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Noninvasive identification of left main and three-vessel coronary artery disease by thallium-201 single photon emission computed tomography during adenosine infusion

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Advanced coronary artery disease, defined as left main or three-vessel coronary disease, was identifiable noninvasively by means of adenosine Tl-201 single photon emission tomography. Among 75 consecutive patients with angiographically documented coronary artery disease, there were 11 patients with the presence (group 1) and 64 patients with the absence (group 2) of advanced coronary artery disease. The lung-to-heart ratio (L/H ratio) of Tl-201 uptake was calculated as the fraction of average Tl-201 counts per pixel in the lung divided by those in the myocardium. The left ventricular dilation ratio (LVDR) was determined as a ratio of left ventricular cavity size in the early image to that in the delayed image. The patients in group 1 had more defects (2.3 ± 0.6 seg. vs. 0.9 ± 0.7 seg., $p < 0.001$), a higher L/H ratio ($35 \pm 4\%$ vs. $28 \pm 5\%$, $p < 0.001$) and a higher LVDR (1.13 ± 0.04 vs. 1.06 ± 0.04, $p < 0.001$) than those in group 2. The diagnostic accuracy of the identification of advanced coronary artery disease was 89% by perfusion defects, 68% by L/H ratio and 81% by LVDR. Stepwise discriminant analysis revealed that LVDR ($F = 36.2$, $p < 0.0001$) and perfusion defects ($F = 8.9$, $p < 0.004$) were the significant and independent discriminators of advanced coronary disease.

Identification of patients with left main or three-vessel coronary disease was enhanced by additional analysis of cavity dilation of the left ventricle and increased Tl-201 activity in the lung.

Key words: thallium-201, adenosine, coronary artery disease

INTRODUCTION

INTRAVENOUS INFUSION of adenosine has been applied as a pharmacologic stress test in combination with thallium-201 (Tl-201) scintigraphy, since adenosine is a direct and potent coronary vasodilator.[1–3] Its safety and potential usefulness have now been confirmed in clinical trials.[4–7]

In patients with multi-vessel coronary artery disease, homogeneous reduction of Tl-201 uptake sometimes fails to reveal all hypoperfused myocardial regions and results in an underestimation of multi-vessel coronary involvement.[8,9] It is important to identify the patients with advanced coronary artery disease, because they carry a high risk of future cardiac events. However, the presence of perfusion defects in multiple vascular territories is not detected with sufficient sensitivity for correct identification of patients with advanced coronary artery disease.[10]

In exercise Tl-201 imaging, the assessment of increased Tl-201 activity in the lung has been utilized as a sign of advanced coronary disease.[11–13] Transient dilation of the left ventricular cavity has also been noted in patients with advanced coronary disease in either exercise[14] or dipyridamole[15] Tl-201 imaging. Nevertheless, the feasibility of additional analysis such as lung Tl-201 uptake and cavity dilation for identifying advanced coronary disease has not been rigorously examined in adenosine Tl-201 imaging. Accordingly, we examined which is the best to use in detecting left main or three-vessel coronary disease: the presence of perfusion defects, lung Tl-201 uptake or dilation of the left ventricular cavity.

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MATERIALS AND METHODS

Subjects

Seventy-five consecutive patients who had undergone adenosine Tl-201 myocardial SPECT and coronary arteriography for the diagnosis of coronary artery disease were enrolled. The study group consisted of 47 male and 28 female with a mean age of 62 years (range 37 to 85). None had previously received percutaneous transluminal coronary angioplasty or coronary-aorto bypass grafting. Thirty-one patients had both a clinical history and electrocardiographic evidence (defined as a diagnostic Q wave of 40 msec or greater) of previous myocardial infarction. Coronary arteriography revealed that 28 patients had single-vessel disease, 18 had two-vessel disease, 9 had three-vessel disease, and 18 had no significant coronary artery stenosis. Two patients had significant coronary stenosis of the left main coronary artery. Significant coronary stenosis was defined as a percent luminar diameter narrowing of 75% or more in either main epicardial artery or major branches. The patients were divided into 2 groups according to the angiographic findings: patients with advanced coronary artery disease, defined as left main or three-vessel coronary disease (group 1, n = 11), and those without advanced coronary disease (group 2, n = 64). All scintigraphy and arteriography tests were performed for clinical purposes after the informed consent was obtained. The study protocol was approved by the Yamagata University Committee on Human Research.

