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Vasodilator Stress Impairs the Left Ventricular Function Obtained With Gated Single-Photon Emission Computed Tomography in Patients With Known or Suspected Coronary Artery Disease

Keiichi Odagiri, MD, PhD; Akihiko Uehara, MD, PhD; Chinori Kurata, MD, PhD

Background: Transient ischemic dilatation (TID) and post-stress dysfunction of the left ventricle (LV) are important markers of severe coronary artery disease (CAD). To clarify the effects of stressor type on TID and post-stress LV dysfunction, changes in LV measurements were compared between patients with exercise- or vasodilator-induced stress.

Methods and Results: The 689 patients referred for technetium-99m tetrofosmin myocardial perfusion imaging were included. Patients were stressed with either a vasodilator (n=236) or exercise (n=453). LV measurements were obtained with ECG-gated SPECT. LV end-diastolic and end-systolic volume indexes (LVEDVI, LVESVI) increased and LV ejection fraction (LVEF) decreased after stress in the vasodilator-stress group. Vasodilator-stress and the summed difference score (SDS) were independent variables that decreased LVEF after stress. Even in patients without reversible defects, vasodilator-stress impaired LV function. There were no differences in the stress-to-rest ratios of LVEDVI (rEDV) and LVESVI (rESV) among patients with normal myocardial perfusion, fixed defects and reversible defects in the vasodilator-stress group, whereas in the exercise-stress group, rESV was significantly higher in the patients with reversible defects than in those without reversible defects. Within the vasodilator-stress group, neither rEDV nor rESV correlated with the SDS.

Conclusions: Vasodilator-stress by itself decreases LVEF after stress. TID should be carefully interpreted when vasodilator-stress is used to detect severe CAD. (*Circ J* 2010; **74:** 2666–2673)

Key Words: Adenosine; Exercise; Ischemia; Left ventricular function; Single-photon emission computed tomography (SPECT)

Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) provides valuable diagnostic and prognostic information in patients with coronary artery disease (CAD).[1–4] The application of the electrocardiogram (ECG)-gating technique to MPI with SPECT enables the simultaneous evaluation of myocardial perfusion and left ventricular (LV) function by use of the quantitative gated SPECT program (QGS).[5–7]

In patients with CAD, the post-stress gated SPECT shows global and regional LV dysfunction.[8,9] Transient ischemic dilatation (TID) on MPI refers to a significant enlargement in the LV size on the stress images compared with the rest images. TID and post-stress LV dysfunction are the specific markers of severe and extensive CAD, and are also independent predictors of cardiac events, although the underlying mechanism of TID is still a matter of controversy.[10–14]

Physical exercise is now commonly used as a stressor. In patients unable to exercise, adenosine and dipyridamole, strong coronary vasodilators, are often used as stressors. To our knowledge, the vasodilators themselves have no direct influence on LV function. However, current studies have reported that adenosine or adenosine triphosphate may impair LV function in patients with normal myocardial perfusion.[15,16] Because TID and post-stress LV dysfunction are used as markers for severe and extensive CAD in clinical examinations, and the cutoff value for an abnormal TID ratio in vasodilator-induced stress is higher than that in exercise stress,[12,17] it is crucial to clarify the effects of vasodilator-induced stress

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Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu (K.O.); Yamaha Health Care Center, Hamamatsu (A.U., C.K.), Japan

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Mailing address: Keiichi Odagiri, MD, PhD, Yamaha Health Care Center, 10-1 Nakazawa-cho, Naka-ku, Hamamatsu 430-8650, Japan. E-mail: k-altair@nifty.com

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by itself on LV function. Therefore, the present study examined (1) the changes in LV volume and LV ejection fraction (LVEF) in patients who underwent exercise stress or a vasodilator-stress test, (2) the independent predictors for a decrease in LVEF after stress, and (3) the difference in the stress-to-rest ratios of LV volumes among patients with normal myocardial perfusion, reversible defects and fixed defects.

Methods

Patients

We selected patients with known or suspected CAD who underwent technetium (Tc-99m) tetrofosmin MPI at Hamamatsu University Hospital between September 2005 and August 2008. Exclusion criteria were patients with an acute myocardial infarction, hypertrophic or dilated cardiomyopathy, arrhythmias (atrial fibrillation, atrial flutter and frequent premature ventricular complexes), left bundle branch block and pacemaker rhythm on 12-lead ECG, and active bronchial asthma. In total, 689 patients (449 men, 240 women; median age 68 years, range 34–90 years) were analyzed retrospectively.

