analysis was used for categoric dependent variables. Kaplan-Meier curves of adverse events over a follow-up period of 1 year were plotted for different groups of patients and, if appropriate, were compared using the log-rank statistic. As in previous TIMI publications, because of the large number of analyses performed, $p = 0.01$ was considered evidence of an association; $p = 0.001$ was considered strong evidence of an association; and $p \leq 0.05$ and >0.01 were considered to indicate a trend (16,17,19–21).

Results

Of a total of 1,473 patients enrolled in the study, 1,271 (86%) underwent stress Tl-201 imaging (92% treadmill exercise, 8% dipyridamole stress). The remaining 202 patients did not undergo perfusion imaging because of death before discharge (26 patients), physician or patient refusal or equipment malfunction (176 patients) (Table 1). Of the 1,271 patients who underwent imaging, 762 (60%) had perfusion abnormalities (reversible defects in 530 [42%], fixed defects in 232 [18%]); 509 patients (40%) had no perfusion abnormalities. Abnormal lung Tl-201 uptake was observed in 227 (18%) patients. The prevalence of increased LHR in patients with and without perfusion abnormalities was 23% (n = 173) and 11% (n = 54), respectively ($p < 0.0001$). The patients were classified into four groups according to the presence or absence of perfusion abnormalities and the presence or absence of an increased LHR, as follows: *Group I* = presence of perfusion abnormality with an increased LHR (n = 173 [14%]); *Group II* = presence of perfusion abnormality with a normal LHR (n = 589 [46%]); *Group III* = no perfusion abnormality with an increased LHR (n = 54 [4%]); *Group IV* = no perfusion abnormality with a normal LHR (n = 455 [36%]).

When all patients with an increased LHR were compared with patients with a normal LHR, no differences in age, gender, prevalence of hypertension and angiographic extent of coronary artery disease were seen (Table 2). Patients with an increased LHR had a higher body weight (85 vs. 78 kg, $p < 0.001$) than the patients with a normal LHR. A greater proportion of patients with an increased LHR had a perfusion abnormality (173 of 227 vs. 589 of 1,044, $p < 0.0001$) compared with patients with a normal LHR. A smaller proportion of

