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Comparing a High-Dose Dipyridamole SPECT Imaging Protocol with Dobutamine and Exercise Stress Testing Protocols. Part II: Using High-Dose Dipyridamole to Determine Lung-to-Heart Ratios

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Abstract. Determination of the severity of coronary artery disease (CAD) by single photon emission computed tomography (SPECT) imaging has previously been shown to have greater sensitivity, specificity, and accuracy when performed with pharmacologic stress using high-dose dipyridamole (HDD), than by standard dose dipyridamole (SDD) or exercise stress (EST) prior to SPECT imaging. The use of lung-to-heart (L:H) ratios has been shown to be valuable in determining the presence or absence of left main (LM) or triple vessel (3V) CAD. Fifty-four patients were studied; HDD (n = 40) or EST (n = 14) was used for the study. These patients underwent L:H ratio analysis, in which anterior views were used 5–10 minutes after the injection of 3 mCi of T1-201. Results of the L:H ratios were compared with the diagnosis of epicardial CAD, as determined by coronary (CA) arteriography. Patients who were "stressed" using either HDD or EST demonstrated statistically greater ($p < 0.001$) L:H ratios if they had LM/3V CAD when compared with patients who had 0–2 significantly stenosed coronary arteries. Though L:H ratios were greater when HDD pharmacologic stress was used, there was no statistical (p = NS) differences between the two groups. Increased L:H ratios with HDD and EST provide excellent markers for LM/3V CAD using T1-201 imaging. Coupled with previously reported SPECT data, the use of HDD shows promise for increasing the diagnostic accuracy of SPECT imaging.

Introduction

Utilization of thallous-201 chloride (T1-201) for myocardial perfusion imaging (MPI) dates back to the early to mid-1970s. The use of T1-201 and other monovalent cations (potassium, rubidium, ammonia, and cesium) is based on Sapirstein's principle, that with increased myocardial blood flow (MBF) changes in extraction fractions occur. For most physiologic conditions the extraction fraction for T1-201 approaches 85–90%, making it in some respects ideal for MPI.

Since the initiation of MPI in the early 1970s it has been recognized that one of the potential problems lies in the detection of "severe" triple-vessel coronary artery disease (CAD) where significant reductions in tracer activity result either in inadequate image acquisition for interpretation (poor count statistics), or the necessary adjustments in image quality can result in false negative reports, where enhancement of images yields results that appear to be normal. Previous work with conventional single photon emission computed tomography (SPECT) has reported varying degrees of sensitivity, specificity, and accuracy, depending on the isotope used [1–13], reader experience [10,14], and type of stress protocol employed [15,16]. Work with pharmacologic stress using dipyridamole date back to the 1970s when standard dosing protocols were initially studied. Work since then has primarily focused on standard dose dipyridamole (SDD) and agents such as adenosine.

The Coronary Artery (CASS) Surgery Study [17] demonstrated that individuals suffering from left main (LM) or triple vessel (3V) CAD may benefit from coronary revascularization (CABG) procedures. Individuals with LM/3V CAD frequently demonstrate evidence of left ventricular (LV) dysfunction which results in increased pulmonary capillary occlusion pressure (PCOP). When these same individuals are studied with T1-201, there is an increased uptake of T1-201 in the pulmonary parenchyma. This results in an increased lung-to-heart (L:H) ratio 5–10 minutes after T1-201 administration and cessation of exercise [18–22].

Increased L:H ratios have also been seen when SDD [23] is used to "stress" the patient, but has not been studied using high dose dipyridamole (HDD) "stress." In 1995 [15] HDD SPECT imaging was reported for the first time. In this study [15] statistically better results were demonstrated when SPECT imaging was completed following pharmacologic stress using HDD, when compared with the results of SPECT imaging following exercise stress (EST) testing.

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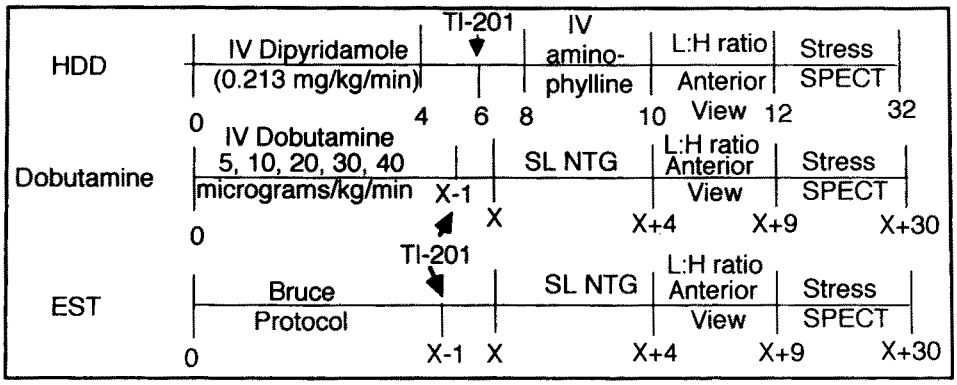