Stress Protocol

All the patients underwent stress myocardial SPECT with Tc-99m tetrofosmin using a 1-day stress/rest protocol.[18] of the 689 patients, 453 performed a symptom-limited exercise stress test in the upright position using a bicycle ergometer (the exercise-stress group).[19] This exercise protocol included a stepwise increase in workload, depending on sex and age. Exercise endpoints were severe angina, physical exhaustion, sustained ventricular tachycardia and dyspnea. At near maximal exercise, a dose of 185 MBq of Tc-99m tetrofosmin was administered and exercise was continued at the same level for 1 min after the injection.

A vasodilator pharmacologic stress test was used for 236 of the 689 patients (the vasodilator-stress group; dipyridamole and adenosine in 75 and 161 patients, respectively). In the vasodilator-stress test, patients were asked to abstain from caffeine-containing foods and beverages, and medications containing xanthine for 24 h. Dipyridamole was administered intravenously at a rate of $0.14\,mg\cdot kg^{-1}\cdot min^{-1}$ for 4 min, and 4 min later, a dose of 185 MBq of Tc-99m tetrofosmin was given intravenously.[20] Adenosine was administered at a rate of $120\,\mu g\cdot kg^{-1}\cdot min^{-1}$ for 6 min, and 3 min later, a dose of 185 MBq of Tc-99m tetrofosmin was given.[2] None of the patients undergoing pharmacologic testing received reversal medications (eg, aminophyline).

Before and every minute during the stress test, the 12-lead ECG was examined. ECG-gated SPECT was acquired 30 min after each test and 4 h after the initial acquisition. For the later ECG-gated SPECT, a dose of 555 MBq of Tc-99m tetrofosmin was re-administered and image acquisition was started 30 min after the injection.

Image Acquisition Protocol

ECG-gated myocardial perfusion SPECT was acquired with a dual-detector gamma camera (Millennium VG, GE Healthcare Technologies, Milwaukee, WI, USA) equipped with high-resolution collimators. SPECT data were acquired from 32 projection views over 180°, extending from the 45° right anterior oblique to the 45° left anterior oblique position, with 45 s/view, on 64×64 matrices with 1.33 acquisition zoom, 16 frames per cardiac cycle with ECG gating, ±50% R-R acceptance window, and 20% energy window centered at 140 keV. The data were processed on a dedicated computer (Xeleris, GE Healthcare Technologies, Haifa, Israel) with the QGS 3.0 software program (Cedars-Sinai Medical Center, CA, USA).[6,7] The images were reconstructed by ramp filter back projection after pre-filtering the projection data with a Butterworth filter (cut-off frequency 0.40 cycle/cm and 10^{th} order). The reconstructed data were projected as tomographic slices in short-, vertical and horizontal axis views. In addition, the images were displayed as polar plots.

Analyses of Myocardial Perfusion and LV Function

The non-gated perfusion images of exercise- or vasodilator-induced stress and the rest studies were displayed in the short-, vertical and horizontal axis views. A semi-quantitative visual interpretation was performed using 20 segments for each of the stress and rest images.[2,21] Each segment was scored using a 5-point scoring system (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake; 4, absent of tracer) by 2 experienced observers in consensus. The summed stress score (SSS) and summed rest score (SRS) were obtained by summing of the scores of 20 segments on the exercise- or vasodilator-stress and rest images, respectively. The summed difference score (SDS) was defined as the difference of SSS and SRS.[17] The perfusion images were classified as normal myocardial perfusion or showing fixed or reversible defects. A defect was considered to be fixed when there was no change between the stress and rest images. A defect was considered to be reversible when there was an improvement in perfusion between the stress and rest images of at least 1 grade in 1 segment or more.

LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were acquired with QGS. The values for the LV volumes were indexed by dividing them with the body surface area (LVEDVI and LVESVI).

Statistical Analysis

All the data are expressed as the mean±standard deviation of the indicated numbers. Categorical variables were compared between the patient groups by chi-square test. Differences between groups were examined by unpaired t-test or 1-way ANOVA followed by Scheffé's post hoc multiple comparison test. Analyses of covariance (ANCOVA) were performed, adjusting for age and sex, to compare mean values of the LV parameters. Differences between scintigraphic scores were examined by Wilcoxon rank-sum test (non-parametrically distributed values). The changes in LV volume and LVEF after stress were examined by a paired t-test. Multiple linear regression analysis was used to assess the independent variables that affect the change in LVEF after stress. Correlations between the stress-to-rest ratios of LVEDVI (rEDV), LVESVI (rESV) and SDS were assessed by Pearson's correlation coefficient (r). A P value less than 0.05 was regarded as denoting a statistically significant difference. The computations were performed using SPSS (Version 11.0; SPSS Inc, Chicago, IL, USA).

