

Dipyridamole Stress Echocardiography vs Dipyridamole Sestamibi Scintigraphy for Diagnosing Coronary Artery Disease in Left Bundle-Branch Block*

Carlo Vigna, MD; Mario Stanislao, MD; Vincenzo De Rito, MD; Aldo Russo, MD; Rosaria Natali, MD; Tiberio Santoro, MD; and Francesco Loperfido, MD

Study objectives: To evaluate dipyridamole stress echocardiography (DSE) for predicting coronary artery diseases (CADs) in patients with complete left bundle-branch block (LBBB).

Design: Comparison of DSE and dipyridamole sestamibi myocardial perfusion scintigraphy (sestamibi).

Setting: Tertiary-care cardiac referral center.

Patients: Fifty-four consecutive patients (26 men; mean [± SD] age, 59 ± 7 years) with complete LBBB (14 patients with left ventricular [LV] dilatation) and intermediate probability of CAD.

Methods: Simultaneous single photon emission CT scan (20 mCi technetium Tc 99m stress/rest sestamibi) and echocardiography (second harmonic imaging) during a two-step (0.56 to 0.84 mg/kg) dipyridamole infusion protocol. Two sestamibi readings were performed. The first reading considered only those studies with reversible defects (sestamibi-1) to be positive. The second reading considered those studies with any defect (sestamibi-2) to be positive. CAD was defined as a ≥ 50% reduction in diameter in at least one major vessel seen on coronary angiography.

Results: CAD was present in 17 patients (31.5%). The global predictive accuracy for CAD was significantly higher for DSE (87.0%) and sestamibi-1 (79.6%) than for sestamibi-2 (57.4%) [$p < 0.01$ vs DSE; $p < 0.05$ vs sestamibi-1]. No significant differences in sensitivity were present, but specificity was significantly higher for DSE (94.6%) and sestamibi-1 (81.1%) than for sestamibi-2 (43.2%; $p < 0.01$ vs both the other two tests). Of 14 patients with LV dilatation, 26.8% were falsely positive for CAD (in some cases for posterior defects) as determined by sestamibi-1 and 64.3% were falsely positive for CAD by sestamibi-2 vs none by DSE.

Conclusions: DSE is at least as accurate as dipyridamole sestamibi scintigraphy for predicting CAD in patients with complete LBBB and tends to be more specific in those patients with underlying LV dilatation. (CHEST 2001; 120:1534–1539)

Key words: left bundle-branch block; myocardial perfusion scintigraphy; stress echocardiography

Abbreviations: CAD = coronary artery disease; DSE = dipyridamole stress echocardiography; LBBB = left bundle-branch block; LV = left ventricle; NS = not significant

Myocardial perfusion scintigraphy often is performed to detect coronary artery disease (CAD) in patients with left bundle-branch block (LBBB). However, stress scintigraphy is not spe-

cific for the frequent occurrence of septal, anterior, and apical defects in the absence of CAD. This diagnostic challenge can be reduced but not eliminated using dipyridamole as a stress agent instead of exercise.^{1,2} To our knowledge, only a few studies^{3,4} have compared echocardiography with myocardial perfusion scintigraphy during dobutamine infusion in patients with LBBB, and, so far, none has compared them during dipyridamole infusion. Accordingly, we analyzed simultaneous dipyridamole stress echocardiography (DSE) and sestamibi myocardial perfusion scintigraphy in a group of patients with complete LBBB and intermediate pretest probability of CAD.⁵

*From the Department of Cardiology (Dr. Vigna, Stanislao, De Rito, Russo, and Santoro), "Casa Sollievo della Sofferenza" Hospital, IRCCS, San Giovanni Rotondo, Roma, Italy; and the Institute of Cardiology (Drs. Natali and Loperfido), Università Cattolica del Sacro Cuore, Roma, Italy. Manuscript received July 21, 2000; revision accepted May 22, 2001.