Fig. 1. Stress protocols. All patients underwent one of two "stress" protocols prior to receiving T1-201 before acquiring L:H ratios and SPECT imaging. HDD was given over 4 minutes with T1-201 given at peak dipyridamole effect 2 minutes after completion of infusion. Aminophylline was used when necessary for reversal of symptoms or ECG changes. Anterior imaging was used for L:H ratio analysis 5–10 minutes after T1-201 administration. EST was continued until symptom or ECG limitation, as noted in the text, with T1-201 given 1 minute prior to cessation of exercise. Anterior planar image acquisition for L:H imaging was started 5–10 minutes after T1-201 administration. Sublingual nitroglycerin was given if discontinuation of exercise did not produce satisfactory improvement, or with HDD if symptoms and/or ECG changes did not reverse with intravenous aminophylline. The protocol for dobutamine is also shown, but discussed elsewhere.

Martin et al. [24] reported increased echocardiographic accuracy following a HDD protocol. In our current study, we investigated the differences in L:H ratios following pharmacologic stress with HDD and after EST to determine if differences existed in the detection of LM/3V CAD as compared with "less severe" disease.

Methods

Study Patients

Fifty-four patients with angina agreed to participate in the study. Of these, 40 were studied using HDD (19 men, 21 women) and 14 (12 men, 2 women) underwent EST prior to L:H ratio analysis and subsequent SPECT imaging. Participants ranged in age from 41 to 89 years and included a total of 31 men and 23 women. All patients enrolled in this study underwent pharmacologic or exercise stress as described below, followed by the intravenous administration of T1-201. Patients were not allowed to participate in the study if they were medically unstable, had "severe" aortic stenosis, had a cardiomyopathy, or were pregnant.

All medications that could blunt heart rate and/or blood pressure response were discontinued 36 hours prior to the study; this included slow calcium channel antagonists, beta-blocking agents, and nitrates. Subjects began fasting 12 hours prior to the study to optimize coronary artery blood flow and minimize gastrointestinal blood flow.

Coronary Arteriography

Coronary arteriograms (CAs) were performed without interventional procedures being performed before the L:H study. The determination of the severity of CAD was made via consensus reading of two angiographers. In the event of disagreement, a third reader established agreement about the severity of stenotic lesions. A stenosed coronary artery was defined as significantly stenosed if it had ≥50% diameter stenosis (% DS) which reflected a stenosis flow reserve (SFR) of 3.6 or less [25].

Physical (EST) and Pharmacologic (HDD) Stress

Exercise stress testing (EST) was used to stress 14 people. This provided an independent assessment of L:H ratios for baseline purposes rather than relying on literature results not matched to this study. Subjects were exercised using the "Bruce" protocol until they reached 100% of their maximum predicted heart rate (MPHR) or where stopped secondary to symptoms (angina, dyspnea, leg pain, or fatigue) or electrocardiographic (ECG) changes consistent with ischemia. One minute prior to the discontinuation of exercise, 3.0 mCi of T1-201 was given intravenously, as shown in Figure 1. If necessary, nitroglycerin (NTG) was given to relieve angina or ST changes detected by ECG monitoring. ECG, blood pressure, and heart rate were monitored during the entire study.

The 40 patients who received dipyridamole stress were given 60 cc of HDD saline (NS) solution intravenously at 0.852 mg/kg over a period of 4 minutes. Two minutes later at peak dipyridamole effect, 3.0 mCi of T1-201 was injected, with L:H ratios later determined following acquisition from the anterior view, which occurred 5–10 minutes after thallium was given. Like patients undergoing EST, patients were monitored throughout the study. If the patients became symptomatic or developed ECG changes consistent with ischemia, intravenous aminophylline was given 1–2 minutes after receiving T1-201 to reverse the dipyridamole [15] effect.