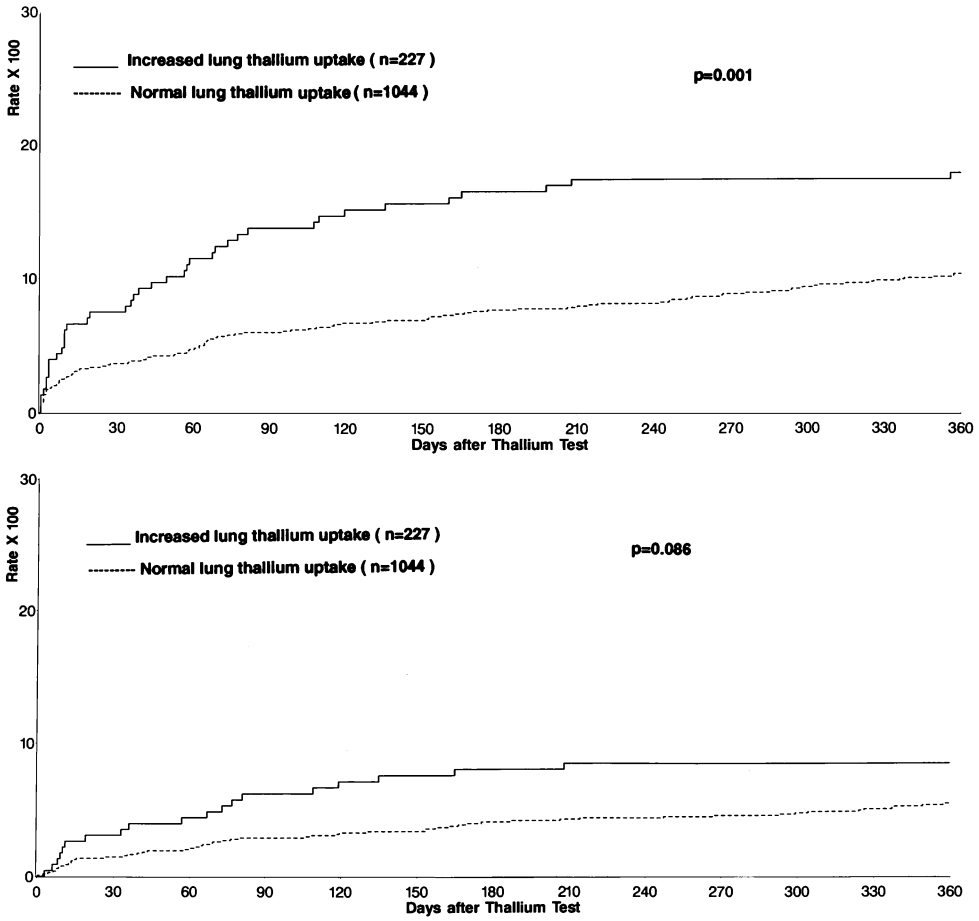

Figure 1. Adverse cardiac events in patients with increased and normal lung Tl-201 uptake over a follow-up period of 1 year. **Top,** All cardiac events. **Bottom,** Myocardial infarction and death only.

patients with an increased LHR were randomized to early invasive strategy (82 of 227 vs. 526 of 1,044, $p < 0.001$), but there was no difference in treatment with t-PA (124 of 227 vs. 510 of 1,044, $p = 0.12$). Patients with an increased LHR had a lower total treadmill exercise time (434 ± 184 vs. 495 ± 191 s, $p < 0.0001$), lower peak heart rate (107 ± 20 vs. 119 ± 22 beats/min, $p < 0.0001$), lower peak blood pressure (148 ± 27 vs. 158 ± 28 mm Hg, $p < 0.0001$) and a higher frequency of angina (22% vs. 15%, $p = 0.006$) but no difference in the frequency of abnormal ST segment depression on the exercise ECG (27% vs. 22%, p = NS) than patients with a normal LHR (Table 2).

When the two groups with increased LHR (Groups I and III) were compared, there was no difference in age, prevalence of hypertension or previous myocardial infarction (Table 3). However, Group III had more women (65% vs. 30%, $p < 0.001$) and a lower prevalence of multivessel coronary artery disease in those undergoing angiographic evaluation (32% vs. 47%, $p = 0.01$) than Group I. The exercise time (407 ± 178 vs. 444 ± 186 s, $p = 0.23$), frequency of angina (15% vs. 25%, $p = 0.1$) and ≥1-mm ST segment depression (19% vs. 30%, $p = 0.13$) were not different between Groups III and I. There was no difference in peak heart rate and peak systolic blood pressure. There was no difference in randomization to treatment categories (Table 3).

When the two groups with normal myocardial perfusion (Groups III and IV) were compared, there were no differences in age, angiographic extent of coronary artery disease or left ventricular ejection fraction (Table 4). However, Group III had more women (65% vs. 39%, $p < 0.001$) and a higher mean body weight (85 vs. 76 kg, $p = 0.001$) than Group IV. Group IV patients had a higher exercise time (516 ± 196 vs. 407 ± 178 s, $p < 0.0001$), greater peak heart rate (119 ± 23 vs. 104 ± 16 beats/min, $p < 0.0001$) and no difference in peak systolic pressure (160 ± 28 vs. 167 ± 28 mm Hg, $p < 0.41$) than Group III patients. There was no difference in frequency of angina or ST segment depression (Table 4) and no difference in randomization to the treatment category.

Revascularization procedures. The frequency of revascularization procedures (PTCA or CABG) at 42 days of follow-up is shown in Table 5 for different groups of patients. The decision to perform these procedures was based on the presence of high risk predischarge Tl-201 images (as previously defined), recurrence of angina either during the hospital stay or after discharge or the occurrence of spontaneous ischemia (≥20 min of ischemic ST segment deviation on 24-h Holter

