Original Article
Early alterations of ischemic myocardial function assessed by velocity vector imaging

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Abstract: Incipient myocardial dysfunction associated with atherosclerosis was observed much earlier than anticipated. We sought to detect what extent of coronary stenosis would lead to regional dysfunctions. Echocardiographic images were obtained in velocity vector imaging (VVI) condition for 40 volunteers and 138 patients with extent stenosis of left anterior descending artery (LAD). Regional functions of middle anterior segments in the left ventricles were evaluated by left ventricular ejection fraction (LVEF), segmental systolic (SRs), early (SRe) and late (SRa) diastolic strain rate, and systolic strain (ε). In contrast to LVEF which displayed a decrease trend with $\geq 75\%$ LAD stenosis, segmental SRe and the ratio of SRe to SRa showed significant reduction since with LAD stenosis < 50%, while ε and SRs decreased with $\geq 50\%$ LAD stenosis ($P < 0.05$). As conclusions, incipient myocardial dysfunction began with < 50% coronary stenosis, mainly manifested with impaired relaxation.

Keywords: Myocardium ischemia, ventricular function, left, echocardiography, velocity vector imaging

Introduction

Atherosclerosis is the main etiologic determinant of the ischemic heart disease and heart failure in the industrialized world. In contrast to traditional views (i.e. ventricular dysfunction with severe coronary stenosis), accumulating evidences indicated that the incipient alterations of myocardial function associated with atherosclerosis may occur much earlier than previously anticipated in recent years [1-3]. For example, a sub study of the Multi-Ethnic Study of Atherosclerosis reported that increased carotid intima-media thickness was related to regional myocardial dysfunction in a population which was free of clinical heart disease [1]. Deng *et al.* found that obesity, a well-known risk factor of cardiovascular disease, was associated with subclinical left ventricular dysfunction [2]. To find out what extent of stenosis in the related coronary artery would induce the initial regional myocardial dysfunction will be essential for the development of more efficient preventive and interventional modalities for ischemic heart disease.

Velocity vector imaging (VVI) is a 2-dimensional echocardiography method based on feature tracking-incorporing speckle and endocardial border tracking, which allows to quantitatively analyze myocardial mechanics and to characterize regional myocardial deformation with endocardial strain and strain rate. Assessments of myocardial regional function derived by VVI have been validated in animal and human studies and offer more advantages in angle independence than the Doppler-derived approach [4-8].

In the present study, we evaluated myocardial dysfunctions of a given left ventricular segment with different severity of stenosis in the related coronary arteries using VVI technique, intending to figure out what extent of coronary stenosis would initiate myocardial dysfunction.

Methods

Study population

This study population was derived from a consecutive series of patients who underwent cor-

Table 1. Baseline and clinical characteristics of the study population

Clinical status	Participants with stenotic LAD				
	Normal	< 50%	50%-74%	75%-99%	100%
Age (years)	52 ± 5	53 ± 6	54 ± 5	55 ± 5	56 ± 3
Male sex	60%	58%	69%	63%	75%
Obesity	48%	56%	63%	55%	66%
Hypertension	35%	39%	44%	45%	24%
Dyslipidemia	45%	53%	56%	55%	59%
Diabetes	23%	25%	31%	24%	34%
Smoking	48%	50%	59%	58%	62%
SBP (mmHg)	135 ± 15	135 ± 15	136 ± 15	138 ± 15	139 ± 16
DBP (mmHg)	86 ± 8	90 ± 8	89 ± 9	89 ± 9	90 ± 8
TC (mmol/L)	4.92 ± 1.60	4.77 ± 0.46	4.25 ± 0.94	4.92 ± 0.48	4.87 ± 0.65
TG (mmol/L)	1.66 ± 0.36	1.69 ± 0.42	1.70 ± 0.37	1.75 ± 0.43	1.76 ± 0.48
LDL-C (mmol/L)	2.65 ± 0.27	2.77 ± 0.45	2.75 ± 0.49	2.77 ± 0.51	2.75 ± 0.38
HDL-C (mmol/L)	1.47 ± 0.46	1.43 ± 0.48	1.34 ± 0.20	1.31 ± 0.52	1.42 ± 0.47
Fasting blood Glucose (mmol/L)	6.00 ± 1.36	6.17 ± 1.44	6.29 ± 1.65	6.22 ± 1.37	6.41 ± 1.53

