High-Dose Dipyridamole and Gated Sestamibi SPECT Imaging Provide Diagnostic Resting and Stress Ejection Fractions Useful for Predicting Extent of Coronary Artery Disease

Richard M. Fleming, MD, FICA, FACA, FASNC, FACP, *Omaha, NE*
Technical support by Larry D. Boyd, CNMT, RDCS

A decline in ejection fraction at stress compared with rest images has been associated with increased severity of coronary artery disease (CAD) and suggests a poorer prognosis. Myocardial perfusion imaging (MPI) using high-dose dipyridamole (HDD) has been shown to more accurately detect CAD than either standard dose dipyridamole (SDD) or exercise-induced stress (EST), but has not been looked at to determine its usefulness in detecting changes in stress and rest ejection fractions. To determine the relationship between changes in left ventricular ejection fraction (LVEF) and the severity of CAD, 36 individuals underwent gated single photon emission computed tomography (SPECT) MPI using HDD. In each case resting and stress LVEFs were determined along with MPI results. Subjects with single-vessel CAD demonstrated an increase in LVEF from 77.8% (sd ±8.8%) to 85.6% (sd ±8.4%) resulting in a statistically significant increase in LVEF of 7.8% ($p = 0.009$). Patients with two-vessel disease showed a smaller increase from 73.2% (sd + 8.3%) to 79.8% (sd + 9.8%) following HDD stress. This increase was statistically ($p = 0.008$) significant. Patients with triple-vessel CAD showed a reduction in LVEF from 67.4% (sd ±14.07) to 65.1% (sd ±16.5%) which represented a decrease in LVEF of 2.7% and approached ($p = 0.25$) but did not reach statistical significance. Both the resting and stress LVEFs were statistically lower ($p < 0.05$) in patients with triple-vessel CAD. Changes in resting LVEF (REF) and HDD pharmacologically induced stress LVEF (SEF) provide a valuable diagnostic marker as to the number of significantly diseased coronary arteries and can be acquired from gated SPECT sestamibi images.

Introduction

Assessment of left ventricular ejection fraction (LVEF) response to exercise compared with results obtained at rest have previously been reported[1-3] with use of Tc-99m pertechnetate as a useful determinant of left ventricular response and severity of coronary artery disease (CAD); however, this approach cannot be used to determine myocardial blood flow. It has additionally been shown that a decline in LVEF with treadmill or bicycle stress implies a greater severity[4] of CAD

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From The Fleming Heart and Health Institute, Omaha, NE

Correspondence: Professor Richard M. Fleming, The Fleming Heart and Health Institute and The Camelot Foundation, 9290 West Dodge Road, Suite 204, Omaha, NE 68114
E-mail: rfmd1@uswest.net

and a poorer prognosis[5,6] for survival over the following 2–5 years.

Studies looking at Tc-99m sestamibi using gated single photon emission computed tomography (SPECT) have shown that sestamibi can provide reliable, useful LVEF results[7-9] including regional wall motion abnormality (RWMA) data.[10,11] These results hold true for both first-pass and treadmill[12,13] stress. The addition of dipyridamole has provided a safe and reliable alternative to treadmill stress. Several variations of high-dose dipyridamole (HDD) have been described[14-29] that have varied in both dose and duration of administration. We began using HDD in 1993 and have described its diagnostic accuracy in comparison with dobutamine and exercise stress[26-29] both in the detection of CAD and as a marker for myocardial viability with thallium, teboroxime, and sestamibi.

To date, comparisons of resting left ventricular ejection fractions (REF) with stress LVEF (SEF) have been reported only for Tc-99m pertechnetate. Since the advent of sestamibi and its increased utilization in gated SPECT imaging, Sestamibi has not been studied to determine if it can provide the same useful diagnostic information as pertechnetate, viz., comparing SEF to REF to assess severity of CAD and left ventricular response to exercise. In order to evaluate the potential use of sestamibi as a combination agent to determine not only myocardial perfusion imaging (MPI) but also differences between REF and SEF, 36 subjects underwent gated SPECT imaging at rest and with HDD.