Correspondence to: Francesco Loperfido, MD, Istituto di Cardiologia, Università Cattolica del Sacro Cuore, Complesso Integrato Columbus, Via G. Moscati, 31/33, 00168 Roma, Italy; e-mail: loperfido@tiscalinet.it

MATERIALS AND METHODS

Patients and Protocol

From January to June 1999, we examined 58 consecutive patients with complete LBBB⁶ and chest pain. Patients who had experienced previous myocardial infarction, unstable angina, or had previously documented CAD were excluded. Other criteria of exclusion were recent pulmonary edema, severe arterial hypertension, ventricular tachyarrhythmias, atrial fibrillation, contraindications to dipyridamole infusion,⁷ and technically sub-optimal echocardiograms (four patients). The final study group consisted of 54 patients (26 men and 28 women) with a mean (\pm SD) age of 59 ± 7 years. The mean pretest probability of CAD in the study patients, which was calculated from age, gender, and chest pain characteristics, was $61 \pm 2\%$.⁵ DSE and sestamibi scintigraphy values were obtained simultaneously under BP and 12-lead ECG monitoring and after discontinuation of all anti-ischemic drugs. A two-step (0.56 to 0.84 mg/kg) dipyridamole infusion protocol was used. The end points were the following: achievement of dipyridamole peak dose; angina; severe hypertension or hypotension; significant ventricular or supraventricular arrhythmias; or new dysynergy. Technetium Tc 99m sestamibi was injected at the end of the dipyridamole infusion. All patients underwent coronary angiography within 7 days of the echocardiographic and scintigraphic studies. Significant CAD was defined as a $\geq 50\%$ reduction in diameter of at least one major vessel.

DSE

A second harmonic imaging procedure was performed in all patients (Sonos 5500 System; Hewlett-Packard; Andover, MA). Studies were digitized in a quad-screen format and were analyzed by two investigators who were blinded to each other's data. The left ventricular (LV) end-diastolic internal dimension was measured by M-mode. The LV ejection fraction was calculated as the mean from 4-chamber and 2-chamber apical views (area-length method). Patients with an LV end-diastolic internal dimension of > 60 mm were considered to have LV dilatation. The LV was divided into 16 segments, according to the guidelines of the American Society of Echocardiography.⁸ Segments tributary of the right and circumflex coronary artery constituted the posterior region. The other segments, including an isolated apical abnormality, constituted the anterior region. Both endocardial shortening and wall thickening were analyzed in all segments, including the ventricular septum. Normal septal motion was considered to be present when, apart from early paradoxical systolic movement, (relatively) normal posterior shortening and thickening were evident in systole.⁹ A wall motion score index was calculated using a 4-point scale (1, normal; 4, dyskinetic). A study was considered to be positive in the presence of a new or worsening wall motion abnormality in one or more segment of one region. The condition of akinesia becoming dyskinesia was not considered.¹⁰ The intraobserver and interobserver variabilities for segmental readings in our laboratory were 2.6% and 3.6%, respectively.

Sestamibi

Stress/rest single photon emission CT was performed (20 mCi Tc 99m sestamibi). Short-axis, horizontal long-axis, and vertical long-axis slices were acquired and were interpreted by two investigators who were blinded to each other's data. The LV was divided into 16 segments which were attributed to the anterior or posterior region, as for echocardiography. Only vertical and

horizontal long-axis slices were used to define the apex. Sestamibi uptake was visually evaluated with the assistance of a circumferential profile analysis. Segmental uptake was classified using a 4-point scale (normal, 0; equivocal or minimally reduced, 1; moderately reduced, 2; severely reduced, 3). Studies were considered to be positive only in the presence of reversible defects (sestamibi-1) or, alternatively, in the presence of any grade-2 to grade-3 defect in at least one segment of one region (sestamibi-2).³ The intraobserver and interobserver variabilities for sestamibi segmental readings in our laboratory were 2.1% and 2.6%, respectively.

