Independent and Incremental Prognostic Value of 201 Tl Lung Uptake at Rest in Patients With Severe Postischemic Left Ventricular Dysfunction

Claudio Marcassa, MD; Michele Galli, MD; Claudio Baroffio, MD; Ermanno Eleuteri, MD; Riccardo Campini, MD; Pantaleo Giannuzzi, MD

Methods

Study Cohort

We studied 124 consecutive patients with a history of ischemic heart disease and severe LV dysfunction (ejection fraction ≤35% at 2D echocardiography or angiography) who were referred to our nuclear cardiology laboratory from January 1994 to December 1996 for a 201 Tl rest-redistribution study, to assess the presence of residual viability in dysfunctional myocardial segments. All patients were clinically stable, with optimized cardiovascular therapy and in New York Heart Association (NYHA) functional class II or III. The study cohort included 30 (24%) patients with severe heart failure, admitted to our hospital for heart transplantation workup and who, after aggressive medical treatment, improved their functional class, thus being able to tolerate the supine position required for tomographic imaging. Patients with unstable angina, recent (<1 month) myocardial infarction, or overt heart failure were excluded. Recent (<3 months) coronary angiography was available in 86 patients and showed the presence of a ≥50% coronary diameter reduction of a major coronary artery in 76 patients (88%). Right heart catheterization data by Swan-Ganz catheterization performed within 48 hours of the 201 Tl study were also available in 19 patients. The study protocol was approved by the local Ethics Committee for Human Research. Informed consent was obtained from all patients.

201 Tl Imaging and Analysis

201 Tl 3 mCi (111 MBq) was injected at rest, in fasting condition; cardioactive drugs were not withdrawn. Images were obtained 10
minutes and 4 hours after injection. The methods for imaging acquisition, reconstruction, and analysis have been previously reported. For the quantification of regional myocardial tracer uptake, a 20-segment LV model was adopted. A segmental 201 Tl uptake <75% of peak myocardial activity was considered abnormal; the tracer uptake defect was classified as severe if <50% and mild-moderate if 50% to 75% of peak myocardial activity. A tracer defect was considered reversible when its abnormal 201 Tl uptake on rest images increased >10% on redistribution images. The LV 201 Tl distribution was also displayed as a polar map and normalized for peak cardiac activity. By comparing the uptake in the lungs with the uptake in the myocardium and mediastinum, pulmonary uptake was scored on a 4-point grading system (0 = lungs poorly visualized; 1 = mild, 2 = moderate, and 3 = marked lung uptake); a score ≥2 was considered abnormal. The interobserver agreement in grading the lung tracer uptake was 95%; discrepancies were resolved by consensus.

For the quantitative analysis, 2 regions of interest were drawn over the left lung and the area of maximal myocardial activity, and the tracer lung/heart uptake ratio (L/H) was calculated as (mean counts/pixel left lung)/(mean counts/pixel myocardium).

Echocardiographic Evaluation

Complete echocardiographic and Doppler ultrasound evaluation were performed in all patients, as previously reported. The left ventricle was divided into 13 segments, and systolic wall thickening and inward wall motion were visually assessed off-line by 2 experienced operators who were unaware of other information. In each segment, contraction was graded on a 4-point scoring system (0 = normal to 3 = dyskinetic) and a wall motion score index was calculated; in cases of discrepancies a consensus was reached. LV volumes were calculated from orthogonal apical views with the biplane area-length method, and the LV ejection fraction was derived. At Doppler examination of mitral diastolic inflow, peak early (E) and late (A) flow velocities, the peak E/A ratio, wave velocity ratio and deceleration time of early filling were measured. The restrictive filling pattern was defined as an E/A ratio ≥2 or the combination of an E/A ratio between 1 and 2 and a deceleration time ≤140 ms. Mitral regurgitation was evaluated by color Doppler flow imaging and scored as absent, mild, moderate or severe according to Helmcke et al.

Follow-Up and Statistical Analysis

Follow-up was obtained at regular intervals in our outpatient clinic or through telephone interviews conducted by trained personnel, personal communication with the patient’s physician, and, in the case of new hospitalization, by reviewing the patient’s hospital records. For the purposes of this study, hard events signified cardiac death or nonfatal myocardial infarction; major events included hard events plus rehospitalization for heart failure.

