Detection of Diastolic Abnormality by Dyssynchrony Imaging — Correlation With Coronary Artery Disease in Patients Presenting With Visibly Normal Wall Motion —

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Background Post-systolic shortening (PSS) is a sensitive indicator of myocardial ischemia.

Methods and Results We have developed a tissue Doppler imaging technique that portrays PSS, and whether PSS correlates with coronary artery disease (CAD) was investigated in 186 patients presenting with chest pain and normal echocardiograms. Delays of the displacement peaks from end-systole were calculated in the apical views and displayed from green (0ms) to red (≥ 100 ms): detection of diastolic abnormality by dyssynchrony imaging (DADI). CAD was judged positive by DADI when the left ventricular segments were color-coded red. Patients subsequently underwent thallium-201 myocardial perfusion single-photon emission computed tomography (n=150), coronary angiography (CAG, n=74), or both (n=37). CAD(–) was defined as negative scintigraphy test and/or no significant coronary artery stenosis by CAG. In 43 patients (23%), CAD(+) was confirmed by CAG as $>75\%$ diameter stenosis. DADI predicted CAD with sensitivity of 60%, specificity of 75%, predictive accuracy of 72%, positive predictive value of 42%, and negative predictive value of 86%. Among 74 patients who underwent CAG, sensitivity was best for the left anterior descending artery.

Conclusions DADI detected the regional diastolic abnormality, which correlated with the presence of CAD in patients presenting with visibly normal wall motion. (Circ J 2009; 73: 125–131)

Key Words: Coronary artery disease; Echocardiography; Tissue Doppler imaging

Chest pain still remains a challenge for clinicians. The possibility of coronary artery disease (CAD) cannot be excluded by normal electrocardiograms or normal echocardiograms at rest. Exercise electrocardiography has found wide acceptance for CAD identification because of its low cost. However, the sensitivity and specificity range from 65% to 80%,¹ and a substantial number of patients are unable to exercise because of comorbidities. Dobutamine stress echocardiography may be a solution, but its interpretation is largely operator dependent.² It would be desirable if the detection of CAD could be done objectively without any provocation tests.

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Post-systolic shortening (PSS) is a delayed ejection motion of the myocardium occurring after aortic valve closure during the generally prolonged isovolumic relaxation time. Both clinical^{3–5} and animal studies^{6–10} have demonstrated that PSS is related to myocardial ischemia.

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We have previously demonstrated that the presence of a positive myocardial velocity during the isovolumic relaxation phase (V_{IR}) detected by spectral tissue Doppler imaging (TDI), which corresponds to PSS, correlates with the presence of CAD among patients presenting with visibly normal left ventricular (LV) contraction.¹¹

Color-coded TDI has facilitated quantitative assessment of ventricular wall motion,^{12–18} so it would be helpful if the presence of PSS was made readily visible by this technique without the need for mapping. In the present study, we aimed to develop a color-coded TDI technique that detects PSS on 2-dimensional (D) echocardiograms: detection of diastolic abnormality by dyssynchrony imaging (DADI). We also prospectively investigated the correlation of the diastolic abnormality detected by DADI with the presence of CAD among patients complaining of chest pain and presenting with visibly normal LV wall motion.

Methods

Patients

Between November 2005 and September 2006, we enrolled 195 consecutive patients complaining of chest pain and presenting with normal LV wall motion evaluated by standard echocardiography in the cardiology outpatient clinic. Consent was given to undergo thallium-201 myocardial perfusion single-photon emission computed tomography (SPECT) and/or coronary angiography (CAG), in addition to echocardiography including TDI. Patients presenting with abnormal echocardiograms, such as wall motion abnormalities, significant valvular disease, dilated or restrictive

cardiomyopathies, LV hypertrophy (the interventricular septum or the posterior wall thickness ≥ 12 mm), pulmonary hypertension (tricuspid valve regurgitation velocity ≥ 2.5 m/s), including a history of prior myocardial infarction, previous coronary angioplasty or bypass grafting, atrial fibrillation or flutter, pacemaker implantation, left bundle branch block, abnormal echocardiograms, and congestive heart failure, were excluded. Nine patients were further excluded from the analysis because of inadequate ultrasound images.