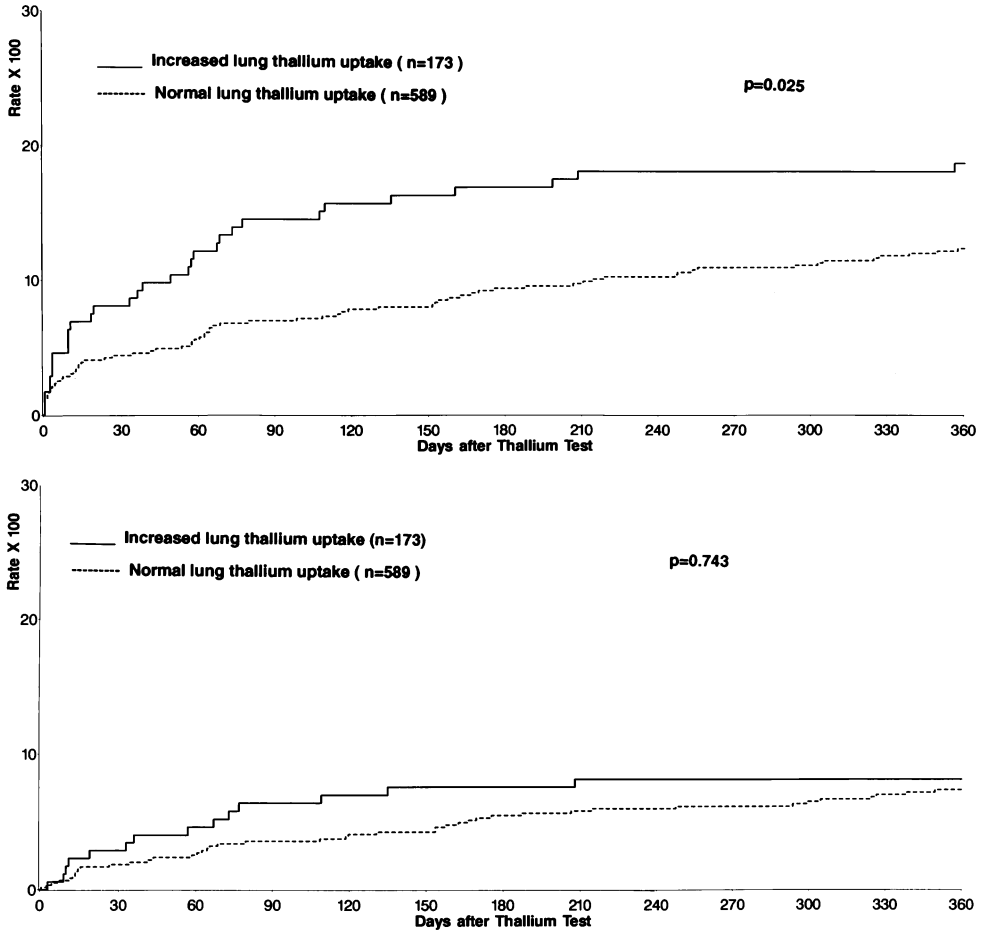

Figure 2. Adverse cardiac events in patients with perfusion abnormalities based on the presence (**solid lines**) or absence (**dotted lines**) of increased lung Tl-201 uptake over a follow-up period of 1 year. **Top,** All cardiac events. **Bottom,** Myocardial infarction and death.

monitor), as previously defined (17). Of the entire patient group, 216 (17%) underwent a revascularization procedure (PTCA or CABG). A total of 122 patients had PTCA, and 100 had CABG (6 underwent CABG after they had undergone PTCA). Twenty-eight percent of patients with an increased LHR underwent revascularization compared with 15% patients with a normal LHR ($p < 0.001$). In the patients with perfusion abnormalities, 32% with an increased LHR (Group I) underwent revascularization compared with 20% with a normal LHR (Group II) ($p = 0.002$), whereas in patients without perfusion abnormalities, 17% with an increased LHR (Group III) underwent revascularization compared with 8% with a normal LHR (Group IV) ($p = 0.02$). The higher incidence of revascularization procedures in the presence of an increased LHR clearly reflects the fact that an increased LHR in the presence of reversible perfusion abnormalities, according to the predefined protocol, was an indication for revascularization, when possible.

Follow-up. Figure 1 shows cardiac event rates over a follow-up period of 1 year in patients with increased versus normal lung Tl-201 uptake for the total patient cohort. There was strong evidence that patients with increased lung Tl-201 uptake had higher frequency of all adverse events ($p = 0.001$), but there was no statistical difference in the incidence of the "hard events" of death or myocardial infarction. Figure 2 shows the follow-up results in patients with and without an increased LHR in the presence of perfusion abnormalities (Group I vs. Group II). Patients with an increased LHR had a trend toward higher cardiac events ($p = 0.025$), although this did not achieve the predetermined level of statistical significance. Figure 3 shows the follow-up results in patients with and without an increased LHR with no perfusion abnormalities (Group III vs. Group IV). There is no statistical difference in the incidence of all cardiac events, but there is a trend toward higher incidence of death and myocardial infarction in patients with increased lung Tl-201 uptake with no perfusion abnormalities ($p = 0.016$). Therefore, despite higher rates of revascularization procedures, patients with an increased LHR had a higher rate of adverse cardiac events over the subsequent 1 year.