Continuous data are reported as mean±SD. A Student’s t test for unpaired data or ANOVA was used to test differences between groups, with Bonferroni’s correction when indicated, and differences in rates of occurrence of categorical variables were compared by the χ² test with Yates’ correction. Linear regression analysis was used to assess the correlation between L/H and hemodynamic, echocardiographic variables, and the extent of “nonviable” LV area. Receiver-operating characteristic (ROC) curves for the prediction of major events were generated with the use of individual L/H values; cut-points were generated at regular intervals and the best threshold was automatically identified as the value minimizing the expression [1 − sensitivity² + (1 − specificity)²]. The area under the curve was obtained according to Hanley and McNeil. Differences in event rates between patients with L/H above or below the cut-point value were analyzed with Kaplan-Meier survival curves and compared by means of the log-rank test.

A Cox logistic regression analysis was used to identify the baseline variables that were independently correlated to hard or major events among those significantly associated on univariate analysis. Patients who underwent surgery were included in the

TABLE 1. Clinical and Instrumental Data

<table>
<thead>
<tr>
<th>History of</th>
<th>Clinical data</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous myocardial infarction</td>
<td>112 (90%)</td>
<td>Calcium channel blockers 13 (10%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>51 (41%)</td>
<td>Nitrates 99 (80%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66 (53%)</td>
<td>Diuretics 95 (77%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>56 (45%)</td>
<td>Digitalis 90 (72%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35 (28%)</td>
<td>ACE inhibitors 98 (79%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>56 (45%)</td>
<td>β-Blockers 27 (22%)</td>
</tr>
</tbody>
</table>

TABLE 2. Echocardiographic Data

<table>
<thead>
<tr>
<th>LV EDVi, mL/m²</th>
<th>LV ESVi, mL/m²</th>
<th>LV ejection fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>119±41</td>
<td>96±32</td>
<td>23±6</td>
</tr>
</tbody>
</table>

TABLE 3. Mitral Doppler Data

<table>
<thead>
<tr>
<th>Peak E velocity, cm/s</th>
<th>Peak A velocity, cm/s</th>
<th>E/A ratio</th>
<th>Deceleration time, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>81±26</td>
<td>67±27</td>
<td>1.6±1.1</td>
<td>153±49</td>
</tr>
</tbody>
</table>

TABLE 4. Restrictive filling pattern

| 56 (45%)              |
TABLE 2. Clinical, Echocardiographic, and Scintigraphic Data in Patients With Normal (Score 0–1) or Abnormal (Score 2–5) 201Tl Lung Uptake at Qualitative Analysis

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>65±9</td>
<td>61±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>18 (33%)</td>
<td>37 (47%)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDVI, mL/m²</td>
<td>115±34</td>
<td>125±44</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV ESVI, mL/m²</td>
<td>85±30</td>
<td>98±41</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>24±5</td>
<td>22±6</td>
<td>NS</td>
</tr>
<tr>
<td>Wall motion score index</td>
<td>2.3±0.3</td>
<td>2.3±0.4</td>
<td>NS</td>
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<td>Peak E velocity, cm/s</td>
<td>76±31</td>
<td>84±22</td>
<td>NS</td>
</tr>
<tr>
<td>Peak A velocity, cm/s</td>
<td>78±24</td>
<td>59±26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.04±1.02</td>
<td>1.2±1.1</td>
<td>&lt;0.01</td>
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<td>Deceleration time, ms</td>
<td>171±2</td>
<td>142±45</td>
<td>&lt;0.01</td>
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<tr>
<td>Restrictive filling pattern</td>
<td>13 (28%)</td>
<td>43 (63%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Severe mitral regurgitation</td>
<td>11 (22%)</td>
<td>34 (44%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Scintigraphic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of “nonviable” segments</td>
<td>4.6±3.7</td>
<td>6.4±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Rest-redistribution</td>
<td>13 (26%)</td>
<td>28 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Scar extent, %</td>
<td>26±13</td>
<td>29±16</td>
<td>NS</td>
</tr>
<tr>
<td>Lung/heart ratio</td>
<td>0.52±0.08</td>
<td>0.71±0.09</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

EDVI indicates end-diastolic volume index; ESVI, end-systolic volume index. Data are reported as mean±SD or as number (percentage).