Statistical Analysis

When appropriate, paired and unpaired *t* tests and χ^2 tests were used. The predictive accuracy for predicting CAD of DSE, sestamibi-1, and sestamibi-2 was compared by the Cochran *Q* test. The same test also was applied to separately compared true-positive results (sensitivity) and true-negative results (specificity) for each diagnostic test. In case of global statistical significance, pairwise multiple comparisons were carried out by McNemar χ^2 test with the appropriate Bonferroni correction. Calculating the percentage of concordant diagnosis, κ values and the corresponding 95% confidence intervals (CIs) constituted the analysis of agreement between the three tests.

RESULTS

General Data

CAD was present in 17 patients (31.5%), 12 of whom had one-vessel CAD, 2 of whom had two-vessel CAD, and 3 of whom had three-vessel CAD. LV dilatation was present in 2 patients with CAD (11.7%) and in 12 patients without CAD (32.4%). Patients with and without CAD were not significantly different as regards gender, age, and prevalence of diabetes, hypertension, or hypercholesterolemia. At baseline echocardiography, the mean (\pm SD) LV end-diastolic internal dimension and the ejection fraction were 54 ± 8 mm and $45 \pm 11\%$, respectively. Septal akinesia or dyskinesia was found in three patients with CAD (17.6%) and in seven patients without CAD (18.9%; difference between the two groups was not significant [NS]).

Dipyridamole Test Effects

Three patients (5.6%) received only the first dose of dipyridamole because of new or worsening wall motion abnormalities. Four patients (7.4%) complained of chest pain during the second dose of dipyridamole. From baseline to the dipyridamole peak dose, heart rate increased from 76 ± 11 to 93 ± 13 beats/min ($p < 0.01$), systolic BP increased from 126 ± 16 to 127 ± 13 mm Hg (NS), diastolic BP increased from 81 ± 6 to 80 ± 5 mm Hg (NS), the rate-systolic BP product increased from $9,589 \pm 1,580$ to $11,736 \pm 1,740$ ($p < 0.01$), and the echocardiographic wall motion score index increased from 1.4 ± 0.3 to 1.5 ± 0.4 ($p < 0.001$).

The diagnostic performances of DSE, sestamibi-1, and sestamibi-2 in study group patients is shown in Table 1 and Figure 1 (separate data for anterior and posterior regions).

The global predictive accuracy for CAD was significantly higher for DSE (87.0%) and sestamibi-1 (79.6%; NS between these two tests) than for sestamibi-2 (57.4%; $p < 0.01$ vs DSE; $p < 0.05$ vs sestamibi-1). A separate analysis revealed no significant differences among the three diagnostic tests in terms of sensitivity (70.6%, 76.5%, and 88.2%, respectively; $p = 0.17$), most probably because of the low number of patients with CAD, whereas specificity was significantly higher for DSE (94.6%) and sestamibi-1 (81.1%; NS between these two tests) than for sestamibi-2 (43.2%; $p < 0.01$ vs both the other two tests).

DSE tended to be more accurate than both sestamibi-1 and sestamibi-2 in the 14 patients with underlying LV dilatation (Table 2). In fact, 26.8% and 64.3% of patients, respectively, had falsely positive responses to sestamibi-1 and sestamibi-2 and no falsely positive responses to DSE (Fig 2). Remarkably, there were three reversible falsely positive posterior defects.

Agreement Among DSE, Sestamibi-1, and Sestamibi-2

Forty-two patients (78%) had concordant DSE and sestamibi-1 responses (κ , 0.49; 95% CI, 0.25 to 0.72). Of 12 patients (22%) with discordant DSE and sestamibi-1 responses, 9 had positive responses on scintigraphy (7 false-positive responses). We found 30 patients (55%) with concordant DSE and sestamibi-2 responses (κ , 0.23; 95% CI, 0.06 to 0.42). Of 24 patients (45%) with discordant DSE and sestamibi-2 responses, 23 had positive responses on scintigraphy (20 false-positive responses).

