Evaluation of Technetium-99m-Sestamibi Lung Uptake: Correlation with Left Ventricular Function

Raffaele Giubbini, Riccardo Campini, Elisa Milan, Orazio Zoccarato, Cesare Orlandi, Pierluigi Rossini, Pantaleo Giannuzzi, Giovanni La Canna and Michele Galli

Nuclear Medicine and Cardiology Departments, Spedali Civili and University of Brescia, Brescia; Fondazione Clinica del Lavoro, Veruno, Italy; and MEDCO Inc., Research Triangle Park, North Carolina

Early 201Tl lung uptake is a well-known phenomenon (1-5). It has been shown to be related to pulmonary edema consequent to a sudden, exercise-induced increase of left ventricular end-diastolic pressure (6). A slow and progressive decrease of pulmonary activity follows, due to the clearance of interstitial water. An early increase in lung uptake has been shown to be an index of left ventricular dysfunction and/or of severe coronary artery disease (CAD) (7-11). This index is important for the functional evaluation and the prognostication of CAD patients (12-16).

Technetium-99m-sestamibi lung uptake has not been thoroughly investigated. The pharmacological characteristics of this tracer differ greatly from those of 201Tl. The tracer distributes in the heart according to blood flow and shows only limited (17,18) changes of regional myocardial distribution over time. This makes delayed acquisition at 60-120 min from administration the standard for 99mTc-sestamibi imaging. Therefore, the potential, transient transit of the tracer in the interstitial space early after administration is generally not evaluated. However, as shown in Figure 1, increased lung uptake of 99mTc sestamibi is occasionally observed, mostly in the planar images acquired for SPECT studies.

The goal of this study was to evaluate the possible functional significance of 99mTc-sestamibi lung uptake in rest and stress images obtained 60-120 min after tracer administration.

METHODS

Study Population

We studied 72 patients with recent (<2 mo) anterior myocardial infarct (MI) and in New York Heart Association functional class I or II (Group 1). All of them were capable of undergoing an exercise stress test without chest pain and/or low threshold electrocardiographic changes indicative of ischemia. All patients were male, ranging in age from 36 to 76 yr, with a mean of 50 ± 8 yr. No patients suffered from a previous MI; they were enrolled consecutively after admission to a rehabilitation center. After giving their informed consent, the patients underwent 99mTc-sestamibi first-pass ventriculography and SPECT imaging as part of their routine functional evaluation post-MI. Coronary angiography was performed in a total of 35 patients. Of these, 19 had single-vessel disease, 8 had double-vessel disease, 3 had triple-vessel disease and 5 did not show significant coronary stenosis. An attempt was also made to evaluate differences in LHR between MI patients with exercise ejection fraction higher (Group 1A) or lower (Group 1B) than 40%.

A control group of 46 gender-matched normal patients (mean age 47 ± 9 yr, Group 2) were also studied in an identical fashion.
These subjects had a pre-test likelihood of CAD <5%, a negative exercise tolerance test and a normal stress and rest Tc-sestamibi study.

**Exercise Tolerance Test**

Patients fasted for at least 4 hr prior to the ETT. The patients underwent a symptom-limited, maximal bicycle exercise stress test to at least 85% of their maximal predicted heart rate, with increasing loads of 25 watts. The test was performed with the subjects sitting in an upright position in front of the gamma camera. Early discontinuation of the exercise test was permitted due to the onset of moderate chest pain, dyspnea, fatigue, 1 mm or greater ST-segment depression or the appearance of arrhythmias. At peak exercise, the patients were asked to stop exercising and a bolus (-0.5 ml) of 1100 MBq 99mTc-sestamibi was administered through a central venous catheter previously positioned either in the superior vena cava or in the right atrium. The transit of the bolus was followed in real time, and the patients were asked to maintain a short period of apnoea (3-5 sec) during the left ventricular filling phase. At the end of the acquisition of the first-pass ventriculogram (16 sec), the patients exercised for an additional 90 sec.

An additional first-pass ventriculographic study was also performed under resting conditions within 24 hr.

**First-Pass Ventriculography**

The method employed for the first-pass ventriculography has been previously described and validated by our group (19). Briefly, a single-crystal LFOV high count rate gamma camera equipped with a high-sensitivity collimator for low energies was used. The studies were acquired in frame mode using a 32 x 32 matrix, 2x zoom, and a 32-sec frame rate. The analysis of the study included the semi-automatic delineation of ventricular margins and valvular planes, interpolative background subtraction and reconstruction of a representative cycle from which ejection fraction, ventricular volumes and parametric imaging were derived. Ventricular ejection fraction was calculated from the following formula:

\[
\text{LVEF} = \frac{\text{EDC} - \text{ESC}}{\text{EDC}},
\]

where LVEF is left ventricular ejection fraction, EDC is end-diastolic counts and ESC is end-systolic counts.