The mean age of the study group was 62±12 years (range 33 to 79 years; 83% men) and the average LV ejection fraction was 23±6%; at coronary angiography, single-vessel and multivessel coronary artery diseases were detected in 16 (19%) and 60 (70%) patients, respectively. At 201Tl imaging, 5.1±3.4 myocardial segments had a tracer uptake <50%, and the extent of “nonviable” area at polar map was 28±15%. The average lung uptake score was 1.7±0.8 and the average L/H was 0.64±0.14. The significant relation between the 201Tl lung uptake at quantitative analysis and the corresponding visual score is reported in Figure 1. The clinical, echocardiographic, and scintigraphic findings of the study cohort are reported in Table 1.

201Tl Lung Uptake: Correlation With Functional and Hemodynamic Variables

At qualitative analysis, lung 201Tl uptake was elevated in 74 patients (60%) and normal in 50 (40%); the clinical and instrumental findings of the study cohort according to the presence of an elevated or normal lung 201Tl uptake are reported in Table 2. At multivariate analysis, severe mitral regurgitation (χ²=6.8, P<0.05) and peak A-wave velocity (χ²=4.2, P<0.05) were independently correlated with an increased lung uptake.

A significant inverse relation was documented between L/H and peak flow velocity of A wave (r = −0.53; P = 0.0005) (Figure 2) or peak E/A flow ratio (r = −0.50; P = 0.0007); no significant correlation was observed between L/H and LV volumes, ejection fraction, wall motion score index, E-wave peak velocity and E-wave deceleration time, or extent of nonviable myocardial area. When L/H and right heart catheterization data were compared, a significant correlation was found only between L/H and wedge pressure (r = 0.66; P = 0.008) (Figure 2).

Follow-Up Data

Patients were followed up for a period of 13±13 months, and follow-up data were obtained in all patients. There were 29 (23%) patients who underwent revascularization and 11 other patients (9%) who underwent heart transplantation. Among the remaining 85 (68%) medically treated patients, revascularization was not planned in 37 patients because of stenotic coronaries supplying an extensive nonviable LV area, and it was not performed in 14 patients because the target vessel was unsuitable for revascularization. In 34 other patients (27%) judged to be at high risk because of severely depressed LV function (ejection fraction <20% and LV end-diastolic volume index >120 mL/m²), additional invasive procedures were not scheduled. At follow-up, 1 patient had a new nonfatal myocardial infarction, 13 patients (10%) died, and 22 (18%) other patients required hospital admission for worsening congestive heart failure. Overall, 36 patients (29%) had major events: Clinical and instrumental findings in patients with and without unfavorable outcome are summarized in Table 3.

Figure 2. Scatterplots showing relations between L/H values (x-axis) and A-wave velocities (left panel) and wedge pressure (right panel).
On the basis of ROC analysis, an L/H value >0.61 best separated patients with and without major events at follow-up (area-under-curve=0.82; sensitivity 83%, specificity 74%) (Figure 3). The clinical and instrumental findings of patients with versus without L/H >0.61 are reported in Table 4. In patients with L/H >0.61, 31 (42%) had a major event, compared with only 5 (10%) patients with L/H ≤0.61 (P<0.001; relative risk 3.91, 95% CI 1.69 to 9.1). The Kaplan-Meier analysis showed that the 4 years survival free of major events was significantly lower in patients with L/H >0.61 than in those with L/H ≤0.61 (P<0.001) (Figure 4). Survival without cardiac death (P<0.05) as well as without rehospitalization as the result of worsening heart failure (P<0.005) was also significantly lower in patients with increased tracer lung uptake (Figure 5).

When the variables that significantly correlated with an adverse outcome at follow-up by univariate analysis were introduced in the logistic regression analysis, an L/H value >0.61 (χ²=10.8; P<0.001) and the presence of a restrictive filling pattern (χ²=3.6; P<0.05) were the sole independent predictors of major events.

Incremental Prognostic Value of Diagnostic Procedures
At the interactive stepwise procedure, the power of models developed at various steps in hierarchic order (clinical data; clinical and echocardiographic results; clinical, echocardiographic, and Doppler results; clinical, echocardiographic, Doppler, and ²⁰¹Tl results) to predict major events is shown in Figure 6. The global χ² value achieved by the addition of the L/H value to the clinical, echocardiographic, and Doppler variables was significantly higher (global χ²=20.8), indicating that ²⁰¹Tl lung uptake still added significant prognostic information.