Thallium-201 Imaging and L:H ratios

For each form of stress (EST, HDD), patients were given 3 mCi of T1-201 either at peak effect (HDD) or 1 minute (EST) prior to cessation of stressor. These two approaches are illustrated in Figure 1. Five to 10 minutes after the infusion of T1-201, the SPECT camera was positioned in the anterior view position where the image occurred. This image was then used to determine regions of interest (ROIs) as shown in Figure 2, with identical ROIs used to compared (counts) lung and heart activity. The L:H ratio was then calculated as shown below in equation 1. Following the initial anterior view used for acquisition of L:H analysis, SPECT imaging was performed as previously [15] described.

$$\text{L:H ratio} = \frac{\text{lung activity (counts)}}{\text{heart activity (counts)}} \qquad \text{Eq 1.}$$

Statistical Analysis

The results of L:H ratios were compared with the number of diseased (≥50%DS) epicardial coronary arteries, as determined by CA. The results of L:H ratios were then compared graphically, with differences between groups compared [26] by the student's two-tailed nonmatched *t*-test.

Results

Lung-to-heart ratios were greater than 0.5 in all patients with either LM or 3V CAD who underwent HDD imaging

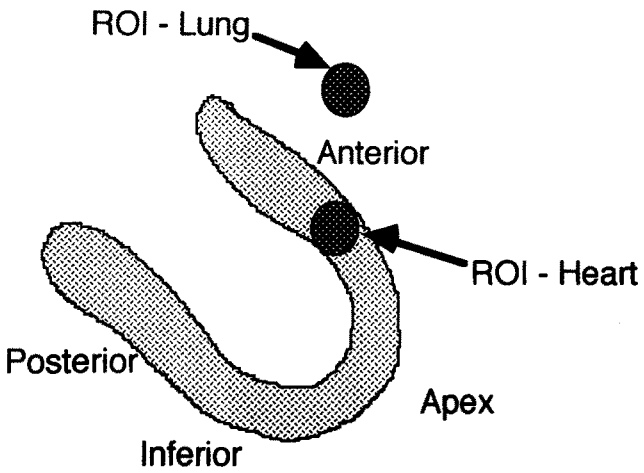

Fig. 2. Regions of interest (ROIs) for Lung-to-Heart ratio analysis. L:H ratios were calculated after completing anterior view acquisition of T1-201. This acquisition begins 5–10 minutes after intravenous injection of T1-201, allowing sufficient time for clearance of the thallium from the blood pool. ROIs are drawn over a normal-appearing region of myocardium with a ROI drawn over the lung fields which represents the exact same number of pixels as that drawn over the left ventricle.

with T1-201. As Table 1 and Figure 3 show these patients had statistically greater ($p < 0.001$) L:H ratios than did patients with 2 vessel (2V) or 1 vessel (1V) CAD. Results were also statistically greater ($p < 0.001$) than for those who had no (0V) significant CAD. As shown in Table 1, patients with LM/3V CAD had statistically greater ($p < 0.001$) L:H ratios than all other patients (HDD 0–2V) combined.

Patients undergoing EST also demonstrated L:H ratios greater than 0.5 if they had either LM/3V CAD. As shown in Table 1, the L:H ratios of patients with LM/3V CAD were statistically greater than those noted for patients with 2V ($p < 0.001$), 1V ($p < 0.001$), or 0V ($p < 0.001$) CAD. Like patients "stressed" with HDD, the presence of LM/3V CAD was associated with a statistically ($p < 0.001$) greater L:H ratio than patients with 0–2V CAD.

The L:H ratios for patients with LM/3V CAD undergoing pharmacologic stress with HDD were greater than for similar patients stressed by EST, however, they were not statistically (p = NS) greater.

Discussion

Differences in L:H ratios (LM/3V vs 0–2V CAD) were unrelated to differences in pharmacologic response to HDD. Similarly, patients stressed via EST achieved satisfactory double products (BP × HR) so as to exclude limitations in exercise capacity as a contributing factor to differences observed in this study. The incidence of side effects was not different from that reported previously [15]. All patients tolerated pharmacologic stress without difficulty.

Patients undergoing either HDD or EST demonstrated statistically increased L:H ratios if they had LM/3V CAD. The results for EST have been reported previously in the literature although protocols frequently stop at 85% MPHR and reveal the L:H ratio cutoff as 0.50. The results for L:H ratios following stress with HDD has not previously been reported. The results for L:H ratios after HDD appear to be more promising than for SDD infusions which were previously reported as similar to EST using L:H ratios of 0.50 as the cutoff for LM/3V CAD.

Differences between L:H ratios in individuals with 0–2V CAD were not statistically significant between HDD and EST approaches. This is consistent with the literature previously published for both SDD and the 85% MPHR approach to EST, which would suggest that patients with 0–2V CAD may not have sufficient LV dysfunction to produce elevations in L:H ratios when they are presenting for evaluation of "angina." Patients experiencing acute myocardial infarction (AMI) may demonstrate elevated L:H ratios if sufficient LV dysfunction occurs as a result of the AMI to increase the PCOP.