Methods

Thirty-six subjects ranging in age from 29 to 81 years of age (22 men, 14 women) who were suspected of having CAD were enrolled in the study after signing an approved consent form at the Institute. Documentation of CAD was confirmed by use of coronary blood flow studies including angiographic evaluation, myocardial perfusion imaging (MPI), intravascular ultrasound (IVUS) evaluation, and/or endothelial dysfunction studies. Patients who had a history of cardiomyopathy, severe valvular disease, unstable angina, pregnancy, or morbid obesity or who had a myocardial infarction, angioplasty, or bypass surgery during the 6 weeks prior to the study were excluded.

Sestamibi Gated SPECT

Each of the patients underwent rest imaging followed by pharmacologic stress using HDD as outlined in Figure 1 and described[26-29] previously. Patients were monitored throughout the resting studies with continuous 3-lead EKG monitoring and with continuous 12-lead electrocardiographic monitoring during the HDD component of the study. Gated SPECT images were acquired using a Siemens 6601 orbiter camera with 75 PMT's and a pixel resolution of 0.35 mm. A LEHR collimator was used with a 20% (+14 keV) window and a 100 × 100 matrix. Thirty-two images were acquired for 60 seconds each, requiring a total of 34 minutes for the step and shoot approach.

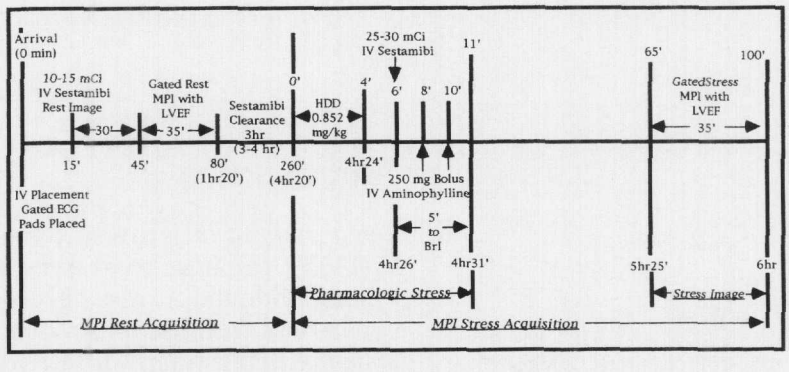

Figure 1. Protocol for resting and high-dose dipyridamole imaging. Patients underwent resting sestamibi imaging followed by high-dose dipyridamole (HDD) imaging as outlined in the protocol. Acquired images are reconstructed for myocardial perfusion imaging (MPI) results and measurement of resting (REF) and "HDD stress" ejection fractions (SEF).

Images were processed with a METZ-NEMA filter. Standard back projection technique was used to reconstruct transaxial tomograms, which were then reoriented to short-axis, vertical, and horizontal long-axis views. This approach was used for both rest and HDD images.

The reconstructed MPI results were interpreted on a 6-point scale as described previously[29] with 7 regions of interest matching coronary artery distribution as previously[30] reported. The REF and SEF determinations were made from reconstructed horizontal and vertical long-axis views by using edge detection to determine differences in left ventricular ellipsoid volumes. An example of the horizontal long-axis views[29] used is shown in Figure 2. Rest diastole (RDV) and rest systole (RSV) represent the resting volumes.

$$[(RDV–RSV)/RDV] \times 100 = REF\ \% \quad (1)$$

Similarly, the lower panel of Figure 2 represents an example of horizontal long-axis images used in the determination of SEF where stress diastole (SDV) and stress systole (SSV) represent the volumes measured during HDD diastole and HDD systole.

$$[(SDV–SSV)/SDV] \times 100 = SEF\ \% \quad (2)$$

Statistical Analysis

Descriptive statistics including mean, median, mode, standard deviation, standard errors, and confidence intervals were determined. The gated REF and SEF results were subgrouped according to the number of coronary arteries involved. Results were then compared by using paired (within groups) and nonpaired (between groups) t tests to determine statistical differences between groups. Differences (delta) from REF to SEF were also calculated and subgrouped to determine differences between groups by using nonpaired t tests. Additionally, box plot representations of the mean, median, and standard deviations were plotted.

