

Comparing a High-dose Dipyridamole SPECT Imaging Protocol with Dobutamine and Exercise Stress Testing Protocols. Part III: Using Dobutamine to Determine Lung-to-Heart Ratios, Left Ventricular Dysfunction, and a Potential Viability Marker

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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 dobutamine than by standard dose dipyridamole (SDD) or exercise stress testing (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. No such work has been previously reported for dobutamine. Twenty-one patients were studied using dobutamine ($n = 7$) or EST ($n = 14$). These results were compared with results from Part II of this series of studies using high-dose dipyridamole (HDD) pharmacologic stress. In this study, patients underwent L:H ratio analysis following injection of 3 mCi of Tl-201, this provides sufficient time for thallium clearance from the blood pool. Results of the L:H ratios were compared with the results of coronary arteriographic (CA) evaluation. Patients who were “stressed” via EST demonstrated statistically greater ($p \leq 0.001$) L:H ratios in patients with LM/3V CAD when compared with patients who had 0–2 significantly stenosed coronary arteries. Patients stressed with dobutamine demonstrated lower L:H ratios ($p = \text{NS}$) in patients with LM/3V CAD than was seen for patients with 0–2 V CAD. Patients stressed with dobutamine had statistically ($p \leq 0.05$) lower L:H ratios than did similar patients stressed with EST. Increased L:H ratios following EST and HDD, as shown previously in Part II of this series, provide excellent markers for LM/3V CAD following Tl-201 injection. The presence of “normal” L:H ratios in patients with LM/3V CAD following dobutamine stress may suggest the presence of “stunned” or “hiber-

nating” myocardium. The presence of “decreased” L:H ratios following dobutamine after HDD or EST has already shown an increased L:H ratio, might suggest a marker for myocardial viability that deserves further investigation.

Introduction

Since the initiation of myocardial perfusion imaging (MPI) in the early 1970s it has been recognized that one of the potential problems lies in the detection of “severe” triple vessel (3V) 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 shown varying degrees of sensitivity, specificity, and accuracy, depending upon the isotope used [1–13], reader experience [10,14], and type of stress protocol employed [15,16]. Work with pharmacologic stress using dipyridamole and dobutamine date back to the 1970s when standard dosing protocols were initially studied.

The Coronary Artery (CASS) Surgery Study [17] demonstrated that individuals suffering from left main (LM) or 3V CAD may benefit from coronary revascularization (coronary artery bypass graft-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 Tl-201, there is an increased uptake of Tl-201 in the pulmonary parenchyma. This results in an increased lung to heart (L:H) ratio 5–10 minutes after Tl-201 administration and cessation of exercise [18–22].

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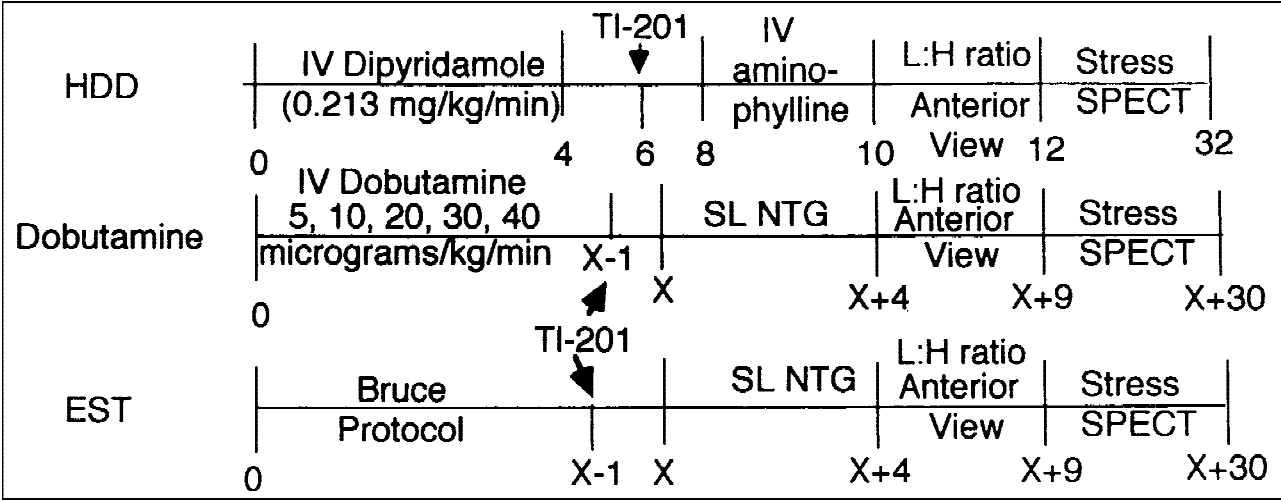