Discussion
An elevated lung ²⁰¹Tl uptake on stress images is considered the result of an increased LV filling pressure caused by transient LV dysfunction. Other proposed mechanisms include increased lung transit time, lung water content, and
A high lung 201 Tl uptake was documented in 36% of patients with cardiomyopathy and congestive heart failure. A close correlation between the amount of lung 201 Tl uptake and wedge pressure was documented by Martinez et al. 12 A significant correlation between L/H and a rise in mean atrial pressure. This mechanism could also explain an increased L/H. In the subgroup of patients undergoing right heart catheterization, we also documented a significant correlation between L/H and wedge pressure; this result further supports the hypothesis that a high resting L/H reflects elevated LV filling pressure. 12

The present study is the first assessing the clinical and prognostic significance of resting lung 201 Tl uptake in comparison with clinical, echocardiographic, and hemodynamic findings in a selected, large cohort of clinically stable patients with severe LV dysfunction. The resting lung uptake of the tracer significantly correlated with other indexes of increased LV filling pressure. Moreover, an elevated lung uptake proved a powerful predictor of adverse outcome, its prognostic information being incremental over that obtained by clinical, echocardiographic, and Doppler examination.

**Lung 201 Tl Uptake and Diastolic Function**

Doppler analysis of mitral flow is a noninvasive technique widely used to assess LV diastolic function in different pathological settings. A close correlation between Doppler-derived diastolic function and invasively-derived hemodynamic parameters has been reported by several authors. Finkelhor et al. correlated peak E- and peak A-wave velocities with L/H in 56 patients undergoing exercise perfusion scintigraphy: higher E-wave velocities were observed in patients with high L/H values. In the present study, severe mitral regurgitation and peak A-wave velocity were the sole independent predictors of increased 201 Tl lung uptake, and a significant inverse linear relation between L/H and A was found. Peak A velocity reflects left atrial loading and systolic function: In the presence of an elevated LV stiffness, a reduced blood volume moves through the mitral valve, irrespective of atrial contraction, causing a reduction in peak A velocity and a rise in mean atrial pressure. This mechanism could also explain an increased L/H. In the subgroup of patients undergoing right heart catheterization, we also documented a significant correlation between L/H and wedge pressure; this result further supports the hypothesis that a high resting L/H reflects elevated LV filling pressure.

**TABLE 4. Clinical, Echocardiographic, and Scintigraphic Data in Patients With (L/H > 0.61) and Without (L/H ≤0.61) High Lung 201 Tl Uptake at Quantitative Analysis**

<table>
<thead>
<tr>
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<th>L/H ≤0.61</th>
<th>L/H &gt; 0.61</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>51</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63±10</td>
<td>61±1</td>
<td>NS</td>
</tr>
<tr>
<td>History of congestive</td>
<td>20 (39%)</td>
<td>35 (48%)</td>
<td>NS</td>
</tr>
<tr>
<td>heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.0±0.3</td>
<td>2.2±0.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Echographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDVi, mL/m²</td>
<td>111±38</td>
<td>122±44</td>
<td>NS</td>
</tr>
<tr>
<td>LV ESVi, mL/m²</td>
<td>85±30</td>
<td>98±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>25±6</td>
<td>23±7</td>
<td>NS</td>
</tr>
<tr>
<td>Wall motion score index</td>
<td>2.3±0.3</td>
<td>2.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Peak E velocity, cm/s</td>
<td>77±29</td>
<td>85±26</td>
<td>NS</td>
</tr>
<tr>
<td>Peak A velocity, cm/s</td>
<td>77±24</td>
<td>58±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.1±0.9</td>
<td>1.9±1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>166±47</td>
<td>147±45</td>
<td>0.06</td>
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<tr>
<td>Restrictive filling</td>
<td>13 (25%)</td>
<td>43 (59%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe mitral regurgitation</td>
<td>10 (20%)</td>
<td>35 (48%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Scintigraphic data</strong></td>
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<tr>
<td>Scar extent, %</td>
<td>29±15</td>
<td>30±6</td>
<td>NS</td>
</tr>
<tr>
<td>No. of “nonviable” segments</td>
<td>5.0±3.1</td>
<td>5.2±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Rest-redistribution, n (%)</td>
<td>13 (25%)</td>
<td>25 (34%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

EDVi indicates end-diastolic volume index; ESVi, end-systolic volume index. Data are reported as mean±SD or as number (percentage).

