American Journal of Therapeutics 0, 1–8 (2015)

Value of Low-Dose Dobutamine Stress Real-Time Myocardial Contrast Echocardiography in the Diagnosis of Coronary Heart Disease

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To investigate the value of low-dose dobutamine stress real-time myocardial contrast echocardiography (RT-MCE) in the diagnosis of coronary heart disease (CHD). A total of 65 hospitalized patients with suspected or confirmed CHD were detected by RT-MCE combined with low-dose dobutamine stress (0.84 mg/kg). Perfusion curves were quantitatively analyzed using QLAB software. Peak intensity (A), slope of curves (β), and perfusion (A × β) were also calculated. Based on the results of coronary angiography, patients were divided into no obvious stenosis group (<50%), mild stenosis group (50%–74%), moderate stenosis group (75%–89%), and severe stenosis group (≥90%). The A, β, and A × β values before and after low-dose dobutamine stress of each group were compared. In the basal state and after low-dose dobutamine stress, the A, β, and A × β values significantly decreased as the stenosis degree of the myocardial segments increased. The same variation tendency was also found in the A, β, and A × β reserve values, and there was significant difference in these reserve values between moderate and severe stenosis groups and no obvious stenosis and mild stenosis groups. Collateral circulation had marked effects on the values of myocardial perfusion parameters and their reserve values, especially in the segments with severe stenosis. Low-dose dobutamine stress RT-MCE can be a sensitive method for clinical diagnosis and risk assessment of CHD and may provide a basis for further treatment of CHD.

Keywords: myocardial contrast echocardiography, dobutamine, coronary heart disease, diagnosis, coronary artery angiography, coronary artery stenosis, coronary flow velocity, myocardial blood volume

INTRODUCTION

Coronary heart disease (CHD) is also known as coronary artery disease (CAD) and is the result of the narrowed blood vessels that supply blood and oxygen to the heart.[1] Clinical manifestations of CAD are acute coronary syndrome comprising myocardial infarction (MI) and unstable angina as well as stable angina pectoris.[2] Globally, CHD is the leading cause of mortality, accounting for nearly 7 million deaths annually worldwide.[3] It is estimated that 1 coronary event occurs every 25 seconds in the United States, with 34% die within the same year, amounting to 1 death every minute.[4] CHD is the single leading cause of death in the United States and most Western countries, killing more than 400,000 Americans per year.[5] CHD has both genetic and environmental precipitants, and the established risk factors for CHD include age, male gender, high low-density lipoprotein cholesterol levels, low low-density lipoprotein cholesterol levels, obesity, diabetes, smoking, and hypertension.[5,6] It is

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The authors have no conflicts of interest to declare.

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known that coronary microcirculation plays a very important role in the diagnosis and management of CHD,[7] and perfusion defects can help identify the culprit vessel, evaluate the revascularization, and predict the recovery of left ventricular (LV) function and prognosis of the patients.[7]

Real-time myocardial contrast echocardiography (RT-MCE) is a novel method for the evaluation of regional myocardial perfusion that uses low mechanical index to minimize microbubble destruction and permits the evaluation of myocardial perfusion in real time.[8,9] RT-MCE uses microbubble ultrasound contrast agents, which are inert gas-filled microbubbles, possessing an intravascular rheology similar to red blood cells, and reach the myocardial microcirculation by intravenous infusion.[10] Compared with other imaging modalities of myocardial contrast echocardiography (MCE), RT-MCE allows the simultaneous microvascular integrity and myocardial blood flow (MBF) using continuous intravenous injection of microbubbles and quantification of acoustic intensity curves in the myocardium.[8,11] Therefore, by using quantitative analysis of RT-MCE, clinicians can assess the myocardial perfusion of patients, noninvasively and accurately.[10] RT-MCE has been widely applied in the detection of viable myocardium, hibernating myocardium, and angiographically significant CAD.[8,11,12] Dobutamine is a synthetic catecholamine functioning primarily through β-receptors.[13] Low doses of dobutamine have inotropic effect that induces the recruitment of the viable myocardium and improvement of wall thickening/motion in these myocardia.[14] In this study, we sought to compare relative parameters of MCE to evaluate the clinical value of low-dose dobutamine stress RT-MCE in diagnosis of CHD.