In a group of patients with complete LBBB and intermediate pretest probability of CAD, DSE was at least as accurate as dipyridamole sestamibi-1 and was definitely more accurate than dipyridamole sestamibi-2 in predicting obstructive CAD. Our data confirmed that myocardial perfusion scintigraphy has limited value in this setting. In fact, when dipyridamole sestamibi was utilized to compare nuclear and echocardiographic methods directly under the same stress agent and to perform delayed scintigraphic acquisitions without interference from echocardiographic recordings, we did not observe any reduction of the commonly reported scintigraphic false-positive responses.^{1,2,11-14} Most fixed defects and many reversible defects of the basal and midportion of the septum occurred, in fact, in patients without CAD. Thus, sestamibi-2 turned out to be quite nonspecific for CAD, and we think that it should be definitively abandoned as a reading method in the presence of complete LBBB. However, sestamibi-1 also was not very specific, although the reversible septal defects noticed in the absence of CAD may derive from true ischemia due to microcirculatory dysfunction,^{15,16} and not simply from dipyridamole-induced flow heterogeneity.¹⁷

DSE was very specific for CAD and, although it is less sensitive than sestamibi scintigraphy for one-vessel disease and in our patients with complete LBBB, it demonstrated an accuracy not inferior to that found in patients without LBBB.¹⁷ This good diagnostic performance of DSE was not anticipated. In fact, the evaluation of stress-induced contractile changes in patients with LBBB traditionally has been difficult to discern even for the experienced observer due to the presence of various degrees of anteroseptal asynergy at rest, which in some cases mimics the effects of an extensive anteroseptal infarction.¹⁸ However, regional wall motion analysis by echocar-

Table 1—Diagnostic Performance in 54 Patients With Complete LBBB

Variables	DSE	Sestamibi-1	Sestamibi-2	p Value
True positives, No. of patients	12	13	15	
False positives, No. of patients	2	7	21	
True negatives, No. of patients	35	30	16	
False negatives, No. of patients	5	4	2	
Global predictive accuracy, %	87.0*	79.6†	57.4	< 0.0004
Sensitivity, %	70.6	76.5	88.2	0.17
One-vessel disease	58.3	66.6	83.3	
Multivessel disease	100	100	100	
Specificity, %	94.6*	81.1*	43.2	< 0.00001

* $p < 0.01$ vs sestamibi-2.

† $p < 0.05$ vs sestamibi-2.