Fig. 1. Stress protocols. All patients underwent one of two approaches to physiologic or pharmacologic stress prior to receiving TI-201 before L:H ratios and SPECT imaging. Dobutamine infusion is titrated up every 3 minutes from 5 μ g/kg/minute to a maximum of 40 μ g/kg/minute or until limited by symptoms or ECG changes, as noted in the text. TI-201 is given 1 minute prior to discontinuation of the dobutamine with L:H imaging started 5–10 minutes later. Likewise, EST is continued until symptom or

ECG limitation with thallium given 1 minute prior to discontinuation of EST with L:H imaging initiated 5–10 minutes later. Sublingual nitroglycerin was given if discontinuation of dobutamine or EST did not produce satisfactory improvement. Anterior imaging is used for L:H ratio analysis 5–10 minutes after TI-201 administration. The protocol for HDD is also shown, but discussed elsewhere.

In 1995 [15] we demonstrated statistically better results when SPECT imaging was completed following pharmacologic imaging with either high-dose dipyridamole (HDD) or dobutamine, when compared with SPECT imaging following exercise stress (EST) testing. This was true regardless of the nuclear tracer being used. In 1997 [23] we demonstrated an increase in L:H ratios in individuals using HDD. In our current study, we investigated differences in L:H ratios following pharmacologic stress with dobutamine and after EST to determine if differences existed in the detectability of LM/3V CAD when compared with patients with “less severe” CAD, as assessed via epicardial coronary arteriography (CA). These results were then compared with that obtained following HDD pharmacologic stress.

artery blood flow and minimize gastrointestinal competition of blood flow which might otherwise reduce SPECT accuracy.

Coronary Arteriography

Coronary arteriograms (CAs) were done without interventional procedures performed prior to the L:H analysis. The determination of the severity of CAD was made via consensus reading of two angiographers. In the event of disagreement, a third reader established the severity of lesion stenosis. A stenotic coronary artery was considered significant if it had $\geq 50\%$ diameter stenosis (% DS), which reflected a stenosis flow reserve (SFR) of 3.6 or less [24].

Physical (EST) and Pharmacologic (Dobutamine) Stress

EST was used as the stressor in 14 individuals. 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 were stopped secondary to symptoms (angina, dyspnea, leg pain, or fatigue) or ischemic electrocardiographic (ECG) changes. One minute prior to the discontinuation of exercise, 3.0 mCi of TI-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 throughout the study.

Participants studied using dobutamine, received dobutamine intravenously beginning with 5 μ g/kg/minute, as shown in Figure 1. The infusion contained 250 mg of dobutamine added to 250 ml of 5% dextrose (D5W) which was increased every 3 minutes to 10, 20, 30, and 40 μ g/kg/minute. The infusion was discontinued at the end of the 3 minutes following maximal dose infusion or sooner if the patient experienced angina, dyspnea, malignant ventricular tachydysrhythmia, hypertensive response, or ischemic changes [15] on the ECG. If patients became symptomatic or required

Methods

Subjects

Twenty-one patients were enrolled for evaluation of angina after agreeing to participate in the study. Of these, 7 were studied using dobutamine (3 men, 4 women) and 14 (12 men, 2 women) underwent EST as the choice of stress prior to SPECT imaging and L:H ratio analysis. Participants ranged from 41 to 89 years of age. These results were then compared with the 40 people (19 men, 21 women) previously investigated in Part II of this study [23], for a total of 61 patients (34 men, 27 women). All patients enrolled in this study underwent pharmacologic or exercise stress as described below, followed by the intravenous administration of TI-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. These included slow calcium channel antagonists, beta-blocking agents, and nitrates. Twelve hours prior to the study subjects began fasting to optimize coronary

