Simultaneous Perfusion Tomography and Radionuclide Angiography during Dobutamine Stress

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The purpose of this investigation was to evaluate the changes in left ventricular function and volumes concurrently with tomographic myocardial perfusion during dobutamine infusion. Methods: Ninety-two patients underwent first-pass radionuclide angiography using a multicrystal gamma camera and myocardial tomography after high-dose (40 μg/kg/min) dobutamine infusion and 99mTc-sestamibi administration. Results: Dobutamine increased systolic blood pressure (p < 0.0001), heart rate (p < 0.00017), left ventricular ejection fraction (p = 0.0001), cardiac output (p = 0.0001) and stroke volume (p = 0.042). The end-diastolic (p = 0.009) and end-systolic volumes (p = 0.0007) significantly decreased. Of 38 patients with cardiac catheterization, 28 had significant coronary artery disease and 10 had normal coronaries. The sensitivity and specificity for coronary artery disease detection by myocardial perfusion tomography were 78% and 90%, respectively. By radionuclide angiography, only 9 of 27 coronary artery disease patients experienced deterioration of wall motion during dobutamine (sensitivity 33%). Conclusion: Changes in myocardial perfusion are more sensitive than changes in left ventricular function for detecting coronary artery disease during dobutamine stress.

Key Words: dobutamine scintigraphy; SPECT; radionuclide angiography; coronary artery disease


Both myocardial perfusion scintigraphy (1-5) and two-dimensional echocardiography (6-12) during high-dose dobutamine infusion have been successfully used in the noninvasive diagnosis of coronary artery disease. Dobutamine may induce myocardial ischemia by significantly increasing myocardial contractility and heart rate relative to changes in coronary flow (13-15). Although a few reports assessed myocardial perfusion and wall motion during dobutamine infusion, these studies have used 99mTc-sestamibi to evaluate myocardial perfusion and two-dimensional echocardiography for evaluating changes in wall motion (8,9).

The use of 99mTc-sestamibi as a tracer enables a simultaneous assessment of changes in myocardial perfusion and ventricular function during a single tracer injection (16). Thus, the purpose of this study was to evaluate the simultaneous changes in left ventricular function and perfusion during high-dose dobutamine infusion.

MATERIALS AND METHODS

Study Patients

The patient population consisted of 92 patients (52 males, 40 females, age range 55 ± 12 yr; mean ± s.d.) referred to our laboratory for dobutamine perfusion scintigraphy. The need for two different types of gamma cameras and scheduling logistics modulated the implementation of the protocol. Consequently, we only included patients where it was possible to obtain perfusion and function data concurrently. Thirty patients had a prior myocardial infarction. Most patients were on anti-anginal medications, including calcium antagonists in 45 patients, nitrates in 24 and beta adrenergic blockers in 9 patients up to the night before the test. Thirty-eight patients had coronary angiography within 2 mo of the dobutamine study. The indications for dobutamine testing were evaluation of chest pain in 53%, dyspnea in 30%, preoperative clearance in 10%, dizziness in 3%, functional assessment of known coronary stenosis in 2% and risk stratification after a myocardial infarction in 2%. All patients had contra-indications to adenosine or dipyriddamole, such as presence of severe chronic obstructive pulmonary disease, asthma, bronchospasm or recent (<12 hr) use of theophylline compounds.

Dobutamine Administration

Dobutamine hydrochloride (Dobutrex, Lilly) was supplied as a sterile aqueous solution with a concentration of 1 mg/ml and was administered using an infusion pump into a peripheral vein at incremental doses of 5, 10, 20, 30 and 40 μg/kg/min, with dose increases every 3 min (Fig 1). After 1 min at the highest dose, 10-12 mCi of 99mTc-sestamibi was injected as a bolus and first-pass radionuclide angiography obtained, with tomographic imaging performed 1 hr later. Approximately 4 hr after the original injection, 22-to-30 mCi of sestamibi was injected at rest and first-pass radionuclide angiograms reacquired, followed within 1 hr by rest tomographic imaging.

Blood pressure, heart rate and a 12-lead electrocardiogram were recorded every minute throughout the dobutamine infusion and until the heart rate returned to <100 beats per min and all symptoms had resolved.

The reasons for termination of dobutamine infusion were as follows. In 60 patients the protocol was completed to a maximal dose of 40 μg/kg/min. In the remaining patients the infusion was prematurely terminated because of: (a) onset of ventricular or supraventricular tachycardia (n = 9); (b) systolic blood pressure >230 mmHg or diastolic blood pressure >130 mmHg (n = 7); (c) >2 mm ST-segment depression (n = 6); (d) systolic pressure <80 mmHg (n = 4); (e) severe angina (n = 3); (f) >2 mm ST-segment elevation in patients without a prior myocardial infarction (n = 3). Twenty-four of the prematurely terminated patients tolerated a maximal dose of 30 μg/kg/min and the remaining 8 patients tolerated a dose of 20 μg/kg/min.