Results

The results of the mean, standard deviation, standard error and 95% confidence intervals for REFs, SEFs, and differences (delta) between HDD and resting ejection fractions are listed in Table I. The results are graphically depicted in Figures 3 and 4. No additional information was

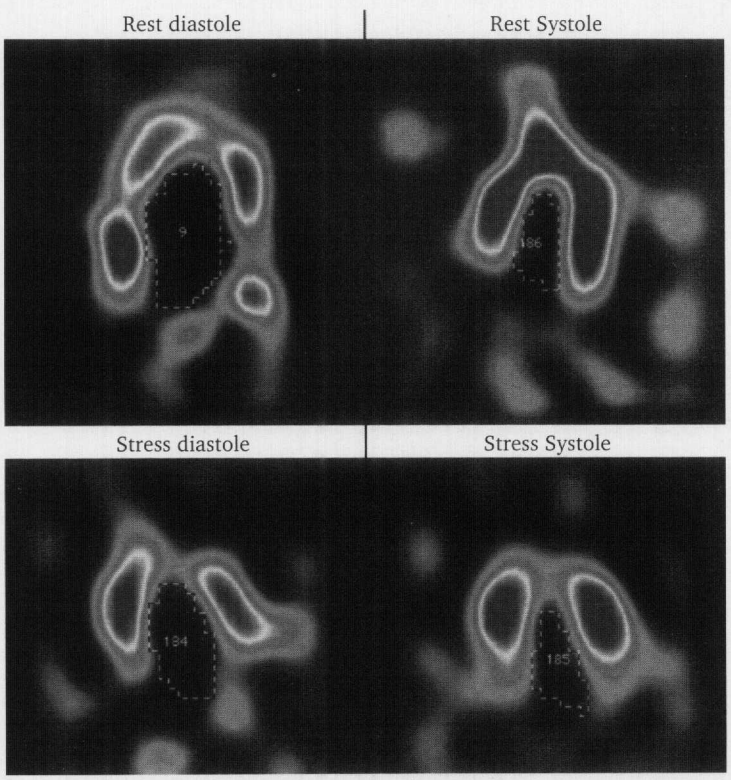

Figure 2. Example of a patient's horizontal long-axis views used to determine REF and SEF. Nuclear images used to determine MPI are shown with the resting images in the top 2 images and HDD stress images presented in the bottom row. Edge detection is used to determine the left ventricular chamber volumes during diastole (top row, left image) and during systole (top row, right image). Images are displayed with the apex at 12 o'clock, the septum displayed on the left (7 to 12 o'clock) and the lateral wall (1 to 5 o'clock) displayed on the right. These same orientations are used in the bottom row with the left image representing HDD diastole and the right image representing the LV during systole following HDD. Measurement can be performed in black and white as well as color algorithms.

Table 1. Descriptive statistics REF, SEF, and differences (delta).

Variable	Number	Mean	Standard Deviation	Standard Error	95% Confidence Interval
REF-1	9	77.80	8.84	2.95	71.01 to 84.59
SEF-1	9	85.62	8.36	2.79	79.19 to 92.05
delta-1	9	7.82	6.88	2.29	2.53 to 13.11
REF-2	13	73.25	8.30	2.30	68.23 to 78.26
SEF-2	13	79.77	9.75	2.70	73.88 to 85.66
delta-2	13	6.52	7.42	2.06	2.04 to 11.01
REF-3	14	67.45	14.07	3.76	59.33 to 75.57
SEF-3	14	65.09	16.53	4.42	55.54 to 74.63
delta-3	14	–2.71	7.20	1.92	1.44 to –6.87

REF-1 = resting ejection fraction single-vessel disease, SEF-1 = stress ejection fraction single-vessel disease, delta-1 = (SEF-1) minus (REF-1). REF-2 = resting ejection fraction two-vessel disease, SEF-2 = stress ejection fraction two-vessel disease, delta-2 = (SEF-2) minus (REF-2). REF-3 = resting ejection fraction triple-vessel disease, SEF-3 = stress ejection fraction triple-vessel disease, delta-3 = (SEF-3) minus (REF-3).