MATERIALS AND METHODS

Ethics statement

The study was carried on with the approval of the First Affiliated Hospital of Harbin Medical University, China. The informed written consents were collected from all eligible patients, and the whole study was performed based on the Declaration of Helsinki.[15]

Study subjects

A total of 65 patients (36 men and 29 women; mean age: 58.83 ± 9.51 (range: 44–76 years); body surface area: 1.38–1.91 m^2) with suspected or confirmed CHD including atypical chest pain (n = 7), stable angina pectoris (n = 13), unstable angina pectoris (n = 16), acute MI (n = 20), and old MI (n = 9) were enrolled in the study. All patients were recently examined by coronary angiography (CAG) and MCE. Patients were excluded from the study if (1) they were allergic to contrast media, (2) had serious arrhythmia, atrial fibrillation, atrioventricular block more than twice or serious obstructive lung disease, and (3) the conditions for transmitting ultrasound were too poor to get satisfactory image quality.

Detection by MCE

MCE was performed using a Philips iU22 ultrasound system equipped with a broadband (1–3 MHz) transducer (S3). The left ventricular ejection fraction (LVEF), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by echocardiography. Patients in the basal state were injected with diluted contrast agent (2.0 mL; SonoVue, Bracco, Italy) through elbow vein. After the myocardium was filled with the contrast agent, high-energy pulse was triggered to destroy contrast microbubbles within the myocardium. Then, the system automatically converted to the low-energy real-time radiography state. The refilling of contrast microbubbles within the myocardium was recorded at apical 4-chamber view, 2-chamber view, and apical longitudinal view. Images collected from 15 consecutive cardiac cycles after providing high-energy pulse were turned into the cineloop, which was stored in the magneto-optical disks for offline analysis. After intracardiac microbubbles disappeared, patients were injected with 0.84 mg/kg dobutamine (Brocade Company, Italy) through the elbow vein or hand vein continuously pumping at a rate of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 6 minutes. The infusion rate (milliliter per minute) = 0.14 $mg \cdot kg^{-1} \cdot min^{-1}$ × body weight (kg) × dobutamine concentration (3 mg/mL). The images of 2-dimensional echocardiogram, HR, SBP, and DBP were recorded and stored at the beginning of dobutamine injection, 3 minutes after dobutamine injection, termination of dobutamine injection, and 5 minutes after the termination of dobutamine injection, respectively. Vital signs and symptoms of the patients were closely monitored during the whole procedure.

MCE images analysis

After the cineloop was imported into the computer, QLAB quantitative analysis software (version 2.0; Philips Ultrasound) was applied for offline analysis. LV 16-segment model recommended by American Society of Echocardiography was used to analyze the collected images, and segmental myocardial images were evaluated by semiquantitative score. With regions of interest (5 × 5 mm) placed at the center of each segment, the refilling process of contrast microbubbles within

the myocardium during 15 consecutive cardiac cycles after providing high-energy pulse was analyzed. Pixel intensity of each frame image was calculated frame by frame by computer. A value and β value were calculated automatically according to the exponential curve fitting equation: $y(t) = A \cdot (1 - \exp^{-\beta t}) + C$, where y (t) (unit: dB) is the pixel intensity in the region of interest in time (unit: s), A (unit: dB) is the platform strength, reflecting the myocardial blood volume, β (unit: s^{-1}) reflects the mean blood flow velocity in the intramyocardial vascular network, and C is a constant, reflecting intercept of the exponential curve on the y axis. The $A \times \beta$ (unit: $dB \cdot s^{-1}$) can reflect the MBF. The ratio of the values of A, β, $A \times \beta$ before and after low-dose dobutamine stress represents their respective stress reserve values.