Results

Patients' Characteristics

The vasodilator-stress group included more female, older and shorter patients (Table 1). The prevalence of previous coronary artery bypass grafting was higher in the vasodilator-stress group, whereas that of previous percutaneous coronary intervention was higher in the exercise-stress group.

Table 1. Comparison of the Clinical Characteristics of Patients With Exercise- or Vasodilator-Induced Stress

	Exercise stress (n=453)	Vasodilator stress (n=236)	P value
Age (years)	65.5±9.1	70.9±9.6	<0.001
Height (cm)	160.2±8.6	156.0±9.0	<0.001
Body weight (kg)	60.6±11.1	53.9±10.6	<0.001
Male	309 (68.2%)	140 (59.3%)	0.023
LVESV <20 ml (at rest)	168 (37.1%)	89 (38.5%)	0.713
Prior MI	97 (19.2%)	44 (18.6%)	0.859
CABG	50 (11.0%)	42 (17.8%)	0.018
PCI	119 (26.2%)	44 (18.6%)	0.030
Hypertension	230 (50.8%)	127 (53.8%)	0.470
Hyperlipidemia	118 (41.5%)	84 (35.6%)	0.140
Diabetes mellitus	162 (35.7%)	76 (32.2%)	0.399
Smoking	66 (20.3%)	30 (14.8%)	0.131
(Unknown)	(129)	(33)	
Nitrate or nicorandil	142 (31.3%)	86 (36.4%)	0.201
HMG-CoA reductase inhibitors	172 (38.0%)	72 (30.5%)	0.054
β-blockers	132 (29.1%)	72 (30.5%)	0.726
Calcium antagonists	206 (45.5%)	97 (41.1%)	0.293
ACEI/ARB	181 (40.0%)	98 (41.5%)	0.744
Antiplatelets	223 (51.4%)	113 (47.9%)	0.379

Values are mean±SD.
LVESV, left ventricular end-systolic volume; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Table 2. Comparison of Hemodynamic and Perfusion Parameters of Patients With Exercise- or Vasodilator-Induced Stress

	Exercise stress (n=453)	Vasodilator stress (n=236)	P value
Hemodynamic parameters			
Heart rate (beats/min)			
Rest	68.3±11.7	71.0±13.5	0.010
Stress	134.5±22.6	84.0±23.0	<0.001
Systolic blood pressure (mmHg)			
Rest	137.7±36.8	126.5±29.2	<0.001
Stress	180.0±31.2	116.7±22.7	<0.001
Double products			
Rest	9,438.5±3,219.0	8,970.3±2,644.7	0.130
Stress	24,358.6±6,378.1	9,860.1±3,910.8	<0.001
Perfusion parameters			
SSS	4.6±7.1	4.8±7.6	0.578
SSS≥14	62 (13.7%)	24 (10.2%)	0.224
SRS	3.1±6.2	3.3±6.7	0.495
SDS	1.5±2.8	1.4±2.7	0.640
SDS≥9	20 (4.4%)	6 (2.5%)	0.149

Values are mean±SD.
SSS, summed stress score; SRS, summed rest score; SDS, summed difference score.

Changes in Hemodynamic Parameters

At rest, heart rate was higher but systolic blood pressure was lower in the vasodilator-stress group (Table 2). The double product of heart rate and systolic blood pressure was, therefore, similar between the 2 groups. In the exercise-stress group, almost optimal exercise-stress was achieved, because the heart rate, systolic blood pressure and double product increased significantly at the peak of exercise (all, P<0.001). In the vasodilator-stress group, heart rate increased and systolic blood pressure decreased at the end of vasodilator-stress (both, P<0.001). Therefore, there was no significant change in the double product.