Discussion

Comparison with previous studies. This study shows that increased LHR on predischarge stress Tl-201 imaging in patients with unstable angina or non-Q wave myocardial

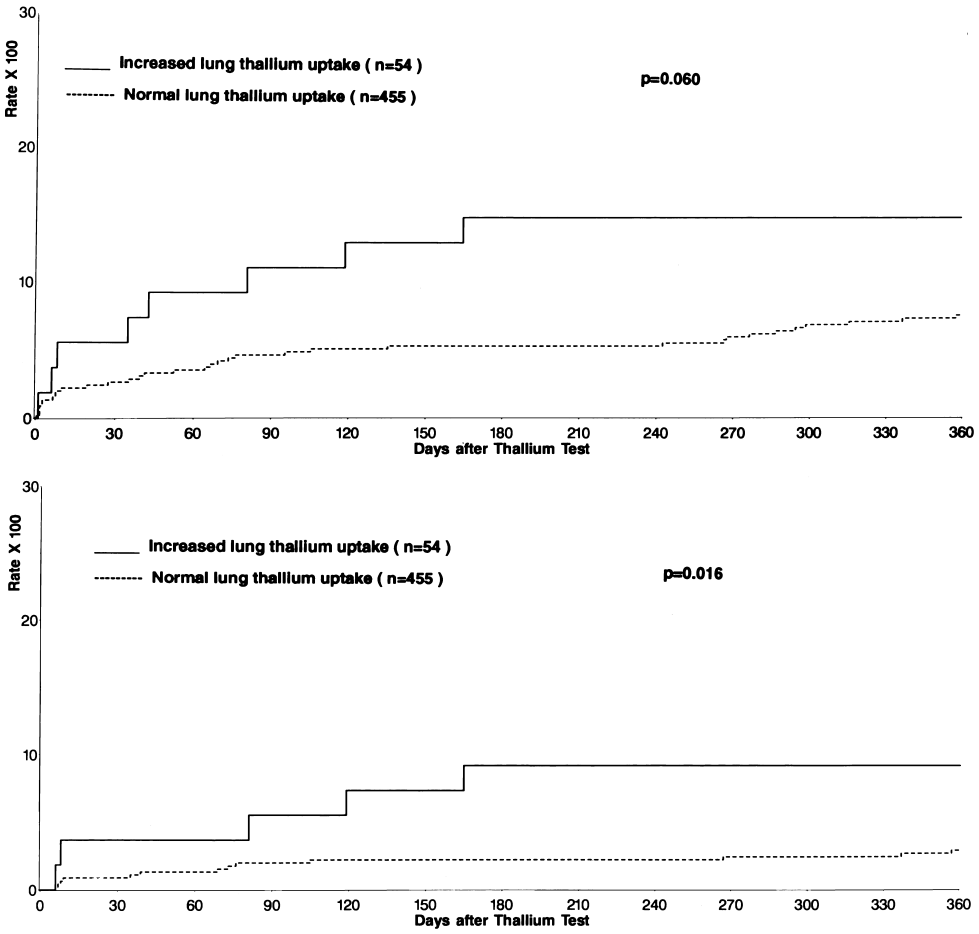

Figure 3. Adverse cardiac events in patients with no perfusion abnormalities based on the presence (**solid lines**) or absence (**dotted lines**) of increased lung Tl-201 uptake over a follow-up period of 1 year. **Top,** All cardiac events. **Bottom,** Myocardial infarction and death.

infarction in the current interventional era continues to be predictive of higher adverse cardiac event rates over the ensuing year. An increased LHR was associated with lower treadmill exercise time, lower peak heart rate, lower peak systolic blood pressure and a higher frequency of angina on exercise. These results are in agreement with studies performed before the widespread use of interventional treatment, when an increased LHR was found to be an adverse prognostic sign in patients with coronary artery disease and was associated with greater extent of coronary artery disease and greater impairment of left ventricular ejection fraction. In the present study, a higher incidence of adverse cardiac events was observed in patients with an increased LHR, despite the fact that an increased LHR in the presence of reversible perfusion abnormalities (i.e., inducible ischemia) was one of the protocol criteria for cardiac catheterization and revascularization. There was a higher rate of revascularization procedures in patients with an increased LHR at 42 days (28% vs. 15%, $p < 0.001$) than in patients with normal lung Tl-201 uptake. Despite a nearly twofold higher rate of intervention, patients with increased lung Tl-201 uptake had a higher adverse cardiac event rate at 1 year. One might expect a lower rate of adverse cardiac events with greater use of revascularization procedures. These differences were seen when all cardiac events (death, nonfatal myocardial infarction and spontaneous ischemia) were taken into consideration. It should be noted that there was a relatively small number of deaths and myocardial infarctions at 1 year (<8%) in this patient cohort, consistent with the current low 1-year rates of mortality and infarction in patients with acute coronary artery disease (22). There was a strong association ($p = 0.001$) between an increased LHR and adverse cardiac events in the overall patient cohort. However, the association could not be further explored in individual patient subgroups because of the relatively lower number of adverse cardiac events.