CAG detection

Multidirectional CAG was performed by an experienced cardiac catheter doctor using Judkins method with a flat panel digital subtraction machine (Philips AlluraXper FD20). Stenosis degree was expressed as the percent diameter stenosis of the inner diameter of the lesion vessel and the inner diameter of the vessel segment that was close to normal. The study subjects were divided into 4 groups according to their vessel stenosis degree: no obvious stenosis group (<50%), mild stenosis group (50%–74%), moderate stenosis group (75%–89%), and severe stenosis group (≥90%). CAG positive means coronary artery stenosis ≥50%, and it was used as a gold standard to calculate the diagnosing value of the MCE in CHD (the clinical value of MEC in the early diagnosis of CHD).

Statistical analysis

To draw the receiver operating curve, compare the diagnostic significance of quantitative parameters of MCE, and calculate the sensitivity and specificity of these parameters using different measurements as limits, SPSS19.0 software was used, and the area under the curve was calculated. Measurement data were presented as a form of mean ± SD, and the normality test was performed. The T test was carried out for the comparison of relevant parameters between 2 groups. One-way analysis of variance method was used for the comparison among several groups (test of homogeneity of variance was performed before the analysis); the least significant difference (LSD) t-test was performed for the pairwise comparison of averages among multiple groups. A value of $P < 0.05$ means there was statistical significance.

RESULTS

Change in indexes of heart function after RT-MCE

None of the 65 patients had allergic reactions or other symptoms after the injection of SonoVue, the sulfur hexachloride contrast agent. After low-dose dobutamine stress, the HR, SBP, DBP, and LVEF of patients significantly increased, and the differences were statistically significant (all $P < 0.01$) (Table 1).

CAG detection

Of all 65 patients, 9 patients (13.85%) had normal CAG, 30 cases (46.15%) were found to have ≥50% single-vessel CAD (20 cases in the left anterior descending artery, 4 cases in the circumflex coronary artery, 6 cases in the right coronary artery), 17 cases (26.15%) had ≥50% double-vessel CAD (9 cases in the left anterior descending coronary artery + right coronary artery, 6 cases in the left anterior descending artery + left circumflex coronary artery, 2 cases in the left circumflex coronary artery + right coronary artery), 9 cases (13.85%) had the 3-vessels CAD. CAG results are shown in Figure 1.

The diagnosing value of RT-MCE and CAG in CHD

As CAG was used as the gold standard, of all the 56 cases with positive CAG, 48 cases were MCE positive and 8 cases were MCE negative. In 9 cases of CAG negative, 8 cases were MCE negative and 1 case was MCE positive. In the diagnosis of CHD using MCE, the sensitivity was 85.71%, the specificity was 88.89%, positive predictive value was 97.96%, negative predictive value was 50.55%, and the accuracy rate of MCE for the diagnosis of CHD was 86.15%. The differences of MCE and CAG in the diagnosis of CHD showed no statistical difference ($P > 0.05$) (Table 2).

Table 1. Changes in indexes of heart function after the low-dose dobutamine stress RT-MCE.

	HR (min^{-1})	SBP (mm Hg)	DBP (mm Hg)	LVEF
Basal state	70.19 ± 11.7	116.7 ± 13.7	72.0 ± 9.5	0.46 ± 0.08
Adenosine stress	88.15 ± 12.11	123.1 ± 12.7	76.0 ± 8.9	0.60 ± 0.09
t	8.559	2.762	2.477	9.373
P	<0.0001	0.0066	0.0145	<0.0001