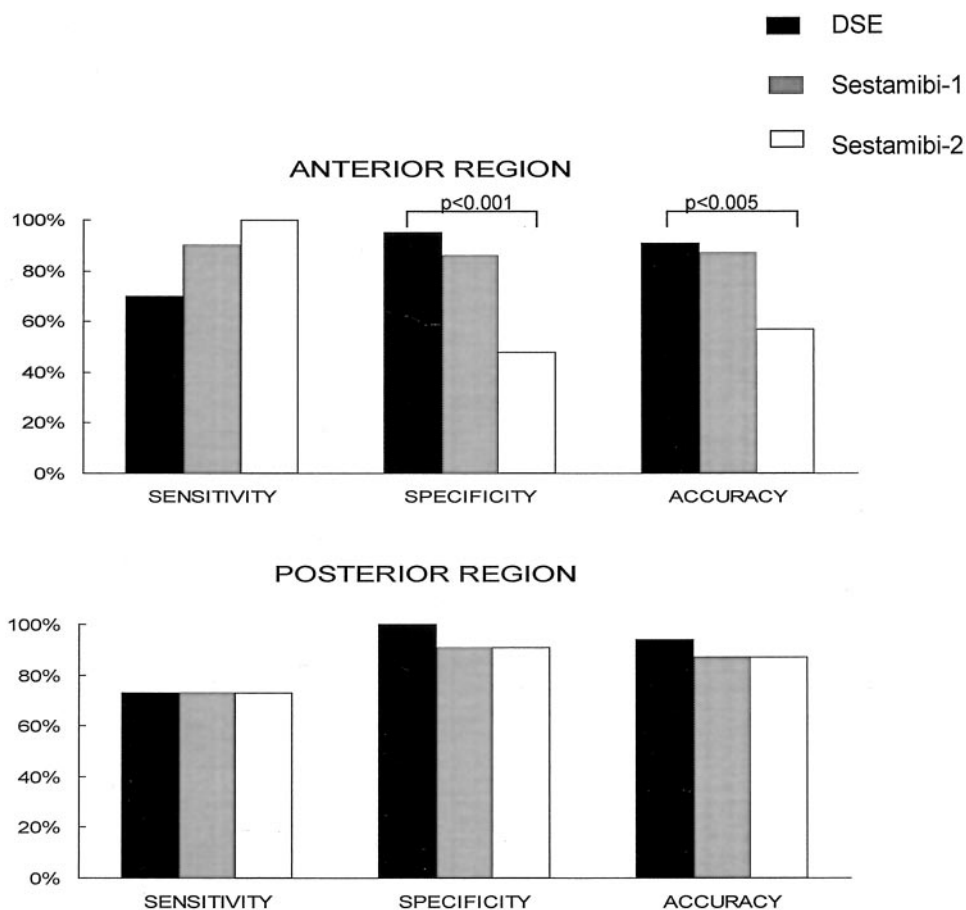


FIGURE 1. Histograms showing the diagnostic performance of DSE, sestamibi-1 and sestamibi-2 for CAD in the anterior (*top*) and posterior (*bottom*) regions.

diography has been substantially facilitated by modern technology, such as second harmonic imaging.¹⁹ In fact, the endocardial border can be optimally imaged in most cases even at the level of the distal portion of the anterior and septal wall, as well as of the entire apex. Further imaging improvement can be achieved in the near field through the fine regulation of gain and focus settings. Modern computerized tools, such as color kinesis, may improve

this approach. Moreover, septal motion can be more confidently evaluated by combining M-mode and two-dimensional echocardiographic analysis, as demonstrated by the recent data from the study by Geleijnse et al.⁹ Thus, giving particular attention also to the contractile behavior of the apex, a biphasic response suggesting inducible ischemia in the anterior region can be diagnosed even in patients showing severe LBBB-linked asynergy at baseline.

A new finding in our study with possible practical implications was that two thirds of patients with LBBB and underlying LV dilatation who were examined by sestamibi-2 and one third of patients with LBBB and underlying LV dilatation who were examined by sestamibi-1 had false-positive responses for CAD, compared with no false-positive responses when patients were examined by DSE. Remarkably, in these patients we observed some very misleading falsely positive posterior defects, which were similar to those noticed in patients with LV hypertrophy and/or dilatation²⁰⁻²² and had been attributed to microcirculatory dysfunction or to partial volume

Table 2—Diagnostic Performance in 14 Patients With Complete LBBB and LV Dilatation

Variables	DSE	Sestamibi-1	Sestamibi-2
True positives, No. of patients	1	1	2
False positives, No. of patients	0	4*	9†
True negatives, No. of patients	12	8	3
False negatives, No. of patients	1	1	0
Global predictive accuracy, %	92.9	64.3	35.7
Sensitivity, %	50.0	50.0	100
Specificity, %	100	66.6	25.0

*Three anterior and three posterior defects.

†Nine anterior and three posterior defects.