Adenosine infusion protocol

All cardiovascular medications were discontinued at least 12 hours before the adenosine test, except for the short-acting sublingual nitrates. Adenosine was infused intravenously at a rate of 0.14 mg/kg/min for 6 minutes[4] with an infusion pump (Nakagawa-Seikousha, Co. Ltd.). At 3 minutes after the start of adenosine infusion, a dose of 111 MBq of Tl-201 was bolusly injected into a separate vein. Blood pressure was measured every minute on the left arm by a standard cuff method and a 12-lead ECG was continuously monitored during the test.

Tl-201 myocardial imaging

Data acquisition and processing: Cardiac imaging was begun 10 minutes after the Tl-201 injection and repeated 3 hours later. All studies were recorded with a large field-of-view rotating gamma camera (Siemens, ZLC-7500 Digtrac) equipped with a parallel hole, high resolution collimator.[15,16] Thirty-two planar images were obtained over a 180° arc from 45° right anterior oblique to the 45° left posterior oblique positions. Each image was accumulated for 30 seconds. The data were stored on a 64 × 64 matrix. Data processing was performed with a nuclear medicine computer (Shimadzu, Scintipac-700). A series of contiguous transaxial images of 6 mm thickness were reconstructed by means of a filtered back projection algorithm without attenuation correction.[15,16] These transaxial slices were then reoriented in the short axis, vertical long axis, and horizontal long axis of the left ventricle.

Image interpretation: The regions with decreased Tl-201 uptake were assessed by 2 independent observers who were not given any information regarding the clinical history and angiographic findings of the patients. The left ventricular myocardium was divided into 5 segments: anterior, septal, inferior, lateral and apical. The 5-point scoring system was used for evaluating the level of myocardial Tl-201 uptake[17,18]: 4 = normal, 3 = slightly reduced, 2 = reduced, 1 = severely reduced, 0 = no activity. In interpreting myocardial images, an uptake score of less than 3 at the early image was considered as a perfusion defect. A number of segments with Tl-201 defects was used for evaluating the size of hypoperfused myocardium. The scintigraphic pattern of left main coronary disease was defined as perfusion abnormalities in combined anterior, septal and lateral regions of the left ventricle. The three-vessel coronary disease pattern was considered to be present when perfusion defects were noted in the territories of all three major coronary arteries.

Measurement of lung Tl-201 uptake (Fig. 1): The unprocessed anterior projection image (number 9 of 32 images) acquired as part of the initial imaging was used to evaluate lung Tl-201 activity.[13] Separate square regions of interest (ROI) were defined for areas of the left upper lung field (6 × 6 pixels in size) and the left ventricular myocardium (4 × 4 pixels in size) as previously reported.[19] The lung ROI was placed over the most intense activity in the lung and was usually at least 5 pixels above the anterior myocardial wall. The myocardial ROI was placed over the myocardium with the peak count density. A lung-to-heart ratio (L/H ratio) was calculated as a fraction of the mean counts per pixel in the lung divided by those in the myocardium.

Measurement of left ventricular dilation ratio (Fig. 2): Dilation of the left ventricular cavity following adenosine was determined quantitatively as reported in the previous study.[15] Briefly, on the short axis images, 6 radial count profiles were created diametrically at 30° intervals. In each profile, the distance between the two count peaks was measured, and the arithmetical average of these six distances was defined as a left ventricular cavity size. The extent of left ventricular dilation was estimated as the ratio of left ventricular cavity size in the early image to that in the delayed image (left ventricular dilation ratio: LVDR).