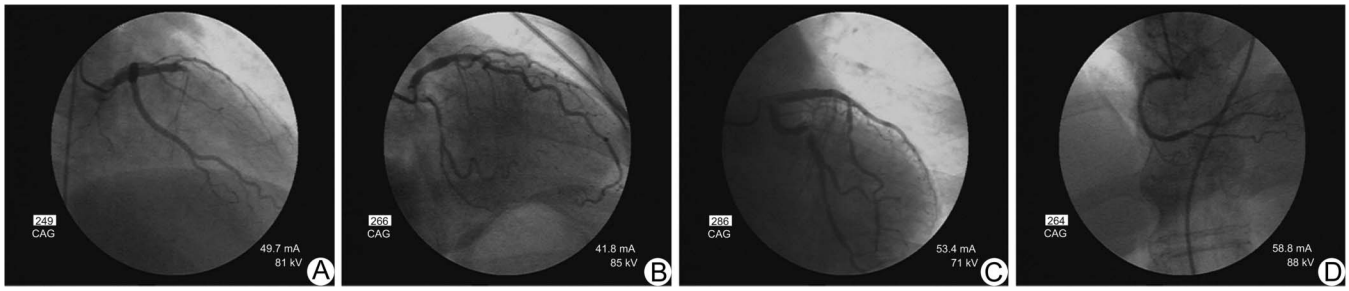

FIGURE 1. Results obtained by CAG; (A) Occluded left anterior descending coronary artery, (B) circumflex coronary artery stenosis, (C) left anterior descending and left circumflex coronary artery stenosis, and (D) Right coronary artery stenosis.

Detection of coronary artery stenosis using RT-MCE

MCE was successfully accomplished among the 65 patients, and they experienced no discomfort during the process. There were 622 blood supply segments of coronary artery with stenosis, of which 117 myocardial segments were excluded because of the lateral shadow and ultrasound transmitting condition and the rest 448 segments were included in the analysis. Of all the analyzed cases, 134 (29.9%) segments were controlled by normal coronary arteries and 314 (70.1%) segments were controlled by coronary artery with ≥50% stenosis. There were 58 (19.7%) segments in mild stenosis group, 73 (22.9%) segments in moderate stenosis group (14 cases with collateral circulation), and 183 (57.4%) segments in severe stenosis group (71 cases with collateral circulation).

Results of quantitative MCE in detecting myocardial segments without collateral circulation with varying degrees of stenosis in the basal state and after low-dose dobutamine stress

Results of quantitative MCE in the detection of myocardial segments without collateral circulation with varying degrees of stenosis in the basal state and after low-dose dobutamine stress are shown in Table 3. In the basal state, as the stenosis degree of the myocardial segments without collateral circulation increased, A, β, and A × β values decreased, and the differences in β value and A × β value were statistically significant among the 4 groups ($P < 0.01$), whereas there was no significant differences in A value ($P > 0.05$). β and A × β values of moderate and severe stenosis groups were significantly lower than those of no obvious stenosis group, and the A × β value of the severe stenosis group was significantly lower than that of mild stenosis group and all the differences were statistically significant ($P < 0.05$). After low-dose dobutamine stress, as the stenosis degree of the myocardial segments without collateral circulation increased, A, β, and A × β values also decreased, and the differences in A, β, and A × β values were statistically significant among the 4 groups ($P < 0.01$), whereas there was no significant differences in A × β values between moderate and severe stenosis groups ($P > 0.05$). The higher the stenosis degree of the coronary artery was, the lower the reserve value of contrast echocardiography of blood supply area. A, β, and A × β reserve values decreased as the stenosis degree increased. However, there was no significant difference between the mild stenosis group and no obvious stenosis group as well as between the moderate stenosis group and severe stenosis group (all $P > 0.05$). For the same segment, A, β, and A × β values of each group after low-dose dobutamine stress were significantly higher than those in the basal state ($P < 0.05$), but there were no marked differences in A values between the moderate stenosis group and severe stenosis group.

Table 2. Diagnostic values of myocardial contrast echocardiography and CAG in CHD.

	CAG		
MCE	+	−	Total
+	48	1	49
−	8	8	16
Total	56	9	65

+, positive; −, negative.

Results of quantitative MCE in detecting myocardial segments with/without collateral circulation in the basal state and after low-dose dobutamine stress

Parameters of quantitative MCE between the segments (coronary artery stenosis degree >75%) with collateral circulation and those without collateral circulation were compared, and the results are shown in Table 4. In the basal state, there was no statistical difference in the A, β, and A × β values between the segments

Table 3. Parameters of myocardial contrast echocardiography and their reserve values of LV segments with different degrees of stenosis in the basal state and under adenosine stress.