First-Pass Radionuclide Angiography

Technically adequate first-pass radionuclide angiography could be obtained in 84 patients. In 8 patients the studies were considered inadequate because of bolus fragmentation (n = 5) or poor count-statistics (n = 3). The studies were acquired in the supine, anterior view with a multicrystal gamma camera using commer-
Technetium-99m-Sestamibi Tomography

Thirty-two images were acquired for 30 sec/frame over a 180 arc using a $64 \times 64 \times 16$ matrix and a high resolution collimator. The processing used a Butterworth filter (order of 5, 50% cutoff), followed by back-projection, transaxial reconstruction and reorientation in the short, horizontal long and vertical long axes (1,2).

The images were visually interpreted by experienced nuclear cardiologists blinded as to any clinical or angiographic information. The $^{99m}$Tc-sestamibi uptake was graded on a scale ranging from 3, denoting normal uptake, to 0, denoting no uptake, with intermediate degrees of 2 for mild hypoperfusion and 1 for moderate hypoperfusion. The vascular territories of the three major coronary arteries were assigned as follows: (1) the anterior, septal, and anterolateral walls of the left ventricle comprised the left anterior descending territory; (2) the inferior-posterior walls comprised the right coronary territory; (3) the postero-lateral wall of the left ventricle comprised the left circumflex territory (1,2,5,15).

Coronary Angiography

In a subset of 38 patients coronary angiography was performed within 60 days of cardiac scintigraphy. The coronary angiograms were visually interpreted by independent cardiologists, unaware of the results of cardiac scintigraphy. A coronary stenosis was considered significant when it compromised the luminal diameter by $\geq 50\%$ of the normal caliber. Significant left main stenosis was considered equivalent to left anterior descending and circumflex stenoses.

Hemodynamic Changes During Dobutamine

Sensitivity and specificity were calculated in standard fashion. Student's paired t-test was used to analyze hemodynamic changes, and the chi square test to compare differences in sensitivity and specificity. The Wilcoxon signed-rank test was used to analyze variables that were not normally distributed. A p value $< 0.05$ was considered significant.

RESULTS

Effects of Dobutamine on Hemodynamics and Left Ventricular Volumes

In the 92 patients studied, significant increases occurred in heart rate ($p = 0.0001$) and systolic blood pressure ($p < 0.00017$) (Fig. 2).

In the 84 patients with technically adequate first-pass studies, significant increases occurred in left ventricular ejection fraction ($p = 0.0001$) and cardiac output ($p = 0.0001$) (Fig. 3). The changes in left ventricular volumes are summarized in Figure 4. The stroke volume index increased significantly ($p = 0.042$), whereas the end-systolic volume index decreased ($p = 0.0007$). The end-diastolic volume index, however, showed only a trend to a decrease during dobutamine infusion ($p = 0.09$).

In the 28 patients with coronary artery disease proven by angiography, there was also a significant increase in heart rate, systolic blood pressure and left ventricular ejection fraction during dobutamine infusion (all $p < 0.05$). Patients with or without angiographic evidence of coronary artery disease had
similar hemodynamic results during dobutamine administration.

Agreement Between Tomography and Radionuclide Angiography
For this comparison, radionuclide angiography was considered abnormal when wall motion deterioration occurred during dobutamine or the global left ventricular ejection fraction failed to increase by ≥5 ejection fraction units. There were 29 patients in whom both tests were normal and 27 in whom both were abnormal. The overall agreement was 67% (56 of 84 patients). The cases showing disagreement were predominantly due to abnormal tomography results with normal radionuclide angiography (19 patients) and, less often, to cases with abnormal radionuclide angiography but normal tomography (9 patients).

Radionuclide Angiography in Patients with Coronary Artery Disease
In the 27 patients with coronary artery disease and an adequate rest and dobutamine first-pass study, only 9 developed regional wall motion abnormalities by first-pass radionuclide angiography (sensitivity = 33%) during dobutamine infusion. Interestingly, seven of these patients (78%) had multivessel coronary disease and two had isolated left anterior descending stenosis.

An abnormal ejection fraction response to dobutamine occurred in 8 patients, whereas either wall motion deterioration or abnormal ejection fraction response occurred in 15 of 27 patients (sensitivity 56%). One patient with an isolated circumflex stenosis went undetected, possibly because the first-pass images were only acquired in the anterior view. The peak heart rate achieved was similar between patients with or without wall motion deterioration (mean of 130 beats/min).

None of the 10 patients with normal coronary angiograms had wall motion abnormality induced by dobutamine, whereas 3 of them had an abnormal increase in left ventricular ejection fraction (<5 units).