Data are mean ± SEM or number [%] of participants. Obesity is defined as male with waistline ≥ 90 cm and female ≥ 80 cm. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg under a quiescent condition, or controlled by specific anti-hypertension drugs. Participants were diagnosed with dyslipidemia when serum lipid levels meet one or more of the following criteria: (1) total cholesterol (TC) ≥ 5.7 mmol/L; (2) triglyceride ≥ 1.7 mmol/L; (3) low-density lipoprotein cholesterol (LDL-C) ≥ 3.64 mmol/L; (4) high-density lipoprotein cholesterol (HDL-C) ≤ 1.04 mmol/L. The presence of diabetes mellitus was defined as fasting plasma glucose ≥ 7.0 mmol/L and/or 2-hr post-glucose load ≥ 11.1 mmol/L or use of specific antidiabetic drug therapy. LAD, the left anterior descending artery.

onary angiography for the diagnosis of coronary artery disease (CAD) in the catheterization lab of our hospital. Exclusion criteria were acute or old myocardial infarction, valvular cardiac disease, cardiomyopathy, severe heart failure (New York Heart Association class IV) and arrhythmia.

Three experienced physicians performed coronary angiography. The distributions of coronary arteries independently, and disagreements were resolved by consensus.

All patients were divided into four groups according to the stenosis severity of the left anterior descending artery (LAD), i.e. < 50%, 50%-74%, 75%-99% and 100%. Moreover, age and sex-matched volunteers with normal coronary arteries were involved as normal controls. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all participants.

Echocardiogram acquisition

Echocardiography was performed within 24 hours before coronary angiography with the patient lying in a lateral decubitus position. A commercially available ultrasound system

(Sequoia 512, Siemens, and Mountain View, CA, USA) and a 2.0-4.0 MHz transducer were involved. High-quality 2-dimensional images were acquired from the standard parasternal and apical (4-chamber, 2-chamber and long-axis) views at a frame rate of 90 to 100 frames per second. The images were stored digitally for subsequent offline analysis.

Echocardiography analysis

Left ventricular ejection fraction (LVEF) for each participant was calculated by online software automatically. 2-dimensional Images were further analyzed offline by the use of VVI analysis software (Research Arena program, TomTec Imaging Systems, Munich, Germany). Middle anterior segment in the left ventricle was determined according to the 16-segment left-ventricle model recommended by the American Society of Echocardiography [9]. By a point-and-click approach, we placed some points on the images along the left-ventricular subendocardium at the end of the systolic phase. Segmental systolic, early and late diastolic strain rate (SR), and systolic strain were calculated. Intra-observer and inter-observer coefficients of variation for the measurements of
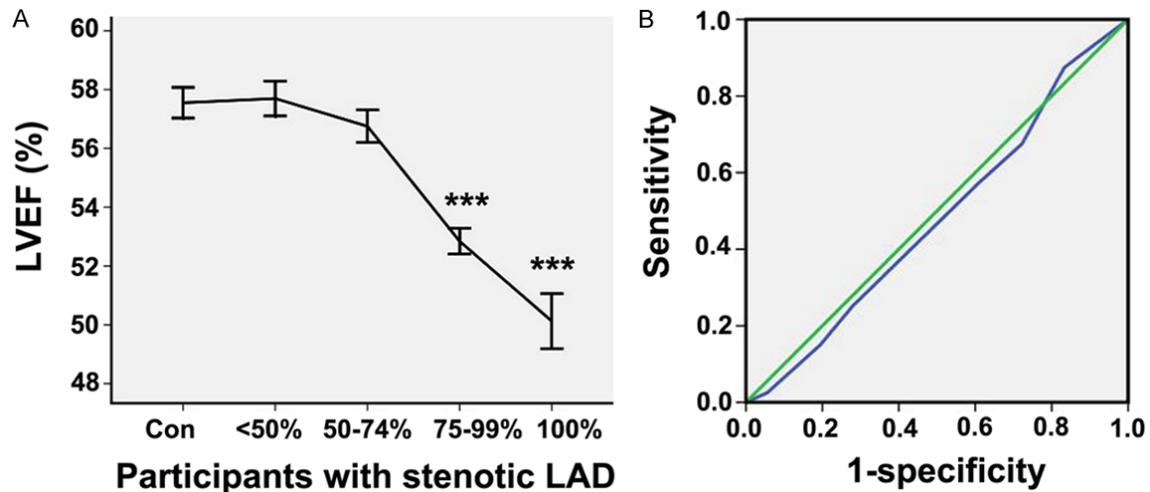
Figure 1. LVEF for the evaluation of myocardial dysfunction. A. Alterations of LVEF with increased stenosis in coronary arteries. ***$P < 0.001$, vs. controls. B. Receiver operating characteristic (ROC) curve of LVEF for the diagnostic value of early myocardial dysfunction. LVEF, left ventricular ejection fraction.

strain and strain rate parameters were analyzed.