Parameters of MCE	Degree of coronary artery stenosis				*F*	*P*
	No obvious stenosis group	Mild stenosis group	Middling stenosis group	Severe stenosis group		
Number of segments	134	58	59	112		
A (dB)						
Basal state	5.28 ± 1.92	5.17 ± 1.15	5.08 ± 0.77	4.89 ± 0.84	1.69	0.1397
Adenosine stress	5.73 ± 1.28*	5.63 ± 1.01*	4.96 ± 0.81†‡	4.70 ± 0.62†‡	26.14	<0.0001
β (s^{-1})						
Basal state	0.26 ± 0.12	0.24 ± 0.09	0.22 ± 0.06†	0.21 ± 0.07†	6.44	0.0003
Adenosine stress	0.67 ± 0.17*	0.52 ± 0.19*†	0.48 ± 0.13*†‡	0.25 ± 0.08*†‡	170.9	<0.0001
A × β value (dB/s)						
Basal state	1.37 ± 0.46	1.31 ± 0.47	1.18 ± 0.37†	1.09 ± 0.32†‡	10.52	<0.0001
Adenosine stress	3.81 ± 1.20*	3.11 ± 1.17*†	1.59 ± 0.82*†‡	1.02 ± 0.37*†‡§	201.6	<0.0001
A reserve	1.20 ± 0.53	1.15 ± 0.16	1.01 ± 0.12†‡	0.99 ± 0.13†‡	9.55	<0.0001
β reserve	2.65 ± 1.07	2.42 ± 0.82	1.44 ± 0.40†‡	1.29 ± 0.34†‡	71.3	<0.0001
A × β reserve	2.89 ± 1.63	2.59 ± 1.01	1.42 ± 0.44†‡	1.27 ± 0.34†‡	55.49	<0.0001

*Compared with basal state, $P < 0.05$.
†Compared with no obvious stenosis group, $P < 0.05$.
‡Compared with mild stenosis group, $P < 0.05$.
§Compared with middling stenosis group, $P < 0.05$.

with/without collateral circulation in each group. However, after low-dose dobutamine stress, β, A × β values, and their reserve values of the segments with collateral circulation were significantly higher than those of the segment without collateral circulation in the severe stenosis group, whereas there was no

Table 4. Correlations between collateral circulation and parameters of myocardial contrast echocardiography.

Parameters of MCE	Degree of coronary artery stenosis			
	Middling stenosis group		Severe stenosis group	
	No collateral circulation	Collateral circulation	No collateral circulation	Collateral circulation
Number of segments	59	14	112	71
A (dB)				
Basal state	5.08 ± 0.77	4.79 ± 1.19	4.89 ± 0.84	4.65 ± 1.48
Adenosine stress	4.96 ± 0.81	4.67 ± 1.22	4.70 ± 0.62	4.52 ± 0.93
β (S^{-1})				
Basal state	0.22 ± 0.06	0.23 ± 0.05	0.21 ± 0.07	0.21 ± 0.08
Adenosine stress	0.48 ± 0.13	0.46 ± 0.20	0.25 ± 0.08	0.34 ± 0.16*
A × β (dB/s)				
Basal state	1.18 ± 0.37	1.15 ± 0.39	1.09 ± 0.32	1.02 ± 0.36
Adenosine stress	1.59 ± 0.82	1.75 ± 0.78	1.02 ± 0.37	1.41 ± 0.63*
A reserve	1.01 ± 0.12	1.02 ± 0.20	0.99 ± 0.13	1.15 ± 0.44*
β reserve	1.44 ± 0.40	1.65 ± 0.85	1.29 ± 0.34	1.71 ± 0.83*
A × β reserve	1.42 ± 0.44	1.74 ± 0.73*	1.27 ± 0.34	1.87 ± 0.91*

*Compared with no collateral circulation with the same degree of stenosis, $P < 0.05$.

significant differences in β and A × β values of the moderate stenosis group ($P > 0.05$). A × β reserve values of the segments with collateral circulation were markedly higher than those of the segments without collateral circulation, and the difference was statistically significant ($P < 0.05$).