The left ventricular end-diastolic volume was calculated using a standard area length method on the end-diastolic frame. The cardiac output was derived from the following formula:

\[
\text{CO} = \text{EDV} \times \text{LVEF} \times \text{HR},
\]

where CO is the cardiac output, EDV is end diastolic volume and HR is heart rate.

The mean pulmonary transit time was determined from the first-pass right ventricular and left ventricular concentration curves, measuring the peak-to-peak time.

**Technetium-99m-Sestamibi Lung Uptake Analysis**

Both subjects of Group 1 and 2 were imaged by 99mTc-sestamibi SPECT using a separate-day protocol; for Group 1 patients, the injection of the tracer was performed during the first-pass RNV. All the subjects of the two study groups were injected with a standard activity of 1100 MBq both at rest or at peak exercise. Imaging was started after 60-120 min after injection of the tracer. The time interval between injection and acquisition was the same for rest and exercise studies. SPECT acquisition was performed on rotating gamma camera/computer system (Elscint Apex 409 or SP-4), equipped with identical high-resolution collimators. Sixty images were obtained over an anterior 180° arc starting from the right anterior oblique view. Each image was obtained for 20 sec, using a 64 x 64 matrix.

For 99mTc-sestamibi lung uptake analysis, a method similar to the one previously described and validated for 201TI by Kahn et al. (20) was used in this study. Briefly, lung-to-heart count ratios (LHR) were calculated on planar projections from the sets of SPECT images. After a standard nine-point smoothing and the identification of the cardiac region, the highest count rate was automatically identified on the anterior projection and on those immediately preceding and following it. A second region of interest (ROI), 8 pixels in diameter and corresponding to the highest lung count rate, was placed by the operator on the left pulmonary region at a distance of at least 5 pixels from the cardiac area (Fig. 2). The average counts per pixel in each ROI was then calculated. Lung uptake was expressed as the mean LHR on the three images. All studies were analyzed by operators blinded to clinical and scintigraphic data.

**Statistical Analysis**

Heart-to-lung uptake ratios were expressed as mean ± s.d. The unpaired Student's t-test was used when comparing the group of patients with anterior MI and the control group. The paired Student's t-test was also used when comparing stress/rest data in the same subjects.

The chi-square test was used to compare the frequency of LHR increase/decrease after exercise in control group and in infarcted subjects. The null hypothesis was rejected with p < 0.05.

**RESULTS**

**Technetium-99m-Sestamibi Lung-to-Heart Uptake Ratio**

In the control group resting and exercise LHR were 0.42 ± 0.05 and 0.37 ± 0.05, respectively. The exercise LHR was significantly lower than the resting LHR (p < 0.001). The patients with prior anterior MI showed LHR...
values which were higher than the controls both at rest (0.47 ± 0.07; p < 0.001) and after exercise (0.46 ± 0.09; p < 0.001). In addition, no changes in LHR were induced in this population by exercise (Fig. 3). Forty out of 46 patients (87%) in Group 2 (Fig. 4A) and 42 out of 72 patients (58%) in Group 1 showed a decrease of the LHR values after exercise (chi-square = 10.8, p < 0.001). Moreover, a significant difference was observed between Group 1A (Fig. 4B) and Group 1B (Fig. 4C), showing a decrease in LHR after exercise in 72% and 36% of subjects, respectively (chi-square = 9.9; p < 0.01).

As shown in Figure 5, the patients with more compromised ventricular function (Group 1B) showed significantly higher LHR, both at rest and after exercise (rest = 0.5 ± 0.07, p < 0.001; exercise = 0.51 ± 0.10, p < 0.001) in comparison to the control group (Group 2) (rest = 0.42 ± 0.05, p < 0.001; exercise = 0.37 ± 0.05, p < 0.001) and to the patients with less severe left ventricular dysfunction (Group 1A) (rest = 0.45 ± 0.06; exercise = 0.42 ± 0.07).