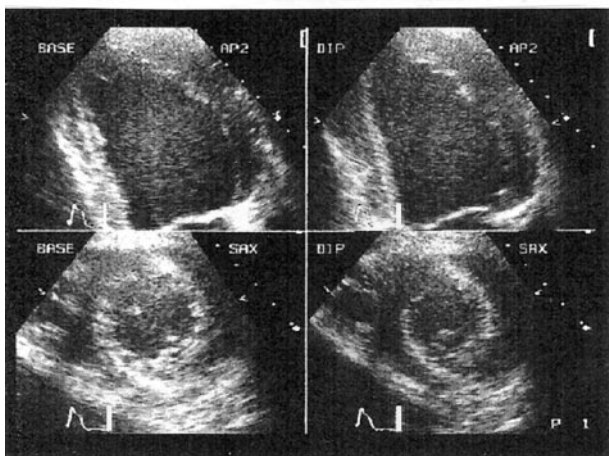
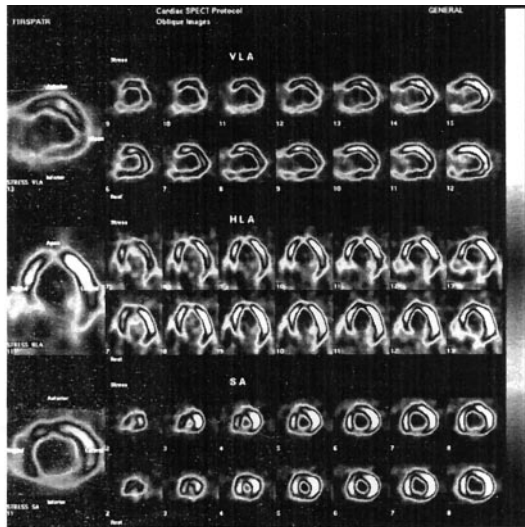


FIGURE 2. Sestamibi single photon emission CT (SPECT) (*top*) and DSE (*bottom*) in a patient with LBBB, LV dilatation, and no CAD. A partially reversible defect of both the anterior and posterior regions is present at the time of sestamibi CT. In contrast, in the DSE images contractile recruitment from baseline (BASE) to peak-dipyridamole stress (DIP) is normal (*top*, apical 2-chamber [AP-2] view; *bottom*: short-axis [SAX] view at the level of papillary muscles; *left*, diastole; *right*, end-systole). VLA = vertical long axis; HLA = horizontal long axis.

effect. However, the cause of these defects in the presence of complete LBBB and LV dilatation remains unclear.

Some important limitations of our study should be acknowledged. First of all, the population examined was relatively small, particularly regarding patients with underlying LV dilatation. Consequently, our dismissal of scintigraphy in this subset of patients should be confirmed with a larger group of patients. Furthermore, we did not use new scintigraphic techniques that allow the combined analysis of myocardial perfusion and wall motion,²³ which might have provided better results than those found in this study. Finally, different results might have been observed in an LBBB population with different pretest probabilities for CAD.

In conclusion, our data show that echocardiography during dipyridamole infusion is at least as accurate as dipyridamole myocardial perfusion scintigraphy for predicting CAD in patients with LBBB and suggest that DSE may be particularly appropriate in patients with underlying LV dilatation.

ACKNOWLEDGMENTS: We gratefully acknowledge the statistical assistance of Dr. Saverio Fusilli (Department of Pathology, Casa Sollievo della Sofferenza Hospital).