Statistical analysis

Data were analyzed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA), and the significance level was set at $P < 0.05$. Quantitative values were expressed as mean ± standard error of the mean (SEM). One-way ANOVA with least significant difference test when equal variances were assumed or with Dunnett test when equal variances were not assumed were carried out in the comparison among multiple groups. Receiver operating characteristic curve analysis (ROC) was performed to identify the sensitivity and specificity of LVEF, strain and strain rate parameters for assessing early myocardial dysfunction.

Results

Clinical characteristics

We enrolled 40 volunteers with normal coronary artery (mean age 52 ± 5 years, 60% males) and 138 patients (mean age 55 ± 5 years, 66% males) including 36 with < 50% LAD stenosis, 32 with 50%-74% LAD stenosis, 38 with 75%-99% LAD stenosis and 32 with a totally occluded LAD. The clinical characteristics and CAD risk factors for all participants were recorded. As shown in **Table 1**, the five groups did not differ in age, sex, obesity, smoking, or clinical risk

factors, including blood pressure, lipid levels or fasting blood glucose.

Left ventricular ejection fraction

We first performed the comparison of LVEF, a traditional and classic parameter of left ventricular function, among groups. As shown in **Figure 1A**, Participants with < 50% and 50%-74% LAD stenosis displayed similar LVEF with the controls. This parameter was significantly decreased in patients with ≥ 75% LAD stenosis ($P < 0.05$).

Regional function of middle anterior segments in left ventricle

We further carried out the comparison of strain and strain rate parameters in the middle anterior segments with different LAD stenosis. As compared with segments with normal LAD, segments with < 50% LAD stenosis displayed decreased early diastolic SR (2.08 ± 0.04 *vs.* 2.56 ± 0.06, *vs.* control, $P < 0.001$) and the ratio of early to late diastolic SR (1.20 ± 0.04 *vs.* 1.51 ± 0.05, *vs.* control, $P < 0.001$), which indicated depressed myocardial relaxation. For segments with 50%-74% LAD stenosis, systolic strain (-22.10 ± 0.68 *vs.* -26.06 ± 0.49, *vs.* control, $P < 0.001$) and systolic SR (-1.92 ± 0.06 *vs.* -2.31 ± 0.08, *vs.* control, $P < 0.01$) were also significantly decreased, indicating impaired systolic function. Segments with 75%-99% LAD stenosis displayed further decrease in systolic
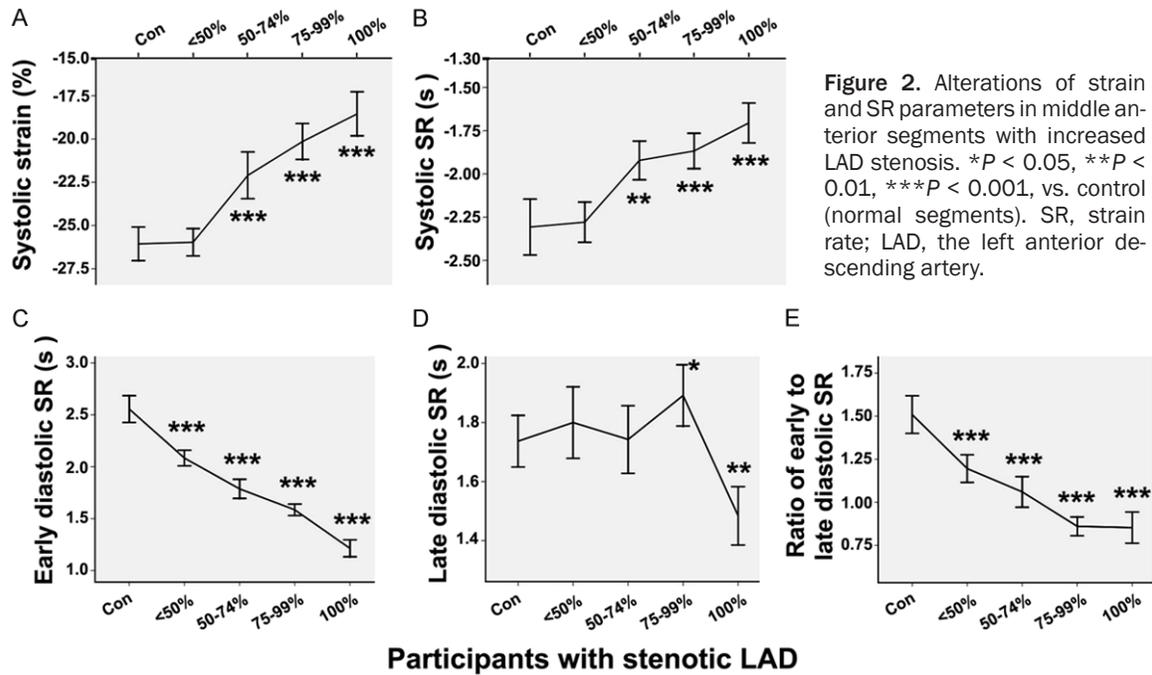
Figure 2. Alterations of strain and SR parameters in middle anterior segments with increased LAD stenosis. *P < 0.05, **P < 0.01, ***P < 0.001, vs. control (normal segments). SR, strain rate; LAD, the left anterior descending artery.