The remaining 186 patients (88 women, mean age 63 years, age range 17–90 years) underwent spectral and color-coded TDI at rest, in addition to standard echocardiography (Fig 1). Subsequently, patients underwent thallium-201

myocardial perfusion SPECT (n=150) and/or CAG (n=74). The study protocol was approved by the Ethics Committee of Kansai Rosai Hospital. All patients gave written informed consent.

Echocardiography and TDI

All patients underwent routine echocardiography, spectral TDI, and color-coded TDI using a cardiac ultrasound diagnostic apparatus (Aplio SSA-770A, Toshiba, Tokyo, Japan) with a 3.6-MHz sector transducer. Echocardiograms were obtained in the left lateral position at end expiration. No stress was placed on the subjects. LV end-diastolic and end-systolic dimensions were measured on 2-D echocardiography-guided M-mode echocardiograms.¹⁹ TDI was performed in the apical 4- and 2-chamber views.

Detection of Diastolic Abnormality by Dyssynchrony Imaging (DADI)

Displacement was calculated from the color-coded TDI-derived velocity data using online software (TDI-Q, Toshiba)^{20,21} In brief, myocardial displacement along the ultrasound beam direction was calculated by temporal integration of the velocity at each myocardial point on the beam. Importantly, this software is capable of Doppler tissue tracking along the beam direction, thereby enabling accurate measurement of the displacement. The accuracy of displacement measured with this system was validated by an in vitro study.²¹ End-systole was estimated from the Doppler velocity when the sum of the velocities obtained from the entire image reached the velocity closest to zero. Subsequently, a time window was set from end-systole in such a way that when the peak of the displacement occurred at the

Fig 1. Block diagram of the study protocol. MOMI, mapping of myocardial velocity imaging; DADI, diastolic abnormality by dyssynchrony imaging; SPECT, single-photon emission computed tomography; CAD, coronary artery disease.

Fig 2. Principles of detection of diastolic abnormality by dyssynchrony imaging (DADI). (A) Displacement curves calculated from the velocity measured from the interventricular septum (yellow line) and from the lateral wall (pink line) in a patient with coronary artery disease. (B) The peak of the pink displacement curve is seen at the time of end-systole, whereas the peak of the yellow curve is delayed from end-systole. DADI portrays the regional delay in the peak of displacement on 2-dimensional echocardiograms by detecting the difference in timing within a specified time interval from end-systole. The color coding ranges from green (earliest) to red (latest) within the specified interval.

Fig 3. Regional wall segments per coronary artery perfusion used for the detection of coronary artery disease (CAD) by detection of diastolic abnormality by dyssynchrony imaging (DADI). CAD was judged positive by DADI when part of the left ventricle was color-coded red (regional delay in the displacement peak ≥ 100 ms) in accordance with the anatomy of the coronary artery branches. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 1 Characteristics of Patients With and Without CAD

	CAD (+) (n=43)	CAD (-) (n=143)	P value
Female	12 (28%)	76 (53%)	<0.01
Age (years)	65±9	63±12	NS
Coronary risk factors			
Hypertension	36 (84%)	83 (58%)	<0.01
Dyslipidemia	33 (77%)	62 (43%)	<0.01
Hyperuricemia	8 (19%)	24 (17%)	NS
Diabetes mellitus	17 (40%)	33 (23%)	<0.05
Current smoking	16 (37%)	31 (22%)	<0.05
SBP (mmHg)	138±18	138±16	NS
DBP (mmHg)	75±12	77±10	NS
Heart rate (beats/min)	65±9	68±12	NS
Echocardiographic data			
LVDd (mm)	48±4	45±4	<0.01
LVDs (mm)	29±3	28±4	NS
FS (%)	40±4	40±5	NS
IVSth (mm)	10±1	9±1	<0.01
LVPWth (mm)	10±1	9±1	<0.01

CAD, coronary artery disease; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVDd, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; FS, fractional shortening of the left ventricular short-axis diameter; IVSth, wall thickness of the interventricular septum; LVPWth, wall thickness of the left ventricular posterior wall.

timing of the estimated end-systole, it was color-coded green, and that when the peak of the displacement was delayed from the estimated end-systole by more than 100 ms, it was color-coded red. In this way, DADI color-coded a delay in the peak of displacement occurring in the whole LV and displayed the anatomical distribution of the delay as a color-coded parametric image on the 2-D echocardiogram (**Fig 2**). Thus, DADI portrayed regional PSS on 2-D echocardiograms. CAD was judged positive by DADI when part of the LV was color-coded red (regional delay in the displacement peak ≥ 100 ms) in accordance with the anatomy of the coronary artery branches (**Fig 3**). The initial time window, which started from the estimated end-systole, was set to 100 ms based on our previous data using spectral TDI.¹¹ Effects of the time window were evaluated in this study at 50, 100, and 150 ms.