Table 1. Two-tailed nonmatched t-test results of L:H ratios for different groups

Group 1 (Average L:H Ratio)	Group 2 (Average L:H Ratio)	Level of Statistical Significance
HDD LM/3V (0.62)	HDD 2V (0.48)	$p \leq 0.001$
HDD LM/3V (0.62)	HDD 1V (0.48)	$p \leq 0.001$
HDD LM/3V (0.62)	HDD 0V (0.48)	$p \leq 0.001$
HDD LM/3V (0.62)	HDD 0–2V (0.48)	$p \leq 0.001$
EST LM/3V (0.62)	EST 2V (0.59)	$p \leq 0.001$
EST LM/3V (0.62)	EST 1V (0.43)	$p \leq 0.001$
EST LM/3V (0.62)	EST 0V (0.43)	$p \leq 0.001$
EST LM/3V (0.62)	EST 0–2V (0.45)	$p \leq 0.001$
HDD LM/3V (0.62)	EST LM/3V (0.62)	p = NS

p = NS is not statistically significant.

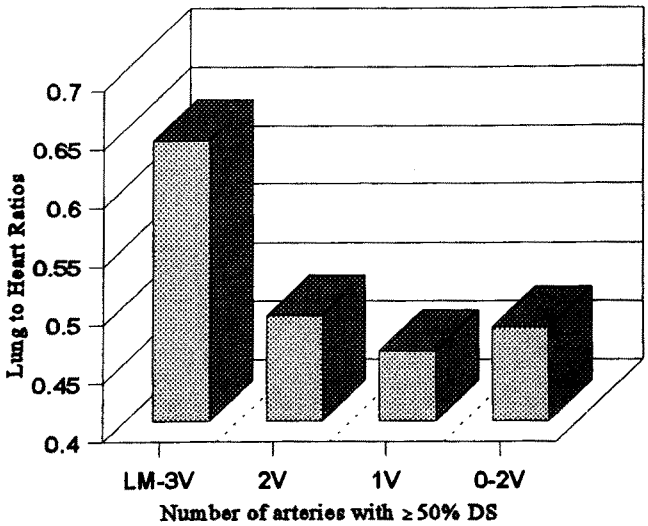

Fig. 3. Lung to heart ratios following infusion with high-dose dipyridamole. The L:H ratio is shown for LM/3V (LM-3V), 2 vessel (2V), 1 vessel (1V), and 0–2 vessel (0–2V) CAD. All L:H ratios are greater than 0.5 for patients with LM/3V CAD.

Conclusion

Lung:heart ratios were statistically different between individuals with LM/3V CAD and patients with 0–2V CAD who were studied with either HDD or EST. Previous work

[15] demonstrated that the use of HDD yielded statistically greater sensitivity, specificity, and accuracy with SPECT imaging than SPECT results obtained following EST or SDD. The addition of L:H ratios with HDD adds potentially useful information in the setting of LM/3V CAD where poor count statistics might result in false negative reporting of SPECT results. The addition of L:H ratios yields supplemental diagnostic information about the function (or dysfunction) of the left ventricle.

Patients with LM/3V CAD have previously been shown [17] to benefit from revascularization procedures, primarily CABG surgery. Given the results of this study, the use of L:H ratios could be helpful in deciding which patients should be referred for further diagnostic evaluation and bypass surgery. Further work should be done to determine if combining the use of stress-reinjection T1-201 [15] approaches, in addition to looking at differences in L:H ratios with HDD and EST, can yield similar results to that seen with positron emission tomography (PET) evaluations of myocardial viability. More work is needed in this area, including investigating other SPECT and PET imaging agents.