Table 1. Two-tailed nonmatched *t*-test results of lung:heart (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 ± 0.11)	HDD 2V (0.48 ± 0.07)	$p \leq 0.001$
HDD LM/3V (0.62 ± 0.11)	HDD 1V (0.48 ± 0.02)	$p \leq 0.001$
HDD LM/3V (0.62 ± 0.11)	HDD 0V (0.48 ± 0.06)	$p \leq 0.001$
HDD LM/3V (0.62 ± 0.11)	HDD 0-2V (0.48 ± 0.06)	$p \leq 0.001$
EST LM/3V (0.62 ± 0.05)	EST 2V (0.59 ± 0.10)	$p \leq 0.001$
EST LM/3V (0.62 ± 0.05)	EST 1V (0.43 ± 0.10)	$p \leq 0.001$
EST LM/3V (0.62 ± 0.05)	EST 0V (0.43 ± 0.07)	$p \leq 0.001$
EST LM/3V (0.62 ± 0.05)	EST 0-2V (0.45 ± 0.09)	$p \leq 0.001$
Dobut LM/3V (0.52 ± 0.02)	Dobut 2V (0.53 ± 0.09)	$p = \text{NS}$
Dobut LM/3V (0.52 ± 0.02)	Dobut 1V (0.53 ± 0.10)	$p = \text{NS}$
Dobut LM/3V (0.52 ± 0.02)	Dobut 0V (0.53 ± 0.01)	$p = \text{NS}$
Dobut LM/3V (0.52 ± 0.02)	Dobut 0-2V (0.53 ± 0.11)	$p = \text{NS}$
HDD LM/3V (0.62 ± 0.11)	EST LM/3V (0.62 ± 0.05)	$p = \text{NS}$
EST LM/3V (0.62 ± 0.05)	Dobut LM/3V (0.52 ± 0.02)	$p \leq 0.005$
HDD LM/3V (0.62 ± 0.11)	Dobut LM/3V (0.52 ± 0.02)	$p \leq 0.005$

discontinuation of the dobutamine infusion, 3 mCi of Tl-201 was given 1 minute prior to discontinuation of the dobutamine.

Thallium-201 Imaging and L:H Ratios

For each form of stress (EST and dobutamine), patients were given 3 mCi of Tl-201 1 minute (EST, dobutamine) prior to discontinuation of stressor. The two protocols used are shown in Figure 1. Five to 10 minutes after the administration of Tl-201, the SPECT camera was positioned anteriorly where image acquisition began. The resultant images and information were used to determine regions of interest (ROIs) L:H ratios as described previously [23]. Following the initial anterior view used for acquisition of L:H analysis, SPECT imaging was performed as previously described [15].

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 by Students two-tailed nonmatched *t*-test [25].

Results

Patients undergoing EST demonstrated L:H ratios greater than 0.5 if they had 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 2 V ($p \leq 0.001$), 1 V ($p \leq 0.001$), or 0 V ($p \leq 0.001$) CAD.

When patients were studied using dobutamine infusion, they yielded lower L:H ratios when they had LM/3V CAD than when they had 0-V ($p = \text{NS}$), 1-V ($p = \text{NS}$) or 2-V ($p = \text{NS}$) CAD. Likewise, when all patients with 0-2 V CAD were grouped together the L:H ratios were higher ($p = \text{NS}$) than they were for patients with LM/3V CAD. The results are shown in Table 1.