Intraobserver agreement of DADI was assessed by a single investigator (T.O.) in a randomly selected 50 patients on 2 separate occasions. Interobserver agreement was also assessed in the same patient population by 2 independent observers (T.O. and S.O.).

Mapping of Myocardial Velocity Imaging (MOMI)

Spectral TDI measurements were also done at the annular and mid-LV levels in the apical 4- and 2-chamber views (8 points in each patient) as previously described.¹⁰ Positive V_{IR} was defined as an upward spike between the end of the systolic ejection phase and the onset of the early diastolic relaxation phase that lasted longer than 100 ms. We determined whether positive V_{IR} was present on the spectral TDI tracings. CAD was considered present if positive V_{IR} was present in 1 or more of the 8 points in each subject.

Thallium-201 Myocardial Perfusion SPECT

Within 1 week of TDI, 150 patients (81%) underwent thallium-201 SPECT with bicycle exercise testing. A dose of 3.0 mCi of thallium-201 was injected intravenously at near-peak exercise, and the exercise was continued for another minute. The patients were scanned with a dual-detector SPECT system equipped with a low-energy, parallel-hole, all-purpose collimator (Optima, GE Medical System, Wakeshaw, WI, USA). The thallium-201 stress

images were obtained within 6 min of thallium injection. Redistribution imaging was performed 4 h later using the same acquisition measurements.²² Identification of the redistribution phenomenon was judged as positive for CAD by an independent physician who was unaware of the results of MOMI and DADI.

CAG

Within 3 weeks of TDI, 74 patients (40%) underwent CAG with multiple views. CAG was interpreted by consensus opinion of 2 physicians who were unaware of the results of SPECT, MOMI or DADI. Coronary narrowing in 1 or more major vessels was graded by visual analysis according to the lumen diameter involved: $\leq 25\%$, 26–50%, 51–75%, 76–90%, 91–99%, or 100%. Critical coronary artery stenosis was defined as $>75\%$ diameter stenosis. CAD was diagnosed when patients had a critical coronary artery stenosis on CAG. Hence, in this study the presence of CAD was confirmed in all patients by CAG (**Fig 1**).

Statistical Analysis

Numerical variables are expressed as mean $\pm$ SD. Unpaired t-test was used for the comparison of patients with and without CAD. We considered results were significant when $P < 0.05$. The optimal cut-off values of the duration of positive V_{IR} and of the time window from end-systole in DADI for discriminating normal from patients with CAD were determined by receiver-operating characteristic curves.

Results

Patient Characteristics

CAD was finally diagnosed by CAG in 43 patients (23%) among the 186 enrolled in this prospective study; 113 patients (61%) were diagnosed as normal by thallium-201 myocardial perfusion SPECT and 30 (16%) by CAG. No significant differences were found between the patients with and without CAD regarding age, hyperuricemia, blood pressure, heart rate, LV diameter at end-systole, and fractional shortening. The proportion of men, hypertension, dyslipidemia, diabetes mellitus, current smoking, LV diameter at end-diastole, wall thickness of the interventricular

Fig 4. Representative images of detection of diastolic abnormality by dyssynchrony imaging (DADI) in the 4-chamber view obtained from a normal subject (A), patient with a 1-vessel disease of the left anterior descending artery (LAD) (B), 1-vessel disease of the left circumflex artery (LCX) (C), 1-vessel disease of the right coronary artery (RCA) (D), and a patient with 2-vessel disease of the LAD and RCA (E). (A) In the normal subject the entire left ventricle is displayed green by DADI. (B) In contrast, the apical septum is color-coded red when the LAD is diseased. (C) The lateral wall, which is supplied by LCX, is color-coded red when the LCX has a 90% diameter stenosis. (D) Only the basal septum is color-coded red when the RCA is diseased. (E) The entire interventricular septum is color-coded red from the apex to the base in 2-vessel disease of the LCX and RCA.