Changes in LV Volumetric Parameters After Stress

There was no significant difference in SSS, SRS or SDS between the 2 groups (Table 2). Additionally, when a cut-off point of SSS ≥14 or SDS ≥9 was applied as an index of severe CAD,[10,17] the proportions of patients with severe CAD

Table 3. Comparison of Left Ventricular Volumetric Parameters at Rest and After Stress

	Rest	Stress	P value
Exercise stress			
LVEF (%)	67.3±12.6	65.9±13.1	<0.001
LVEDVI (ml/m²)	48.3±16.8	46.8±17.2	<0.001
LVESVI (ml/m²)	17.5±13.8	17.9±14.8	0.078
Vasodilator stress			
LVEF (%)	64.4±16.5*	62.1±16.2***	<0.001
LVEDVI (ml/m²)	50.6±23.6	52.5±24.4†	<0.001
LVESVI (ml/m²)	20.9±20.9**	22.8±21.8††	<0.001

On the rest images, LVEF was lower and LVESVI was higher in the vasodilator-stress group than in the exercise-stress group (*P=0.014 and **P=0.017, respectively). On the stress images LVEF was lower and LVEDVI and LVESVI were higher in the vasodilator-stress group than in the exercise-stress group (***P=0.002, †P=0.001 and ††P=0.003, respectively). Values are mean±SD. LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

Table 4. Comparison of Age- and Sex-Adjusted Left Ventricular Volumetric Parameters at Rest and After Stress

	Rest	Stress	P value
Exercise stress			
LVEF (%)	67.9±12.9	66.6±13.1	<0.001
LVEDVI (ml/m²)	47.6±18.9	46.1±19.5	<0.001
LVESVI (ml/m²)	16.9±16.2	17.2±17.1	0.125
Vasodilator stress			
LVEF (%)	63.4±13.5*	61.0±13.5†	<0.001
LVEDVI (ml/m²)	51.9±19.6**	53.8±20.2†	<0.001
LVESVI (ml/m²)	21.9±16.7***	23.9±17.7†	<0.001

On the rest images, LVEF was lower and LVESVI and LVESVI were higher in the vasodilator-stress group than in the exercise-stress group (*P<0.001, **P=0.008 and ***P<0.001, respectively). On the stress images, LVEF was lower and LVEDVI and LVESVI were higher in the vasodilator-stress group than in the exercise-stress group (†P<0.001). Values are mean±SD. Abbreviations see in Table 3.

did not differ between the 2 groups. These results implied that the severity of myocardial perfusion abnormality was similar between groups.

On the rest images LVEF was lower and LVESVI was higher in the vasodilator-stress group than in the exercise-stress group. On the stress images, LVEF was lower and LVEDVI and LVESVI were higher in the vasodilator-stress group than in the exercise-stress group (Table 3). However, both LVEDVI and LVESVI increased significantly after stress in the vasodilator-stress group, whereas LVEDVI decreased significantly in the exercise-stress group. In the both groups, LVEF decreased significantly after stress.

To eliminate the effects of age and sex, we compared the LV parameters between the 2 groups with these factors adjusted by using ANCOVA (Table 4). On both rest and stress images, LVEF was lower and LVEDVI and LVESVI were higher in the vasodilator-stress group than in the exercise-stress group, similar to the values shown in Table 3. Thus, these factors did not influence the LV measurements obtained with ECG-gated SPECT.

Table 5. Partial Regression Coefficients of Variables That Affected the Decrease in LVEF After Stress

	Partial regression coefficient	95%CI	P value
Age (years)	−0.003	−0.020 to 0.027	0.775
Sex (female)	−0.393	−1.339 to 0.553	0.414
Prior MI	0.540	−0.860 to 1.940	0.449
Hypertension	−0.153	−1.147 to 0.840	0.762
Hyperlipidemia	−0.209	−1.213 to 0.795	0.683
Diabetes mellitus	−0.402	−1.422 to 0.617	0.439
Smoking	−0.168	−1.447 to 1.110	0.796
β-blockers	0.323	−0.744 to 1.391	0.552
SSS	−0.052	−0.147 to 0.044	0.288
SDS	−0.378	−0.147 to −0.168	<0.001
Vasodilator stress	−1.198	−2.196 to −0.199	0.019

CI, confidence interval. Other abbreviations see in Tables 1–3.

Multivariate Analyses for Determinate Factors of the Decrease in LVEF After Stress

The partial regression coefficients of patient characteristics and perfusion parameters that affected the decrease in LVEF after stress are shown in Table 5. Only vasodilator-induced stress and SDS were found to be independent variables that decreased LVEF after stress.

Changes in LV Volumetric Parameters in Patients With Normal Myocardial Perfusion or Fixed Defects

Because SDS was selected as an independent variable for the decrease in LVEF, we next investigated the changes in LV volumetric parameters in patients with normal myocardial perfusion and in those with fixed defects on MPI (Table 6) to eliminate the effect of stress-induced myocardial ischemia.