Coronary arteriography

Coronary arteriography was performed with a standard Judkins' technique. All studies were assessed by two experienced cardiologists who had no information relating to the clinical history or scintigraphic results of the patients. Significant coronary stenosis was defined as a

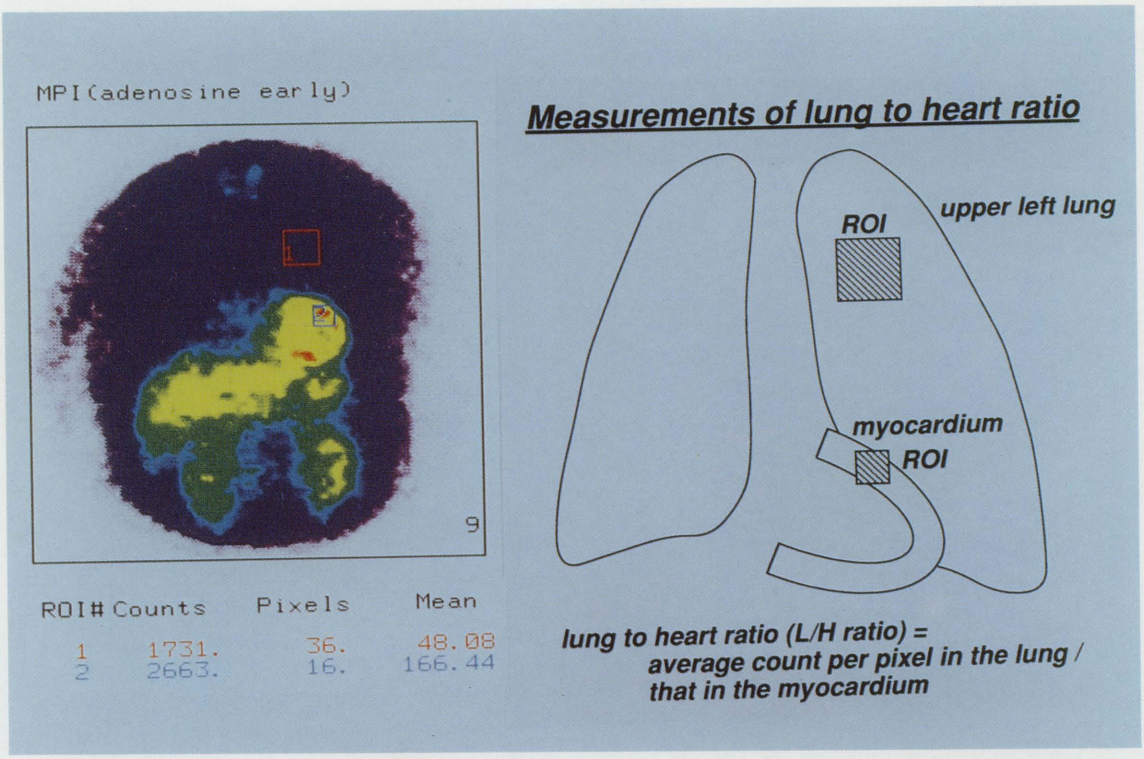

Fig. 1 Square regions of interest were defined for the left upper lung field and left ventricular myocardium on the anterior projection image. The lung-to-heart ratio was calculated as a fraction of the mean counts per pixel in the lung divided by those in the myocardium.