Table 2 Correlations of MOMI and DADI With CAD

Cut-off levels	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
<i>MOMI</i>					
50	85	33	45	27	88
100	66	54	56	30	84
150	7	97	77	43	78
<i>DADI</i>					
50	77	46	53	30	87
100	60	75	72	42	86
150	28	89	75	43	80

MOMI, mapping of myocardial velocity imaging; *DADI*, detection of diastolic abnormality by dyssynchrony imaging; *PPV*, positive predictive value; *NPV*, negative predictive value; *CAD*, coronary artery disease.

septum or LV posterior wall were greater in patients with CAD than in those without CAD (Table 1).

Detection of CAD by DADI

Fig 4 shows representative DADI images from a normal subject and from patients with a variety of CAD: 1-vessel disease involving the left anterior descending artery (LAD), 1-vessel disease of the left circumflex artery (LCX), 1-vessel disease of the right coronary artery (RCA), and 2-vessel disease involving the RCA and LAD. The distribution of PSS, which reflected the presence of coronary artery stenosis in accordance with the coronary perfusion area, was successfully demonstrated by DADI in these images.

Comparison Between MOMI and DADI

The overall sensitivity, specificity, predictive accuracy, positive predictive value, and negative predictive value for detecting CAD by MOMI and DADI are shown in Table 2. Receiver-operating characteristic analysis indicated that the duration of positive V_{IR} of 100 ms was the best cut-off value for MOMI to discriminate normal from CAD; the time window of 100 ms was the best cut-off value for DADI. DADI predicted the presence of CAD with sensitivity of 60%, specificity of 75%, predictive accuracy of 72%, positive predictive value of 42%, and negative predictive value of 86% when a time window of 100 ms was used as the cut-off value. MOMI yielded sensitivity of 66%, specificity of 54%, predictive accuracy of 56%, positive predictive value

Fig 5. Sensitivity, specificity, predictive accuracy, positive and negative predictive values of detection of diastolic abnormality by dyssynchrony imaging for detecting stenoses of the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA).

of 30%, and negative predictive value of 84% for the diagnosis of CAD. Receiver-operating characteristic analysis demonstrated the area under the curve was 0.61 for MOMI ($P < 0.05$) and 0.68 for DADI ($P < 0.01$). Intra- and interobserver agreements of DADI were 98% and 94%, respectively.

Detection of CAD by DADI per Major Coronary Artery Branch

The diagnostic power of DADI for the 3 major coronary artery branches, LAD, LCX, and RCA, was assessed in a sub-analysis of 74 patients who underwent CAG (**Fig 5**). The sensitivity was the best for the LAD among the arteries, specificity ranged from 73% for the RCA to 94% for the LCX, predictive accuracy ranged from 65% for the RCA to 77% for the LCX, and negative predictive value was 82% for the LAD, 78% for the LCX, and 81% for the RCA.

Discussion

Using tissue Doppler-derived displacement timing analysis, we developed a novel modality that noninvasively displays PSS: detection of diastolic abnormality by dyssynchrony imaging (DADI). We also demonstrated in this prospective study that PSS detected by DADI reflects the presence of CAD in patients presenting with visually normal LV wall motion, whose chief complaint is chest pain. This technique does not require provocation, such as exercise or dobutamine.

The sensitivity of DADI for identifying patients with CAD was modest. It was the best in those who had lesions in the LAD, and was lower for the LCX and RCA. Nonetheless, specificity (range 73–94%), predictive accuracy (65–77%) and negative predictive value (78–82%) all ranged around 70–80% regardless of the coronary artery branches (**Fig 5**). It is important to note that the sensitivity and specificity of DADI for detecting CAD were comparable to those of exercise electrocardiography,¹ despite the nonprovocative nature of DADI.