Among patients with both normal myocardial perfusion and fixed defects, both LVEDVI and LVESVI increased, and LVEF decreased after stress in those in the vasodilator-stress group. In contrast, there was no difference in LVESVI or LVEF, but LVEDVI decreased, after stress in those in the exercise-stress group (Table 6).

Next, we compared the changes in LV volume indexes after stress between the exercise- and vasodilator-induced stress groups. In the exercise-stress group, ΔLVEDVI was −1.5±5.3 ml, −2.0±5.9 ml and −1.2±6.3 ml, ΔLVESVI was −0.1±4.2 ml, −0.2±5.4 ml and 1.2±3.6 ml, and ΔLVEF was −0.6±5.7%, −0.1±6.9% and −2.9±5.3% in patients with normal myocardial perfusion, fixed defects and reversible defects, respectively. In the vasodilator-stress group, the respective ΔLVEDVI was 1.7±4.1 ml, 3.6±4.9 ml and 1.4±5.6 ml, ΔLVESVI was 1.7±3.2 ml, 3.0±4.7 ml, and 1.8±4.1 ml and ΔLVEF was −2.0±5.9%, −1.6±4.1% and −2.7±5.3% (Figure 1). The ΔLVESVI was larger in patients with reversible defects than in patients with normal myocardial perfusion in the exercise-stress group. However, there were no differences in ΔLVESVI among the 3 groups in the vasodilator-stress group.

Vasodilator-Dependent Effects on LV Volumetric Parameters

We further investigated whether there were vasodilator-dependent effects on LV volumetric parameters in patients with normal myocardial perfusion (dipyridamole; n=32, adenosine; n=74). There were no differences in the increases in LVEDVI and LVESVI or the decrease in LVEF after stress between

Table 6. Comparison of Left Ventricular Volumetric Parameters at Rest and After Stress in Patients With Normal Myocardial Perfusion and Fixed Defects

	Normal myocardial perfusion*			Fixed defects**		
	Rest	Stress	P value	Rest	Stress	P value
Exercise stress						
LVEF (%)	72.6±10.6	72.1±10.2	0.159	58.6±14.0	58.4±15.8	0.889
LVEDVI (ml/m²)	42.7±11.2	41.1±12.1	<0.001	60.0±22.1	58.0±24.3	0.008
LVESVI (ml/m²)	12.5±8.1	12.4±9.4	0.666	27.8±20.9	27.6±22.9	0.735
Vasodilator stress						
LVEF (%)	71.7±13.8	69.3±13.1	<0.001	57.4±16.0	55.9±16.6	0.039
LVEDVI (ml/m²)	41.9±13.1	43.9±13.4	<0.001	58.2±29.8	61.8±31.1	<0.001
LVESVI (ml/m²)	12.5±9.0	14.4±10.2	<0.001	28.9±28.7	31.9±31.6	0.001

*Exercise stress (n=213), vasodilator stress (n=106); **exercise stress (n=69), vasodilator stress (n=34).
Values are mean±SD.
Abbreviations see in Table 3.