The efficacy of the A, β, and A × β in the diagnosis of CHD

Severe stenosis (>50%) of the coronary artery was used as gold standard. After low-dose dobutamine stress, when using A value to predict CHD, the sensitivity was 73.9%, the specificity was 66.6%, and the area under the curve of the receiver operating curve was 5.205 (Figure 2A); when using β value to predict CHD, the sensitivity was 86.6% and the specificity was 73.9%; the diagnostic threshold was 0.485 by using A value to diagnose the CHD (Figure 2B); when using A × β value to predict CHD, the sensitivity was 90.3% and the specificity was 81.2%; the diagnostic threshold was 2.470 by using A × β value to diagnose the CHD (Figure 2C).

DISCUSSION

Coronary microcirculation plays a very important role in the diagnosis and management of CHD. Detection of perfusion defect can help identify the culprit vessel, evaluate the revascularization, and predict the recovery of LV function and prognosis of patients.[7] RT-MCE is a promising method for noninvasive detection of viable myocardium because of its excellent spatial and temporal resolution, portability, widespread availability, and relatively low cost.[11] In this study, we used the low-dose dobutamine stress RT-MCE and used the QLAB software to quantitatively analyze the MCE images in 65 patients to investigate the clinical value of low-dose dobutamine stress RT-MCE in the diagnosis of CHD.

In our study, we found that the HR, SBP, DBP, and LVEF of patients increased markedly after low-dose dobutamine stress, but no patients had allergic symptoms or any adverse effects, suggesting that low-dose dobutamine can increase myocardial perfusion without severe side effects. These results are consistent with the previous study suggesting that the side effects of dobutamine are negligible in 99% of patients.[16] Dobutamine, with inotropic and vasodilatory properties, can increase the survival myocardial blood supply and improve local ventricular wall motion and has a potential benefit of increasing oxygen delivery (DO_2) or directly improving tissue perfusion.[17,18] Additionally, dobutamine medicates its inotropic action by simulating β_1 and β_2 receptors and increasing intracellular calcium concentration,