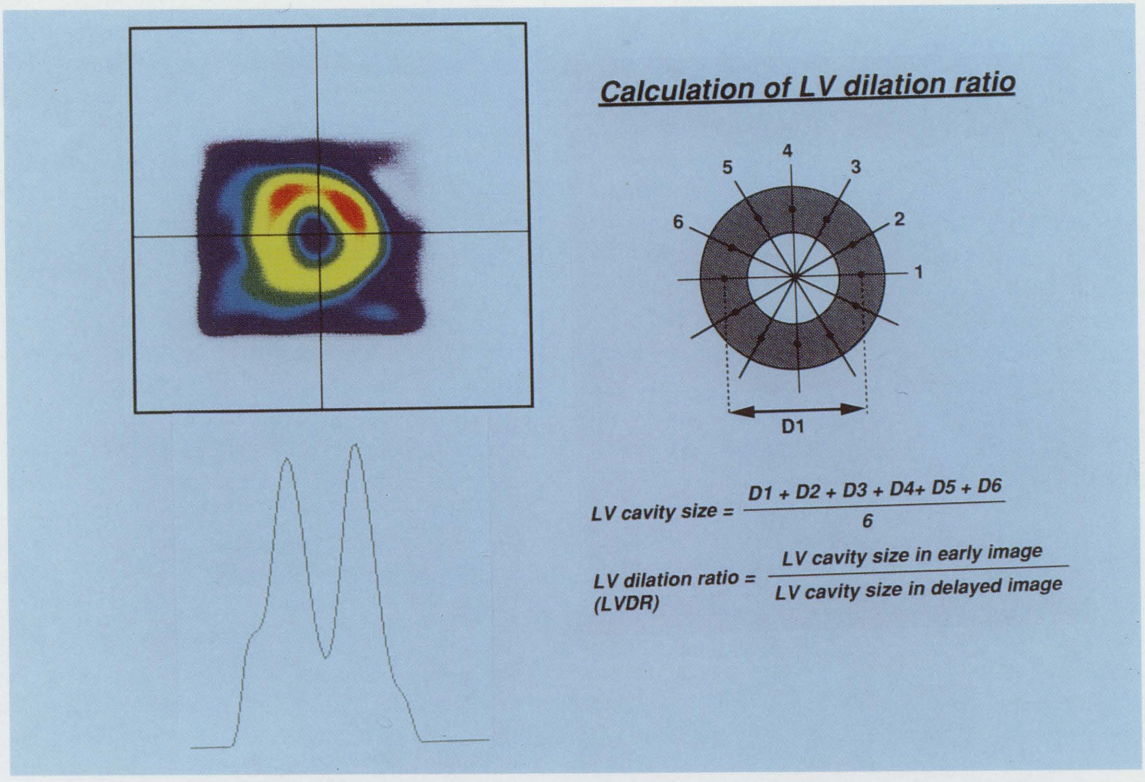

Fig. 2 The arithmetical average of 6 distances derived from radial count profile curves were defined as a left ventricular cavity size. A ratio of left ventricular cavity size in the early image to that in the delayed image was determined as a left ventricular dilation ratio.

Table 1 Clinical, hemodynamic and scintigraphic findings

	group 1 (n = 11)	group 2 (n = 64)	p value
age (year)	61 ± 12	63 ± 9	ns
sex (male)	9 (82%)	38 (59%)	ns
myocardial infarction	7 (64%)	24 (38%)	ns
anginal pain	4 (36%)	12 (19%)	ns
ST depression	6 (55%)	11 (17%)	< 0.01
heart rate (bpm)			
basal	65 ± 10	64 ± 12	ns
peak	78 ± 8	82 ± 13	ns
delta	13 ± 6	18 ± 9	ns
SBP (mmHg)			
basal	136 ± 14	141 ± 24	ns
peak	119 ± 15	121 ± 20	ns
delta	− 17 ± 14	− 20 ± 16	ns
RPP (bpm × mmHg)			
basal	8851 ± 1648	9119 ± 2453	ns
peak	9361 ± 1539	9924 ± 2334	ns
delta	510 ± 1047	804 ± 1706	ns
No. of defects	2.3 ± 0.6	0.9 ± 0.7	< 0.001
L/H ratio (%)	35 ± 4	28 ± 5	< 0.001
LVDR	1.13 ± 0.04	1.06 ± 0.04	< 0.001

group 1: patients with advanced coronary artery disease
group 2: patients without advanced coronary artery disease
SBP, systolic blood pressure; RPP, rate pressure product; No., number; L/H ratio, lung-to-heart ratio; LVDR, left ventricular dilation ratio.

percent luminar diameter narrowing of more than 75% in either main epicardial arteries or major branches.

Statistics

Statistical significance was tested by means of a program of Statistical Analysis System (SAS). In univariate analysis, continuous variables were compared by a Students' t-test, and the differences in proportion (noncontinuous variables) were examined by a chi-square test. To examine which parameters were the most important among the perfusion defects, L/H ratio and LVDR for the detection of advanced coronary artery disease, stepwise discriminant analysis was employed. The enter and removal criteria used in the stepwise discriminant analysis were 0.15 of the p value. Data were reported in mean ± one standard deviation. A p value < 0.05 was considered significant.

RESULTS

Clinical features and hemodynamic and scintigraphic findings were compared between the patients with the presence (group 1) and the absence (group 2) of advanced coronary disease (Table 1). ST depression was more frequently observed in group 1 than in group 2 (55% vs. 17%, $p < 0.01$). The patients in group 1 had more defects (2.3 ± 0.6 seg. vs. 0.9 ± 0.7 seg., $p < 0.001$), a higher L/H ratio (35 ± 4% vs. 28 ± 5%, $p < 0.001$) and higher LVDR (1.13 ± 0.04 vs. 1.06 ± 0.04, $p < 0.001$) than those in group 2.