Detection of Coronary Artery Disease by Dobutamine Perfusion Imaging
In the 28 patients with significant coronary stenoses, 7 had one-vessel disease, 9 had two-vessel disease and 12 had three-vessel disease. Left main coronary artery stenosis was observed in two patients. The overall sensitivity of myocardial tomography was 78% and specificity 90% (Fig. 5). The positive predictive value was 91%, the negative predictive value 75%, and the overall accuracy 81%. The sensitivity and specificity for detecting individual coronary artery stenosis were 81% and 85% for the left anterior descending, 78% and 73% for the right coronary artery and 92% and 78% for the circumflex artery, respectively.

Figure 6 illustrates a patient with three-vessel coronary artery disease who developed perfusion abnormalities during dobutamine infusion, accompanied by deterioration of regional and global left ventricular function.

By combining abnormal results by either tomography or dobutamine radionuclide angiography, the sensitivity would increase to 89%.

DISCUSSION
In this investigation we used ⁹⁹ᵐTc-sestamibi to simultaneously assess myocardial perfusion and left ventricular function during dobutamine infusion.

Effects of Dobutamine on Hemodynamics and Left Ventricular Volumes
High dose dobutamine produced a 67% increase in cardiac output, primarily due to an increase in heart rate and a small increase in stroke volume. Concomitantly, the left ventricular ejection fraction increased and the end-systolic volume decreased, denoting enhanced left ventricular contractility. These hemodynamic effects of dobutamine mimic those of submaximal exercise (1,2,15,18–23), and were similar in patients with or without coronary artery disease.

Detection of Coronary Artery Disease by Dobutamine Perfusion Tomography
High dose dobutamine sestamibi tomography in this study afforded a moderately high sensitivity (78%) and excellent specificity (90%) for overall coronary artery disease detection. Furthermore, arteries with significant stenosis were identified with sensitivities ranging from 78% to 92% and specificities ranging from 73% to 85%. Our results compare favorably with other recently published series using dobutamine as a stressor (1–4). Interestingly, the mean heart rate achieved during dobutamine infusion was only 124 beats/min, and for many patients it was submaximal, in comparison with target heart rates during exercise testing. This may account for the somewhat low sensitivity in this study, compared with our own experience with exercise (87%), dipyridamole (90%) or adenosine (87%) tomography (24–27).
Wall Motion Deterioration During Dobutamine Infusion

As noted by Iskandrian et al. (28), several factors affect the results of radionuclide angiography, including age, sex, intensity of stress and resting ejection fraction (23,25,28–31). Dobutamine elicits a differential increase in myocardial blood flow, with a greater increase occurring in normal vessels relative to those having significant stenosis. This heterogeneity in blood flow may precede the occurrence of ischemia, which is required for one to observe changes in wall motion. In this study, first-pass radionuclide angiography had a low sensitivity (33%) for coronary artery disease detection. Thus, our results suggest that changes in coronary flow distribution occur more frequently than myocardial ischemia during dobutamine. Alternatively, perfusion tomography may simply be more accurate than radionuclide angiography for detecting myocardial ischemia. In support of the latter possibility, 97% of patients during acute, transient coronary occlusion will demonstrate abnormal perfusion tomography, whereas only 59% will develop changes in regional wall motion (17).

When we combined a subnormal increase in ejection fraction with deterioration of wall motion during dobutamine infusion, the overall sensitivity increased to 89%. The specificity of the change in ejection fraction, however, is low, since several normal subjects also failed to increase the ejection fraction by ≥5 units.

Comparison with Previous Studies

Our study contrasts sharply with studies reporting a high sensitivity of dobutamine two-dimensional echocardiography (6–12,32–35). One possible explanation for this discrepancy is that dobutamine may not induce wall motion abnormalities severe enough to be detected by radionuclide angiography. Echocardiography, on the other hand, assesses changes in systolic wall thickening, in addition to endocardial motion. Detection of small regional abnormalities, however, may be difficult when dobutamine renders the left ventricle small and hyperdynamic.

A lower sensitivity of dobutamine two-dimensional echocardiography has been reported in recent studies. Marwick et al. (35) compared exercise and dobutamine echocardiography in the same patients and found a substantially lower sensitivity with dobutamine (54%) than with exercise stress (88%). In that study, dobutamine subaortic tomography had a higher sensitivity (65%) than dobutamine echocardiography. Our present results show an overall sensitivity of tomography which is similar to that of Marwick et al. (35) and even higher than that recently reported by Lahiri et al. (36). Thus, dobutamine may not be a sufficiently powerful stressor to elicit wall motion abnormalities in all patients with coronary artery disease, especially those with single vessel involvement, those using beta-adrenergic blockers or those who cannot tolerate a maximal dose of dobutamine. In fact, a recent critical review of the literature showed an overall sensitivity of 79% for two-dimensional echocardiography, compared to 83% for dobutamine tomography (33). Both of these values are similar to those reported with exercise echocardiography (80%), but lower than those with exercise perfusion scintigraphy (87%) or during perfusion scintigraphy using pharmacologic vasodilation with dipyridamole (90%) or adenosine (88%) (33).