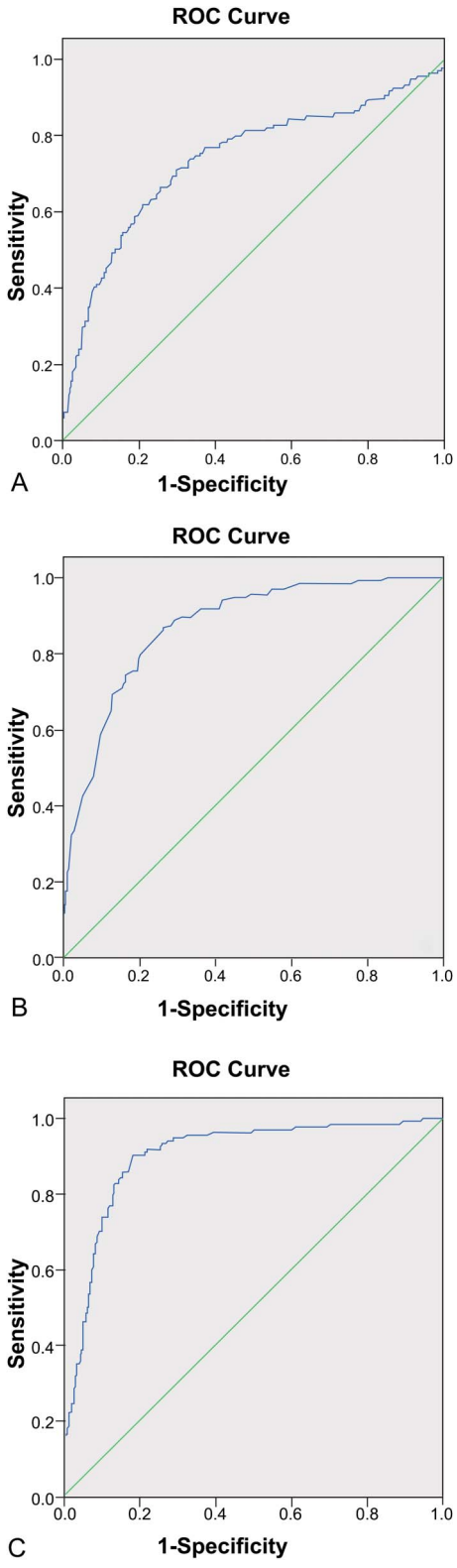

FIGURE 2. Receiver operating curve of A, β, A × β under low-dose dobutamine stress in the diagnosis of CHD; (A) A value, (B) β value, and (C) A × β value.

and low-dose dobutamine has no effect on the stimulation of vascular α_1-receptors, and thereby causes no increase (or could even cause a small decrease) in peripheral vascular resistance.[19] RT-MCE is used for evaluating tissue perfusion and myocardial viability and allows the simultaneous evaluation of global and local myocardial structure, perfusion, and motion, which provides the basis for predicting prognosis of CHD and further clinical decision making.[20] Tsutsui et al[21] reported that dobutamine stress RT-MCE seems to be a feasible and safe tool for evaluating patients with known or suspected CAD. In our study, no statistical significance was observed in the diagnosis of CHD between MCE and CAG, suggesting that although CAG remains the gold standard for the diagnosis of obstructive CAD, MCE is at least as effective in CHD diagnosis.[22]

Our study also showed that as the degree of coronary artery stenosis increased, the values and reserve values of A, β, and A × β were significantly decreased. A is the maximum intensity at the plateau and β is the rate constant that represents the rise rate of acoustic intensity (and thus the microbubble velocity). Clinically, A, β, and A × β indicate myocardial blood volume, MBF mean velocity, and MBF, respectively.[23] The presence of plaques can produce flow-limiting stenosis, or thrombi that interrupt blood flow, and then MBF is lowered, leading to decreased A, β, and A × β values.[24] However, there were no significant difference in A values among the 4 groups in the basal state, whereas significant differences existed in values of A, β, and A × β after low-dose dobutamine stress, suggesting β and A × β might be better parameters for evaluation of perfusion reserve compared with A. The possible reason is that severe coronary stenosis sometimes simulates normal myocardial perfusion in chronic CHD patients. In chronic ischemic patients, the metabolic products that accumulate at the lesion dilate the vessel as chronic compensation. Therefore, the myocardium perfusion at rest is normal.[7] In such instances, low-dose dobutamine stress can detect the areas with impaired perfusion reserve, because the dobutamine directly dilates the coronary artery and improves the coronary flow velocity.[14] In the same segments, the A, β, and A × β values were significantly higher under low-dose dobutamine stress than those in the basal state. The increase of A, β, and A × β values may be because of the fact that these indices reflected the dobutamine-induced increase in coronary artery blood flow. The β and A × β values and their reserve values in severe coronary stenosis with collateral circulation were significantly higher than those in severe coronary stenosis without collateral circulation under low-dose dobutamine stress. This result was supported by the characteristics of collateral circulation, which is an alternative source of blood supply to myocardium.[25]

There are some limitations in this study. First, only a small number of patients volunteered, which limits the impact of the study. Second, image quality of some segments, particularly the anterior and lateral walls, was not acceptable in the end-diastolic phase and not all LV segments of the 65 patients were enrolled. Finally, infusion of myocardium is associated with the coronary artery and the collateral circulation; therefore, it is difficult to differentiate by MCE or CAG.

In conclusion, low-dose dobutamine stress may represent a significant advancement in the diagnosis of CHD without adverse effects involved. Interestingly, our study also revealed that dobutamine stress RT-MCE could provide a basis for predicting prognosis and further treatment of CHD, and dobutamine may be served as a potential and prospective drug therapy for heart diseases. Further studies are essential to validate our findings and confirm the safety and efficiency of low-dose dobutamine stress RT-MCE in the diagnosis of CHD.

ACKNOWLEDGMENTS

The authors acknowledge the reviewers for their valuable advices on this article.

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