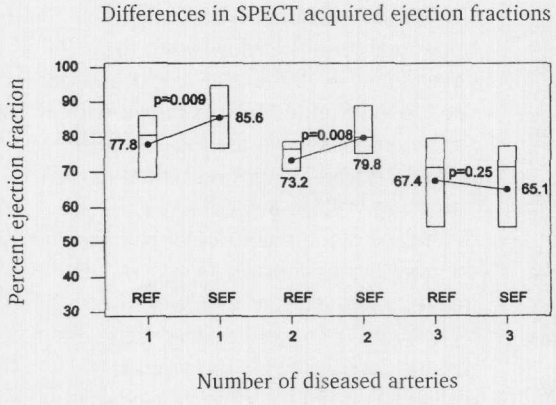

Figure 3. REFs and SEFs. The resting (REFs) and HDD (SEF) ejection fractions are shown with the mean (number), median (horizontal line), and the standard deviation (bar) for each. The p values reflect the statistical significance differences between each.

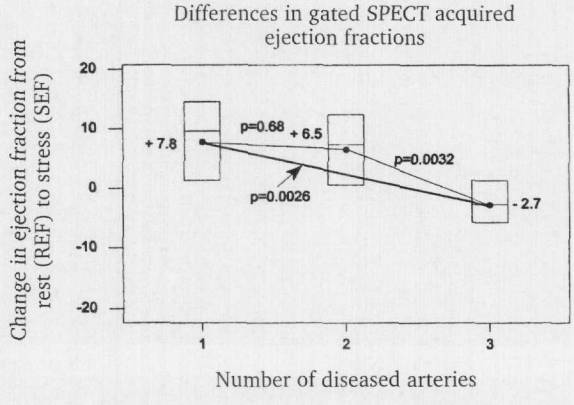

Figure 4. Differences from REF to SEF. The difference between REF and SEF for patients with single-, two-, and triple-vessel coronary artery disease. Results for each are shown with the mean (number), median (horizontal line), and the standard deviation (bar) values. The p values reflect the statistical significance differences between each.

gleaned from the analysis of medians and modes. Patients with single-vessel disease had an average ejection fraction of 77.8% at rest (REF-1), which increased by an average of 7.8% following HDD pharmacologic stress (SEF-1). This increase was statistically significant at $p = 0.009$. Patients with two-vessel disease had an average resting ejection fraction (REF-2) of 73.2%, which increased to an average of 79.8% following HDD stress (SEF-2). This increase was statistically significant ($p = 0.008$) and reflected an average increase in ejection fraction of 6.5%. Patients who had three-vessel disease began with an average resting ejection fraction (REF-3) of 67.4% but following HDD stress showed an average fall in ejection fraction of –2.7% to reach an average HDD stress ejection fraction (SEF-3) of 65.1%. This decline in ejection fraction approached but did not reach statistical significance. The 95% confidence interval for this decrease in ejection fraction was +1.44 to –6.87%.

The difference between baselines REFs revealed a decrease in REF as the number of vessels with disease increased. REF-1 at rest (77.8%) was greater than that seen with two-vessel disease REF-2 (73.2%); however, there was no statistically ($p = 0.24$) significant difference. Similarly, the REF-3 was lower (67.4%) than that reported for REF-2 (73.2%) but was not statistically ($p = 0.20$) significant. There was, however, a statistically lower ($p = 0.042$) resting ejection fraction for patients with three-vessel disease (REF-3 was 67.4%) than for patients with one-vessel disease (REF-1 was 77.8%).

Ejection fractions following HDD stress were decreased as coronary artery disease worsened. Patients with single-vessel disease had an average ejection fraction (SEF-1) of 85.6%, which was greater than that seen with two-vessel disease (SEF-2), an average value of 79.8%. These differences were not statistically ($p = 0.15$) significant. Differences between SEF-2 (79.8%) and SEF-3 (65.1%) were significant ($p = 0.0099$) as were the differences ($p = 0.0008$) between SEF-1 (85.6%) and SEF-3.