### Comparison Between LHR and LVEF

A statistically significant correlation was found between LHR values and LVEF as obtained by first-pass radionuclide ventriculography both at rest (y = −0.49e−0.006x, r = 0.51; p < 0.001) and during exercise (y = −0.46e−0.006x, r = 0.6; p < 0.001) (Fig. 6). A weak inverse linear corre-
loration was observed between Δ EF (exercise EF–rest EF) and Δ LHR (exercise LHR–rest LHR) (y = −0.32 × −0.03; r = 0.25; p < 0.05). LHR values did not correlate with other hemodynamic parameters, including pulmonary mean transit time, cardiac volumes and cardiac output.

An attempt was also made to utilize this type of analysis of lung uptake to diagnose patients with exercise-induced depression of ventricular function. An LHR of 0.47 (calculated as the mean value in the control population plus 2 s. d.) was used as threshold. Values greater than 0.47 were considered indicative of exercise-induced left ventricular dysfunction. By this approach, LHR values higher than 0.47 were found in 22 of the 32 patients with EF < 40% and depression of ventricular function. An LHR of 0.47 (calculated as the mean value in the control population plus 2 s. d.) was used as threshold. Values greater than 0.47 were found in 22 of the 32 patients with EF < 40% and in only 6 of the 40 patients with EF > 40%. A sensitivity of 69% and a specificity of 85% was therefore found for the 0.47 LHR threshold in predicting a depressed ejection fraction at stress.

No significant difference was found in rest and exercise LHR values between patients affected by single-vessel or multiple-vessel disease (rest: 0.42 and 0.44, respectively; p = n.s.; exercise 0.44 and 0.46; p = n.s.)

**DISCUSSION**

The presence of transient cavitary dilatation and lung uptake during $^{201}$TI scintigraphy is indicative of exercise-induced left ventricular dysfunction, the most important prognostic indicator in patients with CAD and post-MI.

Several clinical and experimental studies have demonstrated a correlation between lung uptake and left ventricular dysfunction, expressed as an increase in pulmonary artery wedge pressure both at rest (1,9) and after exercise (30). In addition to ischemic heart disease, other pathological conditions such as valvular disease (9) and idiopathic cardiomyopathies (25) may be associated with an increased lung uptake.

In our study, we have shown that $^{99m}$Tc-sestamibi lung uptake is significantly higher in patients with left ventricular dysfunction than in normal subjects. In the control population, LHR values drop during an exercise stress test. On the contrary, no overall exercise-induced changes of LHR were observed in the diseased population. In addition, the subset of patients with more severely compromised left ventricular function and with stress EF values lower than 40% showed an increase in LHR values after exercise stress. Stress LHR values were also shown to inversely correlate with EF values in patients with left ventricular dysfunction.

An attempt was also made to identify patients with severely depressed left ventricular function (EF < 40%) by using the upper limit of the normal range as a cut-off. This technique demonstrated a good specificity (85%), but limited sensitivity (69%).

Several mechanisms may be responsible for increased $^{201}$TI lung uptake, including augmented pulmonary transit time with consequent enhancement of extraction and increases in interstitial water and/or pulmonary permeability. Furthermore, in patients with triple-vessel coronary disease, an increase in lung-to-heart ratios may be the function of diminished myocardial activity rather than increased lung activity. Another mechanism for the relative increase in thallium lung activity, which needs to be considered at 60–120 min, is the possibility that this could be an artifact due to accelerated myocardial clearance.

The same mechanisms may also explain the results presented in this study with $^{99m}$Tc-sestamibi. However, substantial differences exist in the techniques that are practically feasible with the two tracers. With $^{201}$TI, the evaluation is done a few minutes after administration since lung uptake is a dynamic process that tends to normalize already at 18 min following the end of exercise stress (26). Technetium-99m-sestamibi image acquisition in our study was performed 60–120 min after tracer administration, since perfusion imaging is performed with this tracer after hepatobiliary clearance has removed most of the subdiaphragmatic activity. The persistence of relatively high values of lung uptake at these time intervals may be due to the differences in kinetics previously described for these tracers. Unlike $^{201}$TI which behaves as a potassium analogue, $^{99m}$Tc-sestamibi is retained within the cellular mitochondrial matrix (23,24) with limited washout over time (17,18). Therefore the increased levels of lung uptake in patients with left ventricular dysfunction persisting after over 60 min from the injection of the radiopharmaceutical, may be related to increased lung tissue uptake and retention. This procedural difference in the timing of evaluation of lung uptake, in comparison with $^{201}$TI, does not affect the capability of the test to discriminate between normal subjects and patients with left ventricular dysfunction.