References

1. Iskandrian AS, Heo J, Kong B, et al. (1989) Effect of exercise level on the ability of thallium 201 tomographic imaging in detecting coronary artery disease: Analysis of 461 patients. J Am Coll Cardiol 14:1477–1486.
2. Esquivel L, Pollock SG, Beller GA, et al. (1989) Effect of the degree of effort on the sensitivity of the exercise thallium 201 stress test in symptomatic coronary artery disease. Am J Cardiol 63:160–165.
3. Van Train KF, Berman DS, Garcia EV, et al. (1986) Quantitative analysis of stress thallium 201 myocardial scintigrams: A multicenter trial. J Nucl Med 27:17–25.
4. DePasquale EE, Nody AC, DePuey EG, et al. (1987) Quantitative rotational thallium 201 tomography for identifying and localizing coronary artery disease. Circulation 77:316–327.
5. Dilsizian V, Rocco TP, Freedman NMT, et al. (1990) Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 323:141–146.
6. Kayden DS, Sigal S, Soufer R, et al. (1991) Thallium 201 for assessment of myocardial viability: Quantitative comparison of 24-hour redistribution imaging with imaging after reinjection at rest. J Am Coll Cardiol 18:1480–1486.
7. Seldin DW, Johnson LL, Blood DK, et al. (1989) Myocardial perfusion imaging with technetium-99m SQ 30217: Comparison with thallium 201 and coronary anatomy. J Nucl Med 30:312–319.
8. Hendel RC, McSherry B, Karimeddini M, et al. (1990) Diagnostic value of a new myocardial perfusion agent, teboroxime (SQ 30217) utilizing a rapid planar imaging protocol. Preliminary results. J Am Coll Cardiol 16:855–861.
9. Iskandrian AS, Heo J, Nguyen T, et al. (1991) Myocardial imaging with Tc-99m teboroxime: Technique and initial results. Am Heart J 121:889–894.
10. Fleming RM, Kirkeeide RL, Taegtmeyer H, et al. (1991) Comparison of technetium-99m teboroxime tomography with automated quantitative coronary arteriography and thallium 201 tomographic imaging. J Am Coll Cardiol 17:1297–1302.
11. Iskandrian AS, Heo J, Kong B, et al. (1989) Use of technetium-99m isonitrile (RP-30A) in assessing left ventricular perfusion and function at rest and during exercise in coronary artery disease, and comparison with coronary arteriography and exercise thallium 201 SPECT imaging. Am J Cardiol 64:270–275.
12. Sinusas AJ, Beller GA, Smith WH, et al. (1989) Quantitative planar imaging with technetium-99m methoxyisobutyl isonitrile: Comparison of uptake patterns with thallium-201. J Nucl Med 30:1456–1463.
13. Gibbons RJ, Verani MS, Behrenbeck T, et al. (1989) Feasibility of tomographic technetium-99m hexakis-2-methoxy-2 methylpropylisonitrile imaging for the assessment of myocardial area at risk and the effect of acute treatment in myocardial infarction. Circulation 80: 1277–1286.
14. Trobaugh GB, Wackers FJTh, Sokole EB, et al. (1978) Thallium 201 myocardial imaging: An interinstitutional study of observer variability. J Nucl Med 19:359–363.
15. Fleming RM, Rose CH, Feldmann KM (1995) Comparing a high-dose dipyridamole SPECT imaging protocol with dobutamine and exercise stress testing protocols. Angiology 46(7):547–556.
16. Leppo JA (1989) Dipyridamole-thallium imaging: The lazy man's stress test. J Nucl Med 30:281–287.
17. Passamani E, Davis KB, Gillespie MJ, et al. (1985) A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med 312:1665.
18. Boucher CA, Zir LM, Beller GA, et al. (1980) Increased lung uptake of thallium-201 during exercise myocardial imaging: Clinical, hemodynamic and angiographic implications in patients with coronary artery disease. Am J Cardiol 46:189–196.
19. Gibson RS, Watson DD, Barabello BA, et al. (1982) Clinical implications of increased lung uptake of thallium-201 during exercise scintigraphy two weeks after myocardial infarction. Am J Cardiol 49: 1586–1593.
20. Kushner FG, Okada RD, Kirshenbaum HD, et al. (1981) Lung thallium 201 uptake after stress testing in patients with coronary artery disease. Circulation 63:341–347.
21. Levy R, Rozanski A, Berman DS, et al. (1983) Analysis of the degree of pulmonary thallium washout after exercise in patients with coronary artery disease. J Am Coll Cardiol 2:719–728.
22. Kahn JK, Carry MM, McGhie I, et al. (1989) Quantitation of postexercise lung thallium-201 uptake during single photon emission computed tomography. J Nucl Med 30:288–294.
23. Okada RD, Dai Y, Boucher CA, Pohost GM (1984) Significance of increased lung thallium-201 activity on serial cardiac images after dipyridamole treatment in coronary heart disease. Am J Cardiol 53: 470–475.
24. Martin TW, Seaworth JF, Johns JP, et al. (1992) Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. Ann Intern Med 116:190–196.
25. Fleming RM, Harrington GM (1994) Quantitative coronary arteriography and its assessment of atherosclerosis. Part II. Calculating stenosis flow reserve from percent diameter stenosis. Angiology 45(10): 835–840.
26. Snedecor GW, Cochran WG (1979) *Statistical Methods,* 6th ed. The Iowa State University Press, Ames, Iowa, USA.