Participants with stenotic LAD

Table 2. Diagnostic value of LVEF, strain and SR parameters for early myocardial dysfunction

Variable	Cutoff point	Sensitivity	Specificity	AUC
LVEF	56.5%	57.5%	38.9%	0.479
Systolic strain	-25.46	55%	58.3%	0.525
Systolic SR	-2.20	50%	66.7%	0.476
Early diastolic SR	2.20	85%	75%	0.873
Late diastolic SR	1.72	50%	60%	0.540
Ratio of early to late diastolic SR	1.31	80%	75%	0.783

LVEF, left ventricular ejection fraction; SR, strain rate; AUR, area under receiver operating characteristic (ROC) curve.

strain, systolic SR, early diastolic SR and the ratio of early to late diastolic SR, and also increased late diastolic SR (1.74 ± 0.04 *vs.* 1.89 ± 0.05, *vs.* control, *P* < 0.05). As expected, segments with total occluded LAD exhibited worst regional function. The alterations for each strain and SR parameter in middle anterior segments with different severity of LAD stenosis were summarized in **Figure 2A-E**.

Intra- and inter-observer variation

The intra-observer variation coefficients for systolic strain, systolic SR, early diastolic SR and late diastolic SR were 7.2 ± 2.1%, 6.2 ± 1.6%, 5.2 ± 1.8%, 6.8 ± 1.2%, respectively. The inter-observation coefficients for the above

parameters were 6.8 ± 1.8%, 6.7 ± 1.8%, 6.1% ± 2.0%, 7.0 ± 1.5%, respectively. There was no significant difference between intra- or inter-observer measurements of the above parameters.

Diagnostic use of the strain and SR parameters

We performed ROC analysis for the sensitivity and specificity of LVEF, strain and SR parameters for evaluating the early myocardial dysfunction. Operational cutoff values with corresponding predictive characteristics were shown in **Table 2**. ROC analysis revealed early diastolic SR and the ratio of early to late diastolic SR showed high sensitivity (85% and 80%, respectively) and specificity (both 75%) at a cut-off value of 2.20 and 1.31, respectively, for the detection of early myocardial dysfunction (**Figure 3A** and **3B**). In contrast, LVEF displayed poor ability in the evaluation of incipient myocardial dysfunction (**Figure 1B**).

Discussion

Few studies have unclosed the relationship of myocardial dysfunction and the coronary artery conditions, though the results suggested much
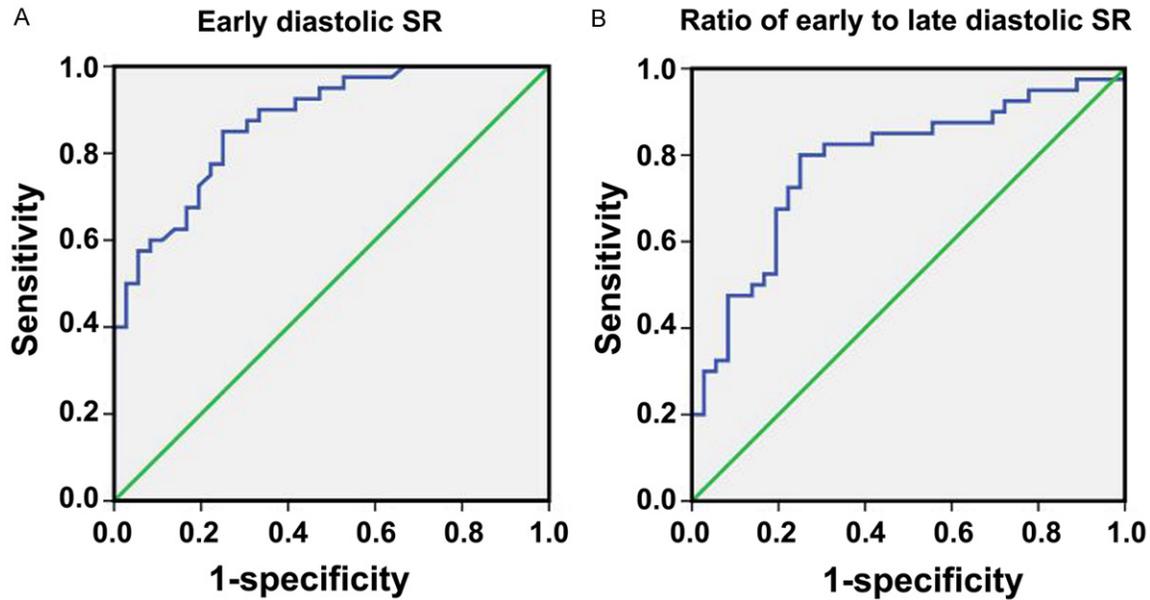
Figure 3. ROC curve of early diastolic SR (A) and the ratio of early to late diastolic SR (B) to detect early myocardial dysfunction. SR, strain rate; ROC, receiver operating characteristic curve.