Effect of treatment. When the effect of treatment assignment on increased LHR was evaluated, there was no difference in treatment with t-PA, but a significantly lower proportion of patients with an increased LHR were in the early invasive treatment group (36% vs. 50%), which suggests a possible greater efficacy of early invasive strategy in these patients than more conservative strategies.

Increased LHR without perfusion abnormalities. Increased LHR without apparent perfusion abnormalities was seen in a relatively small proportion of patients (4% of the entire patient cohort). Despite an apparent absence of perfusion abnormalities, a trend toward a higher adverse cardiac event rate persisted in this group. An increased LHR with no

perfusion abnormalities was seen more often in women and in patients with a higher body weight. It is possible that an increased LHR in this group may in part be an artifact of nonuniform soft tissue attenuation rather than a result of exercise-induced left ventricular dysfunction. Because breast and other soft tissue may overlap the cardiac region of interest more than the lung fields, more of the radioactivity emanating from the heart would be attenuated than that from the lung fields, thereby resulting in an artifactually higher LHR. Nevertheless, despite an apparent lack of perfusion abnormalities, these patients demonstrated a trend toward a higher adverse cardiac event rate on follow-up than those with normal lung Tl-201 uptake with no perfusion abnormalities. Artifact of soft tissue attenuation alone may not be entirely responsible for this phenomenon. Soft tissue attenuation may also result in difficulty in identifying perfusion abnormalities and in differentiating true perfusion abnormalities from the attenuation artifacts. Lower workload on exercise as indicated by lower total exercise time and peak heart rate in this group may also have contributed to an apparent lack of perfusion abnormalities in this group. This in turn may have resulted in lower rates of cardiac catheterization and revascularization in these patients: 17% of patients with abnormal lung Tl-201 uptake and normal myocardial perfusion (Group III) underwent revascularization compared with 32% of patients with increased lung Tl-201 uptake and perfusion abnormalities. It is also possible that a higher body weight in this cohort may be an independent risk factor for a higher rate of adverse cardiac events. In this sense, an increased LHR in this group could be an epiphenomenon. Diastolic dysfunction with resultant abnormal elevation in end-diastolic pressure and capillary wedge pressure on exercise may have resulted in lower exercise capacity and increased LHR on exercise despite an apparent absence of exercise-induced ischemia. Whatever the mechanism, quantitatively increased lung Tl-201 uptake in the absence of perfusion abnormalities indicates a trend toward a higher cardiac event rate.

Study limitations. The TIMI-IIIB study enrolled patients with a strong clinical suspicion of unstable angina or non-Q wave myocardial infarction at the time of presentation. Therefore, the results may not be directly extrapolated to other groups of patients, such as those with low pretest likelihood of coronary artery disease. Furthermore, submaximal exercise for stress perfusion imaging may contribute to a relatively high proportion of studies with no apparent perfusion abnormalities (40%) despite a high likelihood of coronary artery disease in the overall patient cohort. Planar imaging used in the TIMI-IIIB study has a somewhat lower sensitivity for the detection of coronary artery disease than SPECT imaging, particularly in single-vessel and for left circumflex coronary artery disease (1). Coronary angiography at presentation was performed only in patients randomized to the early invasive strategy. Therefore, coronary angiographic and left ventricular ejection fraction data are available only in 50% of patients. In keeping with recent trends of declining mortality and infarction rates in patients with coronary artery disease, event rates were relatively low in this patient cohort. Thus, only larger differences in the events could be detected. Finally, an increased LHR was a predefined criterion for identification of "high risk" patients in the presence of reversible perfusion abnormalities, thereby leading to selection of such patients for revascularization. This selection would certainly confound analysis of the role of an increased LHR as a prognostic indicator. Nevertheless, despite this factor, which could mitigate against detection of any adverse outcome, an increased LHR continued to be associated with an adverse prognosis.

Conclusions. The results of this study indicate that in the current era of aggressive interventional management, an increased quantitative LHR on predischarge submaximal stress Tl-201 imaging continues to be an adverse prognostic sign in patients presenting with unstable angina or non-Q wave myocardial infarction. An abnormal LHR in the absence of myocardial perfusion abnormalities was seen mainly in women and in overweight patients but nevertheless indicates a tendency toward a higher adverse cardiac event rate.

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