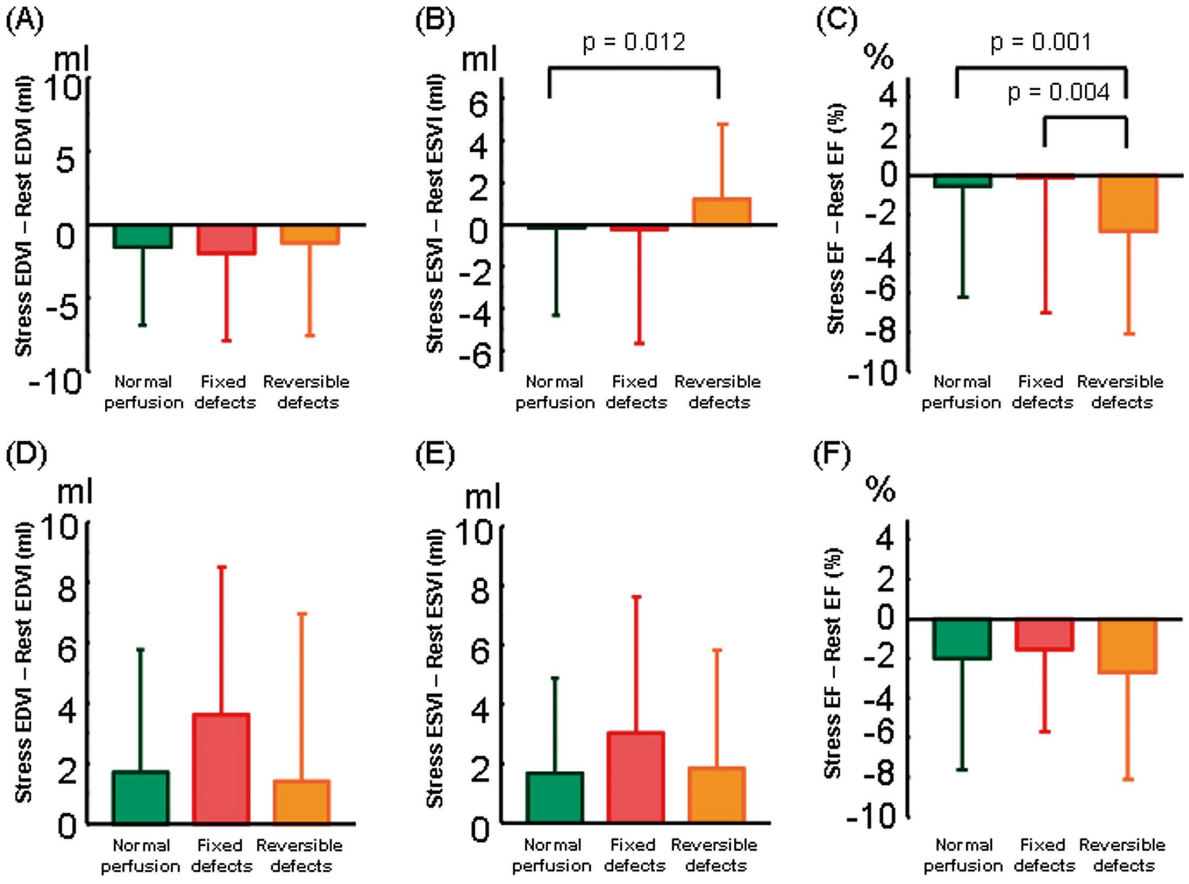

Figure 1. Comparison of differences between LVEDVI on stress and rest images, between LVESVI on the stress and rest images, and between LVEF on the stress and rest images, from patients with normal myocardial perfusion, fixed defects and reversible defects in the exercise-stress group (A–C) and in the vasodilator-stress group (D–F). The number of patients with normal myocardial perfusion was 213, 69 had fixed defects and 171 had reversible defects in the exercise-stress group, and in the vasodilator-stress group it was 106, 34 and 96, respectively. Values are mean±SD. LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end systolic volume index; LVEF, left ventricular ejection fraction.

patients with dipyridamole-stress and those with adenosine-stress (ΔEDVI, ΔESVI and ΔLVEF: 2.2±1.6 ml/m², 2.8±9.4 ml/m² and −0.50±5.1% in dipyridamole-stress, and 1.6±4.3 ml/m², 2.1±3.0 ml/m² and −2.7±5.5% in adenosine-stress, P>0.05, respectively).

Comparisons of Stress-to-Rest Ratios of LVEDV and LVESV

Because TID has been established as a diagnostic parameter of stress MPI,[10,12,20,22–24] we evaluated whether vasodilator-stress affected rEDV and rESV. The patients were divided into 3 groups (normal myocardial perfusion, fixed defects and