The L:H ratios of patients undergoing EST were statisti-

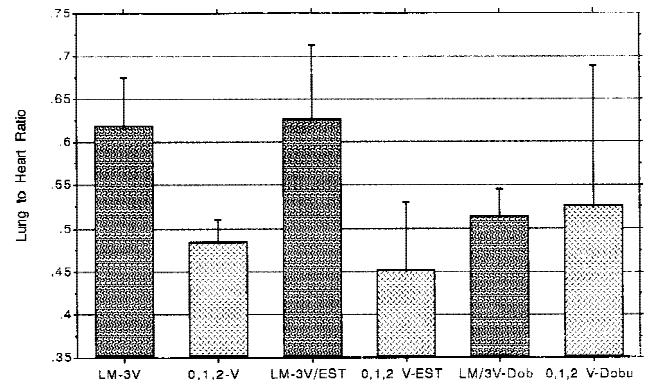


Fig. 2. Lung to heart ratios following “stress” with high-dose dipyridamole (HDD), exercise stress (EST) testing and dobutamine (Dobut). Lung to heart (L:H) ratios are shown on the Z-axis with results seen for HDD, EST, and dobutamine shown for patients with left main/triple vessel (LM-3V) CAD and patients with 0-2 vessel CAD (0-2V) on the Y-axis. L:H ratios were statistically greater for patients with LM/3V CAD who were studied with HDD or EST. Patients studied with dobutamine did not demonstrate such differences. Both HDD and EST yielded statistically greater L:H ratios in patients with LM/3V CAD than that seen in patients undergoing dobutamine stress.

cally ($p \leq 0.005$) greater for LM/3V CAD than they were for patients stressed by dobutamine. No statistical differences were seen between patients stressed by dobutamine or EST if they had 0-2 V CAD (Table 1 and Figure 2).

Discussion

Differences in L:H ratios were unrelated to inadequate response to dobutamine. Patients stressed via EST likewise achieved satisfactory double products ($\text{BP} \times \text{HR}$) so as to exclude limitations in exercise capacity as a contributing factor in the differences observed in this study. The incidence of side effects was not significantly different from that reported previously [15]. Patients were assigned to only one pharmacologic approach to reduce patient radionuclide exposure and increase patient participation in the study. All patients tolerated pharmacologic stress without difficulty.

Those undergoing EST demonstrated statistically increased L:H ratios if they had LM/3V CAD. The results for EST have been reported previously in the literature with the L:H ratio cutoff set at 0.50 for LM/3V CAD. The results for L:H ratios following stress with HDD was recently reported [23] and appeared to be more promising than the results seen following SDD infusion.

Table 1 and Figure 2 show the results of L:H ratios following HDD [23], EST, and dobutamine stress. Patients with LM/3V CAD had statistically ($p \leq 0.001$) greater L:H ratios when studied using HDD or EST, but failed to demonstrate such increases following dobutamine infusion. No differences ($p = \text{NS}$) were seen in the L:H ratios between groups (HDD, EST, or dobutamine) for individuals with 0-2 V CAD. This is consistent with the literature previously published for both SDD and the 85% MPRH approach to

EST, which would suggest that patients with 0-2 V CAD (free of significant prior myocardial infarction) may not have sufficient LV dysfunction to produce elevations in L:H ratios when they are being evaluated for angina. Patients experiencing acute myocardial infarction (AMI) may demonstrate elevated L:H ratios if sufficient LV dysfunction has occurred, resulting in an increase in the PCOP.

Those individuals stressed with dobutamine did not demonstrate elevations in L:H ratios when they had LM/3V CAD. The use of dobutamine L:H ratios alone does not provide sufficient information to determine the extent of CAD [15]. There are two possible explanations for this. (1) Dobutamine does not provide sufficient pharmacologic stress to detect such differences. This seems unlikely given the previous success with SPECT imaging using dobutamine [15]. (2) The use of dobutamine might improve the function of “stunned” and/or “hibernating” myocardium sufficiently to decrease the level of LV dysfunction, leading to a reduction in PCOP and decreased retention of thallium within the pulmonary parenchyma with a resultant decrease in the L:H ratio. Though echocardiographic data [26] would tend to support this contention, this increased inotropic contractility may be having its effect at the cellular level by simply increasing intracellular calcium which could potentiate cellular injury.

Conclusion

Lung:heart ratios are statistically different between individuals with LM/3V CAD and those with 0-2 V CAD who are 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 after 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 to benefit from revascularization procedures, primarily CABG surgery [17]. Given the results of this study, the use of L:H ratios could be helpful in deciding which patients might benefit from further diagnostic evaluation and possibly intervention or coronary artery bypass surgery. Further work needs to be done to determine if combining the use of stress-reinjection TI-201 approaches [15], in addition to looking at differences in L:H ratios with HDD, EST, and dobutamine, can yield results similar to those seen with positron emission tomography (PET) evaluation of myocardial viability. Additional work is needed in this area, including investigating other SPECT (sestamibi, tetrofosmin) and PET imaging agents using HDD and dobutamine stress.

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