No correlation was found between LHR and the number of diseased vessels in the 35 patients who underwent coronary angiography, but it has to be taken into account that the majority of the patients had a left anterior descending coronary stenosis, which can be associated with severe left ventricular dysfunction (7,8).

In our study, the calculation of the LHR of $^{99m}$Tc-ses-
tamibi was done on the anterior images of SPECT acquisition. This procedure was previously proposed for 201Tl (20,22). Kahn et al. found a high correlation between SPECT LHR obtained 17 min after tracer injection and LHR calculated on planar images pre-SPECT (20). A high correlation has been reported as well between lung uptake and CAD severity and left ventricular dysfunction (22). Moreover, Illmer et al. (28) studied different approaches for LHR calculation from SPECT studies and confirmed a better accuracy to predict planar LHR values of the method based on the calculation of LHR on the anterior images rather than on tomographic slices. As suggested by Mannting et al. (29) to limit the statistical inaccuracy of the measure the LHR was calculated on more than one image (three anterior views in our study).

Technetium-99m-sestamibi lung uptake in normal subjects appears to be higher than that reported for 201Tl. The postexercise lung-to-heart ratio values reported in the literature for 201Tl range from 0.24 to 0.28 (20,22,28). In our study, we report a value of 0.37 ± 0.05 for 99mTc-sestamibi, which is also higher than that reported by Mannting et al. (27) and Najm et al. (21) for the same tracer utilizing planar imaging. We think that these differences may be mainly related to different selection criteria of the ventricular ROIs adopted by the different authors.

CONCLUSION

Lung uptake quantification during 99mTc-sestamibi SPECT studies should allow the identification of patients with left ventricular dysfunction. We have demonstrated differences in LHR values between normal subjects and post-MI patients. However, we have no information at the present time on the prognostic value of the technique. The population evaluated in this study is highly selective and does not allow gathering of meaningful prognostic data. Further trials should be performed to study how 99mTc-sestamibi lung uptake correlates with long-term survival.

ACKNOWLEDGMENTS

The authors thank Mrs. Aurora Vaccari, Mrs. Lina Facchetti and Mrs. Giacoma Romolo for their excellent technical support. This paper was presented at the 39th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA 1992.

REFERENCES

26. Rodenheiler JA, Boucher CA, Strauss HW, Pohost GM, Okada RD. De-
crease in the ability to detect elevated lung thallium due to delay in commencing imaging after exercise. *Am Heart J* 1985;110:830–835.


(continued from page 11A)

FIRST IMPRESSIONS

EXTENSIVE THROMBOTIC DISEASE CAUSED BY PROTEIN-S DEFICIENCY

PURPOSE

A 33-yr-old white female presented with lower extremity pain and nonpitting edema. She was referred for a radionuclide venograph of both lower extremities. An attempt to perform a conventional contrast venogram at another institution was unsuccessful even after venous cutdown. The radionuclide venograph shows extensive thrombotic disease associated with insufficiency, multiple collateral channels and inferior vena caval obstruction (Fig. 1). Further laboratory work-up revealed that the patient had protein-S deficiency.

RED BLOOD CELL LABELING

Red blood cells were labeled by first reconstituting a pyrophosphate kit with 3 ml sterile, pyrogen-free isotonic saline. After waiting 5 min, 1.5 ml of the “cold” pyrophosphate was administered by direct venipuncture in an antecubital vein.

TRACER

Technetium-99m-pertechnetate (370 MBq) in about 2 ml for each foot, 15 min after pyrophosphate administration.

ROUTE OF ADMINISTRATION

Subcutaneous injection at the interdigital space between the first and second toes simultaneously on the right and left feet with tourniquets at the ankles.

IMAGING TIME AFTER INJECTION

Approximately three minutes after pertechnetate injection, at which time activity appeared in the cardiac blood pool.

INSTRUMENTATION

Siemens Body Scan System at 15 cm per minute for whole-body imaging from foot to head.

CONTRIBUTORS

Drs. Ming Huang, David C. Yank, Sleiman Naddaf, Christopher Georgeiou, Suzette Powell and Joseph Giovanniillo, The Methodist Hospital, Brooklyn, New York.
Evaluation of Technetium-99m-Sestamibi Lung Uptake: Correlation with Left Ventricular Function

Raffaele Giubbini, Riccardo Campini, Elisa Milan, Orazio Zoccarato, Cesare Orlandi, Pierluigi Rossini, Pantaleo Giannuzzi, Giovanni La Canna and Michele Galli