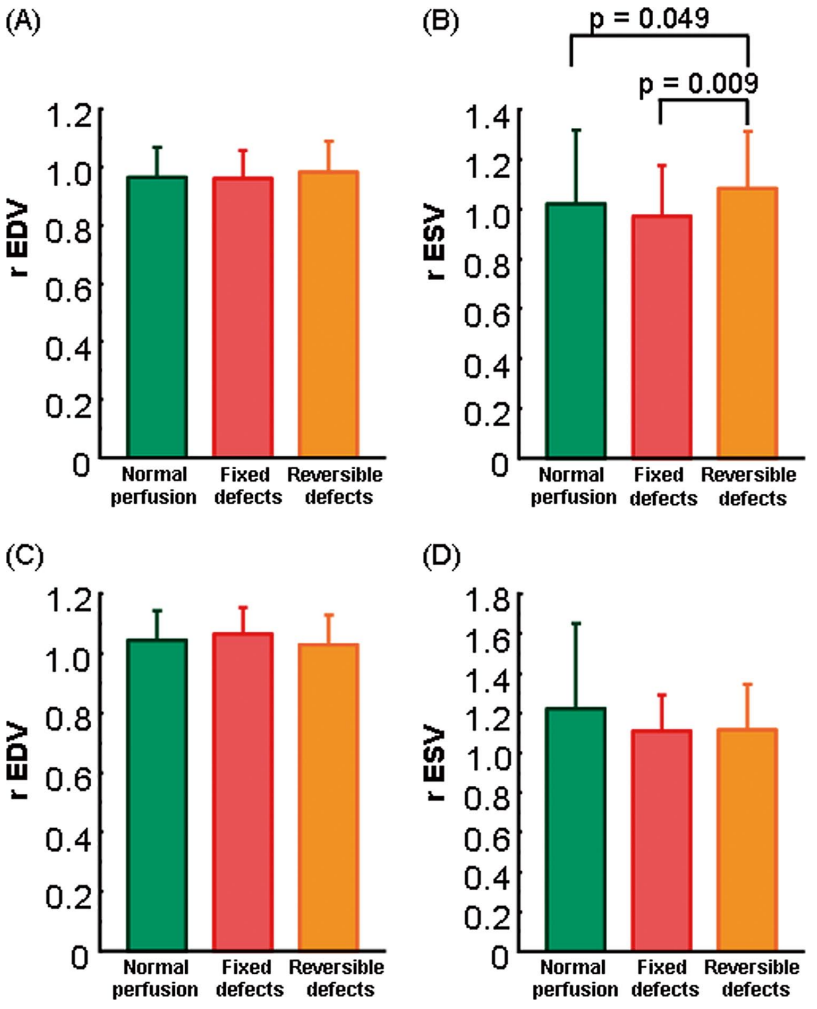

Figure 2. Comparison of the stress-to-rest ratios of the left ventricular end-diastolic and end-systolic volume indexes (rEDV and rESV) in patients with normal myocardial perfusion, fixed defects and reversible defects in the exercise-stress group (**A**, **B**) and in the vasodilator-stress group (**C**, **D**). The number of patients with normal myocardial perfusion was 213, 69 had fixed defects and 171 had reversible defects in the exercise-stress group, and in the vasodilator-stress group it was 106, 34 and 96, respectively. Values are mean±SD.

reversible defects). As shown in **Figure 2**, rEDV was similar among the groups, but rESV was slightly, but significant, larger in the patients with reversible defects than in those with fixed defects in the exercise-stress group (normal myocardial perfusion, fixed defects and reversible defects: rEDV, 0.97±0.10, 0.99±0.10 and 0.98±0.11, P=0.180; rESV, 1.02±0.30, 0.97±0.21 and 1.08±0.23, P=0.004; respectively). However, in the vasodilator-stress group, there were no significant differences in rEDV and rESV among the 3 groups (normal myocardial perfusion, fixed defects and reversible defects: rEDV, 1.04±0.10, 1.07±0.09 and 1.03±0.10, P=0.184; rESV, 1.22±0.43, 1.11±0.18 and 1.11±0.23, P=0.052, respectively).

In patients with a small heart, rEDV and rESV tended to under- or over-estimation. Therefore, we excluded patients with ESV <20 ml on either the rest or stress image to eliminate the influence of a small heart. There were also no significant differences in either rEDV or rESV among the patients with normal myocardial perfusion, fixed defects and reversible defects (normal myocardial perfusion, fixed defects and reversible defects: rEDV, 1.02±0.09, 1.06±0.09 and 1.03±0.09, P=0.211; rESV, 1.11±0.20, 1.12±0.16 and 1.09±0.17, P=0.647, respectively) in the vasodilator-stress group.

Furthermore, within the exercise-stress group, both rEDV and rESV significantly correlated with SDS (r=0.276, P<0.001 and r=0.151, P=0.001, respectively), whereas the vasodilator-stress group did not show such relations (rEDV: r=0.062, P=0.353; rESV: r=0.020, P=0.767, respectively).

Discussion

The present study revealed that (1) vasodilator-induced stress with adenosine or dipyridamole impaired LV function in patients with known or suspected CAD, (2) vasodilator-induced stress and SDS were independent variables that decreased LVEF after stress, (3) even in patients with normal myocardial perfusion and fixed defects, vasodilator-induced stress impaired LV function, and (4) there were no differences in the stress-to-rest ratios of LV volumes among those with normal myocardial perfusion, fixed defects or reversible defects in the vasodilator-stress group, whereas rESV was larger in the patients with reversible defects than in patients with normal myocardial perfusion or fixed defects in the exercise-stress group. To our knowledge, this is the first study to demonstrate impairment of LV function by vasodilator-induced stress in patients with and without reversible defects on MPI.