REFERENCES

- O'Keefe JH, Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercise thallium-201 for detecting coronary artery disease in patients with left bundle-branch block. *J Am Coll Cardiol* 1993;21:1332-1338
- Burns RJ, Galligan L, Wright LM, et al. Improved specificity of myocardial thallium-201 single-photon emission computed tomography in patients with left bundle-branch block by dipyridamole. *Am J Cardiol* 1991; 68:504-508
- Mairesse GH, Marwick TH, Arnesi M, et al. Improved identification of coronary artery disease in patients with left bundle-branch block by use of dobutamine stress echocardiography and comparison with myocardial perfusion tomography. *Am J Cardiol* 1995; 76:321-325
- Yanik A, Yetkin E, Senen K, et al. Value of dobutamine stress echocardiography for diagnosis of coronary artery disease in patients with left bundle-branch blockage. *Coron Artery Dis* 2000; 11:545-548
- Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979; 300:1350-1358
- Flowers NC. Left bundle-branch block: a continuously evolving concept. *J Am Coll Cardiol* 1987; 9:684-697
- Picano E, Marini C, Pirelli S, et al. Safety of intravenous high-dose dipyridamole echocardiography. *Am J Cardiol* 1992; 70:252-256
- Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989; 2:358-367
- Geleijnse ML, Vigna C, Kasprzak JD, et al. Usefulness and limitations of dobutamine-atropine stress echocardiography for diagnosis of coronary artery disease in patients with left bundle-branch block: a multicentre study. *Eur Heart J* 2000; 21:1666-1673
- Arnesi M, Fioretti PM, Comel JH, et al. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol* 1994; 73:896-899
- Caner B, Rezaghi C, Uysal U, et al. Dobutamine thallium-201 myocardial SPECT in patients with left bundle-branch block and normal coronary arteries. *J Nucl Med* 1997; 38:424-427
- Knapp WH, Bentrup A, Schmidt U, et al. Myocardial scintigraphy with thallium-201 and technetium-99m-hexakis-methoxyisobutylisonitrile in left bundle-branch block; a study in patients with and without coronary artery disease. *Eur J Nucl Med* 1993; 20:219-224
- Tawarahara K, Kurata C, Taguchi T, et al. Exercise testing and thallium-201 emission computed tomography in patients with intraventricular conduction disturbances. *Am J Cardiol* 1992; 69:97-102

- 14 Vaduganathan P, Zuo-Xiang HE, Raghavan C, et al. Detection of left anterior descending coronary artery stenosis in patients with left bundle-branch block: exercise, adenosine or dobutamine imaging? *J Am Coll Cardiol* 1996; 28:543-550
- 15 Ono S, Nohara R, Kambara H, et al. Regional myocardial perfusion and glucose metabolism. in experimental left bundle-branch block. *Circulation* 1992; 85:1125-1131
- 16 Skolidis EI, Kochiadakis GE, Koukouraki SI, et al. Phasic coronary flow pattern and flow reserve in patients with left bundle-branch block and normal coronary arteries. *J Am Coll Cardiol* 1999; 33:1338-1346
- 17 Picano E, Lattanzi F. Dipyridamole echocardiography: a new diagnostic window on coronary artery disease. *Circulation* 1991; 83(suppl):III-19-26
- 18 Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle-branch block: the effect of interventricular asynchrony. *Circulation* 1989; 79:845-853
- 19 Mulvagh SL, Foley DA, Belohlavek M, et al. Image enhancement by noncontrast harmonic echocardiography: Part I. Qualitative assessment of endocardial visualization. *Mayo Clin Proc* 1998; 73:1062-1065
- 20 Dunn RF, Uren RF, Sadick N, et al. Comparison of thallium-201 scanning in idiopathic dilated cardiomyopathy and severe coronary artery disease. *Circulation* 1982; 66:804-810
- 21 LeGrand V, Hodgson JM, Bates ER, et al. Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. *J Am Coll Cardiol* 1985; 6:1245-1253
- 22 Sinusas AJ, Shi QX, Vitols PJ, et al. Impact of regional ventricular function, geometry, and dobutamine stress on quantitative ^{99m}Tc-sestamibi defect size. *Circulation* 1993; 88:2224-2234
- 23 Danias PG, Ahlberg AW, Clark BA, et al. Combined assessment of myocardial perfusion and left ventricular function with exercise technetium-99m sestamibi gated single-photon emission computed tomography can differentiate between ischemic and nonischemic dilated cardiomyopathy. *Am J Cardiol* 1998; 85:1253-1258