When changes (delta 1, 2, and 3) between SEFs and REFs were compared (Table I and Figure 4), decreases in the ejection fraction from REF to SEF were seen as the number of diseased arteries increased. While changes from REF-1 to SEF-1 were an average of 7.8% higher, the increase from REF-2 to SEF-2 was less pronounced at 6.5%. This difference was not statistically significant ($p = 0.68$). However, when REF-3 to SEF-3 was analyzed, there was a 2.7% reduction (–2.7%) and when compared with two-vessel (+6.5%) and single-vessel (+7.8%) disease, this reduction demonstrated a statistically significant difference of $p = 0.0032$ and $p = 0.0026$ respectively.

Discussion

Assessment of left ventricular ejection fraction is a useful prognostic indicator of the presence or absence of significant limitations in coronary blood flow seen either with left main or triple-vessel coronary artery disease. Individual post-stress LVEF that falls by 5% or greater has previously been used as a marker to indicate the need for or potential benefit of surgical intervention. Resting and stress multiple gated acquisitions (MUGAs) have previously provided this information without supplying information regarding coronary flow. This method of diagnostic evaluation of both coronary blood flow and changes in LVEF provides complementary information regarding patient management. This approach can also be used to evaluate patients scheduled for chemotherapy involving cardiotoxic agents.

The REFs decreased from an average of 77.8% in individuals with single-vessel disease to 73.2% with two-vessel and 67.4% with three-vessel disease. This decrease in LVEF at rest (REF) suggests that left ventricular ejection fraction drops as a consequence of atherosclerosis. All patients in this study had adequate blood pressure control, and despite differences in hypertrophy as documented by echocardiography, patients with thickened ventricles did not skew the results, nor did differences in regional wall motion abnormalities affect the results.

Similarly, the results of SEFs also showed lower SEFs following HDD stress as the number of arteries affected increased. Differences between three-vessel and two vessel, as well as three-vessel and single-vessel disease, were statistically significant and are consistent with a decreased ability of the left ventricle to increase blood supply to the left ventricle in the presence of increasing coronary artery disease. More significant is the differences between REFs and SEFs. Patients with two-vessel disease were able to increase LVEF in response to HDD stress, but not to the same extent as patients with single-vessel disease. Patients with three-vessel disease typically demonstrated reductions in SEF compared with

REF and in some cases required coronary artery bypass graft surgery (CABGS) following angiography. The patient represented in Figure 2 had a 20.5% drop from REF to SEF and proceeded to a nonemergent CABGS resulting in complete resolution of her symptoms.

The comparison of SEF to REF has largely been discontinued with the introduction of Tc-99m MPI isotopes (teboroxime, sestamibi, tetrafosmin, etc) since they provide significantly better MPI imaging results than those seen with thallium 201 (Tl-201), even though some physicians still prefer Tl-201. As a consequence, fewer people undergo first-pass radionuclide studies with Tc-99m pertechnetate (despite the useful information it provides) with the exception of those few patients being followed up while receiving cardiotoxic (eg, adriamycin) chemotherapy. Some interest has been given toward looking at SEFs and regional wall motion abnormalities (RWMAs) following the "stress" component of MPI studies, although this may be more financially than diagnostically or therapeutically driven.

This study shows not only important differences between REFs and SEFs when looked at individually but also the diagnostic value of comparing changes in SEF to REF for any given patient. Patients whose EFs drop following HDD stress are indicative of patients with triple-vessel coronary artery disease who may require further surgical intervention. The results of MPI imaging provide an accurate noninvasive diagnosis of coronary artery disease. In addition the use of this HDD approach with measurement of both REF and SEF can further subcategorize patients that may require further intervention in addition to medical management.

Conclusion

This study demonstrates the ability to use sestamibi to obtain information not only about myocardial blood flow but also about left ventricular response as measured by changes in REF and SEF. Previously the ability to acquire information about both has been limited by the isotopes and technology available. The diagnostic coupling of HDD, sestamibi, and technologic advances in nuclear cardiac imaging allows for the determination MPI, REF, SEF, and RWMA all at the same time. The results of RWMAs simultaneously obtained with these patients were consistent with regions of prior non-Q wave and Q wave myocardial infarctions and is the subject of another paper. Further work needs to be done to determine the effect that differences in REF and SEF may have on predicting long-term survival and the potential benefit of following up chemotherapy patients with this approach when they receive cardiotoxic medications or radiation over the left chest wall (eg, breast cancer patients).

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