When a L/H ratio higher than the mean + 2 standard deviations in patients with normal coronary arteries (n = 12) was considered as abnormal, the normal upper limit for the L/H ratio was 30%. Similarly, the normal upper limit for LVDR was defined as 1.10 from the values in patients with normal coronary arteries. The sensitivity, specificity and accuracy of correctly identifying advanced coronary disease by perfusion defects, the L/H ratio and LVDR are shown in Figure 3. Perfusion defects of left main or three-vessel disease pattern were noted in 5 of 11 (45%) patients in group 1. The presence of abnormal L/H ratio and LVDR detected 9 (82%) and 8 (73%) patients as having advanced coronary disease, respectively. In patients in group 2, the absence of advanced coronary disease was correctly identified in 62 (97%) patients by perfusion defects, 42 (66%) patients by the L/H ratio, and 53 (82%) patients by LVDR. The diagnostic accuracy for the presence of advanced coronary artery disease was 89% by perfusion defects, 68% by the L/H ratio and 81% by LVDR.

We then examined which is the most important in determining advanced coronary disease among clinical, hemodynamic, electrocardiographic, and scintigraphic findings using stepwise discriminant analysis. As shown in Table 2, LVDR ($F = 36.2$, $p < 0.0001$) and perfusion defects ($F = 8.9$, $p < 0.004$) were determined to be the first and second independent and significant correlates of advanced coronary disease.

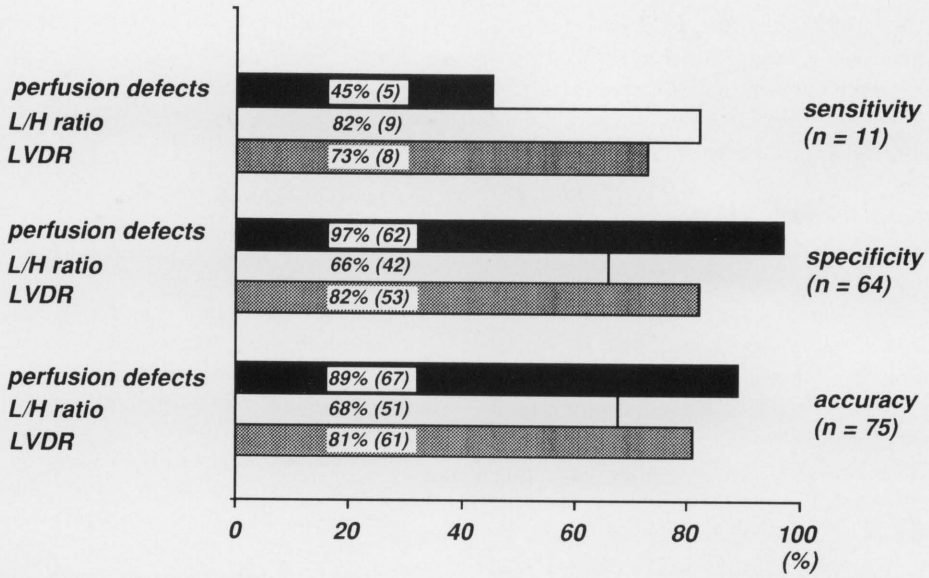

Fig. 3 The sensitivity, specificity and accuracy for the detection of patients with advanced coronary artery disease. L/H ratio, lung-to-heart ratio; LVDR, left ventricular dilation ratio.

Table 2 Significant discriminators for the detection of patients with advanced coronary artery disease

step	variable	F value	p value
1	LVDR	36.2	0.0001
2	perfusion defects	8.9	0.004

LVDR, left ventricular dilation ratio.

DISCUSSION

Intravenous infusion of adenosine in combination with Tl-201 imaging has now been accepted as a pharmacologic stress test, because adenosine is a direct and potent coronary vasodilator with a short half-life. The coronary vasodilator effect of dipyridamole infusion is indirect through increased endogeneous adenosine levels. The vasodilator response after dipyridamole infusion has been shown to be variable and prolonged for up to 20 minutes. In contrast, the vasodilatory effect of adenosine is extremely short with an effective half-life of 30 seconds and appears to be consistent and near maximal.[20] The short-lasting effect of adenosine is advantageous when rapid serial assessments of coronary blood flow are repeated. Furthermore, serious adverse reactions with adenosine usually can be managed by simply discontinuing the infusion.