CONCLUSION

High-dose dobutamine subaortic tomography affords a moderately high sensitivity and a high specificity in the diagnosis of coronary artery disease. Perfusion imaging is more sensitive than first-pass radionuclide angiography during dobutamine infusion. Whether perfusion imaging will be consistently more sensitive than two-dimensional echocardiography, as suggested recently (33), remains to be established.

REFERENCES

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Pleural Effusion and Ventilation/Perfusion Scan Interpretation for Acute Pulmonary Embolus

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This study was conducted to determine if pleural effusion size affects ventilation/perfusion (V/Q) scan interpretation algorithms for acute pulmonary embolus (PE). **Methods:** Retrospective analysis identified 163 consecutive patients undergoing angiography for PE with radiographic evidence for pleural effusion. V/Q scanning was performed in 94 (58%) of cases and reported using original Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria. Effusions were classified as small, large, and/or bilateral. Radiographic and scintigraphic results were correlated with regard to size and location of abnormalities. **Results:** Of the 163 patients, 57 (35%) had angiographically-proven PE, 77 (47%) had at least one large pleural effusion and 86 (53%) had a small effusion; 33 (43%) with large effusions and 24 (28%) with small effusions had emboli at angiography. Thirty-six of 119 patients (30%) with clear chest radiographs (a control group) had PE. Thus, large effusions were associated with a higher incidence of PE than those with small effusions or clear lungs (p < 0.05). Of those with V/Q scanning, 26 of 94 (28%) had a solitary large effusion, with 12 (46%) positive for emboli. V/Q-matched abnormalities limited to effusion size were found in 16 with a solitary large effusion and 10 with a solitary small effusion. In both groups, 50% were angiographically positive for emboli. Twenty-three (66%) of 35 with bilateral effusions had corresponding V/Q-matched defects at one (n = 11) or both (n = 12) lung bases, and 9 (39%) were positive for emboli. In total, 45% with a V/Q-matched defect of equivalent size to the effusion were angiographically positive for PE. **Conclusion:** Pulmonary emboli are associated with pleural effusions of all sizes. Matched V/Q defects corresponding to radiographically-evident pleural effusions are of intermediate probability for PE. Thus, revision of the traditional lung scan interpretive criteria based upon pleural effusion size is not warranted. **Key Words:** pulmonary embolus; ventilation/perfusion scan; pleural effusion


The association between pulmonary emboli (PE) and pleural effusions has long been known. In two large series, approximately 50% of those with proven pulmonary emboli had a pleural effusion (1,2). However, the role this radiographic finding plays in the interpretation scheme for the ventilation/perfusion (V/Q) scan is less well defined. Traditionally, any radiographic abnormality, including an effusion, that is comparable in size to matched perfusion and ventilation defects renders the region (and in most cases the V/Q scan) indeterminate for pulmonary embolism (3). Bedont and Datz (4), however, noted that only 2 of 53 (4%) patients with matched V/Q defects in the region of a pleural effusion had documented thromboembolic disease. They, therefore, concluded that such defects should be considered of low probability for PE. Recently, based upon reanalysis of Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial data, several authors have suggested that the size of the pleural effusion and its associated matched defect can influence the interpretation of the V/Q scan (5). In this new scheme, large effusions are associated with a low probability of PE and small effusions (defined as costophrenic angle blunting) are associated with an intermediate chance of embolism. A pleural effusion is not relevant if it does not cause an associated perfusion defect. Preliminary data from our recent study on chest radiograph findings and their effect on V/Q scan interpretation did not support this revision (6). This study was conducted to determine if pleural effusion size correlates with the presence of emboli, and to verify if effusion size alters V/Q scan interpretation.

**METHODS**

**Patients**

A retrospective search identified all consecutive patients undergoing pulmonary angiography for the indication of pulmonary embolism between January 1, 1990 and December 31, 1992 at our institution (n = 622). During this time period, 2,544 ventilation/perfusion scans were performed for detection of pulmonary emboli. In every case of pulmonary angiography, images were obtained of both lungs separately in the anteroposterior projection. When these views were initially negative, magnification views were obtained of the lung bases in the oblique projection. The results of angiography were used as the gold standard for the presence or absence of emboli.

All patients had either posterolateral or anterolateral chest radiographs within 24 hr of angiography. Based upon the written...