The post-stress LV dysfunction in QGS has been reported to be usually concomitant with severe and extensive myocardial ischemia induced by exercise stress.[8,10] Previous studies have shown that vasodilator-induced stress can also induce

post-ischemic LV dysfunction and TID.[12,20,22,25,26] The present study demonstrated that LV function was impaired after vasodilator-induced stress, as well as after exercise stress (Table 3). Because the study population included patients with reversible perfusion defects, the transient LV dysfunction and TID could be ascribed to severe myocardial ischemia during vasodilator-induced stress. Because it is well known that vasodilator-induced stress is less likely to produce myocardial ischemia than exercise stress, we examined the variables responsible for the decrease in LVEF after stress by using multiple linear regression analyses, and only vasodilator-induced stress and SDS were independent variables (Table 5). A previous study also described vasodilator-induced stress as an independent variable influencing LVEF in patients with normal myocardial perfusion.[16] Furthermore, the present study demonstrated that both the increases in LV volumes and decrease in LVEF occurred after vasodilator-induced stress, even in patients with normal myocardial perfusion and with fixed defects (Table 6).

Although the mechanisms by which vasodilator-induced stress impairs LV function remain unclear, several hypotheses are proposed. First, when exogenous adenosine is administrated or endogenous adenosine is produced by dipyridamole infusion, the binding of adenosine to an A_1 adenosine receptor has an anti-adrenergic effect that leads to a reduction in myocardial contractility.[27,28] The anti-adrenergic effect of adenosine is caused by inhibition of adenylate cyclase mediated via a pertussis toxin-sensitive G protein,[27,29] thereby altering membrane currents, excitation-contraction coupling and mitochondrial metabolism.[27,30,31] Second, vasodilator-induced stress might cause a relative or absolute decrease in subendocardial blood flow.[32] Finally, a reduction in systemic blood pressure by vasodilator-induced stress increased heart rate and decreased LV volume loading. The increase in heart rate might have affected LV function, although we did not investigate the changes in heart rate during image acquisition. However, because the half-life of adenosine in blood or in the interstitial spaces is within a few seconds,[33] it is unlikely that the direct effects of adenosine remained 30 min after the administration of adenosine or dipyridamole. Furthermore, in the present study, the impairment of LV function in patients with dipyridamole-induced stress was similar to that with adenosine-induced stress in which a faster vasodilator effect was expected. We therefore consider that modulation of the downstream signals of adenosine receptors is most likely for the LV dysfunction observed with vasodilator-induced stress.[27,30,31]

In clinical practice, rEDV and rESV, which can be automatically measured, are used as indicators of TID and post-ischemic LV dysfunction. Actually, in the present exercise-stress group, rESV was larger in patients with reversible defects than in those with normal myocardial perfusion and fixed defects. However, in the vasodilator-stress group, there were no differences in rEDV or rESV among the 3 groups. The reason for this lack of difference was unclear. However, some possible explanations are suggested. As shown in Figure 1, the ΔLVESVI was larger in patients with reversible defects than in patients with normal myocardial perfusion in the exercise-stress group; however, there were no differences in ΔLVESVI among the 3 groups in the vasodilator-stress group. The LVEDVI was also increased after stress in the vasodilator-stress group. These results suggest that not only the post stress contractile dysfunction, caused by the modulation of the downstream signals of adenosine receptors, but also a relative or absolute decrease in subendocardial blood flow might relate to the lack of difference in rEDV and rESV among the 3 groups in the vasodilator-stress group.

The present study results suggest that the interpretation of TID and post-ischemic LV dysfunction should be made carefully when vasodilator-induced stress is used to detect severe and extensive CAD.

Study Limitations

A major study limitation was the underestimation of LV volume in patients with small hearts (especially in women). When a small heart was defined as ESV <20 ml, the percentage reached 74% for women,[34] and in our study population 37.5% of the patients were defined as having a small heart. In those patients, therefore, the LV volumes and LVEF obtained by QGS were less accurate.[35] Furthermore, our study failed to provide regional wall motion analysis or correlation with coronary anatomy, as well as any subsequent coronary events. Finally, in our study population, there were a few patients with severe and extensive CAD (Table 2), a population bias that might affect the rEDV and rESV.

In conclusion, vasodilator-induced stress impaired LV function in patients with and without reversible defects, whereas exercise stress did so only in patients with reversible defects. Although the time course of the changes in LV function after vasodilator-induced stress remains to be investigated further, the present findings suggest that vasodilator-induced stress might itself impair LV function, and caution must be paid to he interpretation of TID and post-ischemic LV dysfunction when vasodilator-induced stress is used.

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