Tl-201 perfusion imaging has been widely accepted as a useful method for the noninvasive evaluation of patients with coronary artery disease. However, in multi-vessel disease, homogeneous reduction of Tl-201 uptake sometimes fails to reveal all hypoperfused myocardial regions and results in an underestimation of coronary involvement.[8,9] This limitation will occur as a result of the "spatial relative" nature of perfusion defects analysis.[10] To overcome such disadvantages of Tl-201 imaging, additional analysis such as the assessment of lung Tl-201 activity [11–13] and cavity dilation of the left ventricle[14,15] has been utilized for the detection of advanced coronary artery disease.

Increased lung Tl-201 activity in the immediate post-exercise imaging is noted in patients with advanced coronary artery disease and correlated with the exercise-induced increases in pulmonary capillary pressure due to left ventricular dysfunction.[11] A quantitative assessment of lung Tl-201 activity expressed as the ratio of lung to myocardial counts (L/H ratio) has been proposed as a sign of advanced coronary disease in exercise Tl-201 SPECT.[13] Recently, Nishimura et al. has reported that, in adenosine Tl-201 imaging, lung Tl-201 uptake is higher in patients with multi-vessel disease than in those with single-vessel disease.[21] In the present study, the increase in the L/H ratio during adenosine infusion could identify the patients with advanced coronary artery disease (sensitivity 82%). The increase in the L/H ratio during adenosine suggests that adenosine-induced changes in myocardial blood flow produced sufficient ischemic left ventricular dysfunction to raise the left ventricular filling pressure and thus pulmonary capillary pressure.[19] Recently, Iskandrian et al.[22] have reported that multivessel thallium abnormality, increased lung thallium uptake, and ST depression are predictive variables for high risk patients with coronary artery disease. The L/H ratio may be utilized for the detection of advanced coronary disease in adenosine Tl-201 SPECT as reported in exercise Tl-201 imaging.

We have previously reported that apparent dilation of the left ventricular cavity on Tl-201 SPECT reflects diffuse subendocardial hypoperfusion induced by dipyridamole, and quantitative assessment of cavity

dilation, LVDR, is useful for the detection of patients with three-vessel disease.[15] In patients who showed signs of cavitary dilation, the left ventricular ejection fraction measured by radionuclide ventriculography did not change after dipyridamole infusion. It has also been shown in exercise Tl-201 imaging that transient dilation of the left ventricle is observed in patients with extensive coronary disease.[14] Sugihara et al. have reported that exercise-induced subendocardial ischemia in patients with hypertrophic cardiomyopathy can be detected as dilation of the left ventricular cavity on exercise Tl-201 SPECT.[23] Iskandrian et al. have indicated that, in adenosine Tl-201 imaging, cavity dilation of the left ventricule is also noted in patients with coronary artery disease and reflects adenosine-induced subendocardial ischemia.[6] However, they did not comment on the relation of cavity dilation to the extent of coronary artery disease, and the diagnostic value of cavity dilation in adenosine Tl-201 imaging has not been rigorously examined. In the present study, the presence of perfusion defects correctly detected only 45% of patients with advanced coronary disease, whereas the L/H ratio and LVDR identified 82% and 73% of patients as having advanced coronary disease, respectively. Stepwise discriminant analysis revealed that LVDR was the most powerful in the detection of advanced coronary disease. Because the coronary vasodilatory effects of dipyridamole are achieved predominantly through adenosine, adenosine induces unfavorable endocardial/epicardial blood flow distribution due to the "coronary steal" phenomenon at the area distal to critical stenosis.[24,25] It is considered that the relative decrease in subendocardial perfusion during adenosine is detected as the apparent dilation of the left ventricular cavity on Tl-201 images. It is speculated that the assessment of dilation of the left ventricular cavity is useful for the detection of advanced coronary disease, because diffuse hypoperfusion around the subendocardium is represented as cavity dilation on Tl-201 images.

CONCLUSION

Additional analysis of increased Tl-201 uptake in the lung and cavity dilation of the left ventricle provides complimentary information for the identification of patients with left main or three-vessel coronary disease.

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