earlier incipient myocardial dysfunction than anticipated. In this study, by use of VVI technique, we assessed myocardial functional alterations in a given segment, i.e. the middle anterior segment in the left ventricle, with a detailed boundary of the related coronary (LAD) stenosis involving normal, < 50%, 50%-74%, 75%-99% and complete occlusion (100%). We found that the incipient myocardial dysfunction happened at LAD stenosis < 50%, mainly manifested with the impaired myocardial relaxation. Myocardial contractile dysfunction followed with increased LAD stenosis. Furthermore, we demonstrated that strain and SR parameters based on VVI technique showed better efficiency for detection of early myocardial dysfunction than classic LVEF parameter.

There is a well known perfusion-contractility match in cardiac tissue, i.e., the contractility of the tissue is proportional to the perfusion rate of the tissue, even in normal cardiac tissue. This could partially explain the altered myocardial function even in the segments with mild coronary setenosis. Experimental studies and clinical observations have demonstrated that ischemia affects the LV diastolic function earlier than the systolic function [10-12]. Pouleur H *et al.* calculated LV regional peak filling rate in the CAD patients and determined that large areas with impaired distensibility were fre-

quently present in patients with angina pectoris even in the absence of clinical signs of ischemia and of an earlier myocardial infarction [11]. Diastolic function is modified to a variable extent, with a variable contribution from altered myocardial relaxation, increased muscle stiffness, and ventricular interaction and chamber passive dilatation. The impairment of myocardial relaxation plays the central role, which has been quantified in multiple clinical and experimental studies, and the ventricular passive dilation serves as a compensatory for the impaired relaxation. Consist with these findings; our results revealed that early diastolic SR, a myocardial relaxation-related parameter, decreased first with mild stenosis in LAD. Contractile functional impairments followed with moderate LAD stenosis.

Strain is a measure of change in shape and therefore represents deformation. Strain rate is the temporal derivative of the strain, and indicates the intrinsic rate of the deformation of a myocardial segment. Strain and strain rate are relatively independent of overall cardiac movement and tethering of the neighboring segments, and therefore are basic descriptors of both the nature and the function of cardiac tissue and may better reflect the intrinsic myocardial contractility and relaxation [13-15]. Experimental studies have demonstrated the

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superiority of deformation indices (strain and strain rate) over "pump indices" such as left ventricular ejection fraction (LVEF) and fractional shortening, and also motion indices such as myocardial velocity and displacement [16, 17]. Ultrasonic strain and strain rate measurement were first introduced on the basis of Doppler tissue imaging, which is a 1-dimensional method with angle-dependence. Strain and SR parameters based on echocardiography offer advantages over magnetic resonance imaging-derived approach: satisfactory sensitivity to detect myocardial dysfunction conveniently, economically and non-invasively. Velocity vector imaging (VVI) is a 2-dimentional image-based, angle-independent approach of measuring myocardial velocity and deformation based on speckle tracking. Several studies have shown that this technique can characterize myocardial deformation (strain) and the rate of deformation (SR) [18-20]. Consist with these findings, our results demonstrated that strain and SR based on VVI technique, especially early diastolic SR and the ratio of early to late diastolic SR parameters, could detect early myocardial dysfunction with high sensitivity and specificity than the classic LVEF.

In summary, myocardial incipient dysfunction, mainly manifested with impaired relaxation, began with mild stenosis (< 50%) in the related coronary artery. Strain and SR parameters based on VVI technique, especially early diastolic SR and the ratio of early to late diastolic SR, can be efficient in detecting the early alterations of myocardial dysfunction.

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Disclosure of conflict of interest

None.

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