**Figure 4.** Survival free of major events in patients with low (closed line) and high (dotted line) L/H.

**Figure 5.** Survival free of cardiac death (A) or survival free of worsening congestive heart failure (B) in patients with low (closed line) and high (dotted line) L/H.

**Figure 6.** Incremental prognostic value of clinical, echocardiographic, Doppler, and scintigraphic variables. Bars represent χ² statistic when clinical (A); clinical and echocardiographic (B); clinical, echocardiographic, and Doppler (C); and clinical, echocardiographic, Doppler, and scintigraphic data (D) were sequentially added.
Prognostic Implications

Patients with severe LV systolic dysfunction are at high risk of death; assessment of diastolic function has been recently suggested to add information regarding their risk stratification. An abnormal relaxation pattern characterized by a restrictive physiology frequently occurs in patients with extensive damage and, in patients with depressed LV function, diastolic dysfunction may play an important role in determining clinical signs and symptoms. A significant correlation between hemodynamic indexes of pulmonary congestion and survival has been documented. This relation supports the link between a restrictive filling pattern at Doppler analysis and prognosis. Patients with a restrictive LV physiology after acute myocardial infarction were found to be in a particularly high-risk subgroup. Of note, in our study, 2 markers of diastolic dysfunction (an L/H >0.61 and a restrictive Doppler filling pattern) emerged as the sole independent predictors of poor prognosis. Since abnormalities of systolic and diastolic function frequently coexist, a marker of global LV dysfunction such as an increased 201Tl lung uptake may result a powerful marker of poor outcome. Unlike other studies that used a >0.50 L/H as a cutoff to identify high-risk patients undergoing stress 201Tl imaging, in our study, based on resting imaging, a higher L/H cutoff value (ie, 0.61) was found by ROC analysis to be the best discriminate patients at increased risk of major events. Differences in pulmonary mean transit time, pulmonary pressures, or vascular permeability at rest or during stress could explain the discrepancy in cutoff values. We also determined how well an increased resting 201Tl lung uptake performs when clinical and echo-Doppler findings have already been taken into account.

In the whole study cohort, roughly 75% of the left ventricle, on average, was viable. Since the LV ejection fraction was only 23%, this suggests that most of the viable segments were dysfunctional and presumably hibernating. For various reasons, however, only 23% of the patients underwent subsequent coronary revascularization. A consistent amount of myocardial viability in LV dysfunctioning regions is a powerful predictor of outcome. In patients with >7 viable segments out of 11 myocardial segments at preoperative rest-redistribution 201Tl imaging, Ragosta et al showed that mean LV ejection fraction significantly improved after coronary surgery. Pagley et al showed that the 201Tl extent of myocardial viability was the best predictor of transplant-free survival. Moreover, the extent of viable and potentially jeopardized myocardium has been shown a powerful predictor of mortality in medically treated patients. In contrast to these retrospective studies, in our study, which evaluated a more selective population with severe LV dysfunction, advanced functional class, and predominant symptoms of heart failure, the myocardial viability extent did not emerge as a significant predictor either of hard or of major events at follow-up.

Limitations

Our results were obtained in patients with ischemic heart disease and may not apply to patients with LV dysfunction of different causes. We found a significant correlation between the capillary “wedge” pressure and L/H, although invasive measurements were obtained in a limited number of patients and were performed within 48 hours of the scintigraphic study. If some degree of discordance in results is expected between invasive and noninvasive studies performed over separate days, any misclassification, however, would attenuate the results; so the true relations are likely to be even stronger than observed. We noninvasively assessed LV filling pressures by echocardiographic mitral inflow Doppler analysis; other accurate methods have been recently proposed. Finally, results of 201Tl imaging regarding the amount of LV viable tissue influenced the decision to perform coronary surgery in some patients; on the other hand, the degree of the thallium lung uptake, the topic of our study, played no role in the surgical decision.

Conclusions

Our data suggest that in patients with severe LV dysfunction undergoing 201Tl scintigraphy for the assessment of residual viability, an elevated tracer uptake in the lungs should also be considered by clinicians as having powerful prognostic significance. Abnormal L/H is easily and automatically detectable by standard 201Tl imaging and identifies a subgroup of patients with poor prognosis and in whom a very aggressive management seems warranted.

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References


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