PSS is a delayed ejection motion of the myocardium

during the prolonged isovolumic relaxation time.^{3–10} It is frequently observed in patients with CAD presenting with LV asynergy.^{23–25} Earlier studies have demonstrated the presence of abnormal diastolic function in patients with CAD without evidence of systolic wall motion abnormalities by radionuclide angiography or digitized cineangiography.^{26–28} Kondo et al have also demonstrated that delayed outward LV wall motion in the isovolumic relaxation phase by digital subtraction high-frame-rate echocardiography was indicative of CAD.²⁹ In our experience, a positive myocardial velocity occurring during the isovolumic relaxation phase as detected by the spectral tissue Doppler mapping technique (MOMI) was indicative of critical coronary artery stenosis in patients complaining of chest pain with visibly normal LV contraction.¹¹ Furthermore, increased amplitude of PSS during dobutamine stress echocardiography detected the presence of CAD using tissue Doppler strain rate imaging.³⁰ Those earlier observations are in accordance with our findings that a diastolic abnormality detected at rest by DADI has significant correlation with the presence of CAD in patients presenting with visibly normal LV wall motion.

On the other hand, PSS does occur in approximately one-third of the normal population.³¹ Voigt et al reported that pathologic PSS and physiologic PSS were distinguished by using the cut-off value of 90 ms for the duration.³¹ Our study results demonstrated that the best cut-off value for the delay in the displacement peak was 100 ms for DADI, which was in good agreement with the cut-off value for abnormal PSS using strain rate reported by Voigt et al.³¹

In theory, displacement is inherently affected by tethering (ie, motion from the adjacent myocardium).³² In fact, the base to the apex gradient in displacement is normally present. Using strain or strain rate appears to be more relevant for detecting localized abnormalities such as PSS than using displacement. Surprisingly, however, DADI detected the localization of PSS in the LV. In DADI, the delay of displacement peaks was measured, not from end-diastole, but from end-systole, for a limited duration as short as 100 ms. Because the LV myocardium temporarily shows a

velocity closest to zero at end-systole, DADI can highlight moving tissue from adjacent tissue that is not moving, thereby enabling location of PSS even though displacement is theoretically affected by tethering. Another robust aspect of using displacement rather than strain or strain rate is the reproducibility of the data. Displacement is directly calculated by the integration of Doppler velocity, resulting in much greater signal-to-noise ratio than strain or strain rate. Unlike strain or strain rate, the displacement calculation does not include subtraction or differentiation, both of which increase errors. In addition, neither the apex to base gradient nor the angle dependence of displacement affects the results in DADI, because timing analysis is independent from the amplitude of the data. Finally, Doppler measurement is superior to a 2-D speckle tracking technique in terms of time resolution. Thus, it is suitable for measuring the events lasting less than 100 ms.

MOMI uses a spectral tissue Doppler technique, which can be performed with any commercially available ultrasound machines. On the other hand, MOMI involves a tedious mapping technique, and much fewer sampling points than DADI. DADI has enabled us to visualize the presence of PSS with a few clicks of buttons, and better reflected the presence of CAD than MOMI.

Clinical Implications

Because DADI can be performed without provocation, it is particularly safe and easy to perform in patients with coexisting morbidities, such as peripheral artery disease in the lower limb, orthopedic diseases, or cerebrovascular diseases in the elderly. This simple methodology has a comparable sensitivity and specificity to those of exercise electrocardiography, with a relatively high negative predictive value. Accordingly, it may be used as a noninvasive, nonprovocative diagnostic supplement in place of exercise electrocardiography in patients complaining of chest pain and presenting with normal echocardiograms, with an addition of a few more minutes to routine echocardiography. Future application of DADI to dobutamine or exercise echocardiography may further enhance the diagnostic power of DADI for the detection of CAD.

Study Limitations

First, this study was a single-center study including a relatively small number of patients. Second, 79% of the normal subjects (113 of 143 subjects) were diagnosed as normal by thallium-201 SPECT without CAG, so some may have had CAD. Nonetheless, normal findings in stress SPECT were associated with an average annual hard event rate of merely 0.6% (death or nonfatal myocardial infarction).³³ In other words, CAD included in the normal subset of patients was considered minimal in view of clinical significance. In addition, the sub-analysis that included only those with CAG demonstrated a similar correlation. Third, PSS may also occur in nonischemic conditions such as LV hypertrophy, LV systolic dysfunction, and left bundle branch block.^{34–36} We excluded those showing abnormal echocardiograms, so it is important to note that DADI should not be used for the detection of CAD in those showing abnormal echocardiograms. Nonetheless, this nonprovocative test would still be clinically relevant because many patients suspected of having angina pectoris for the first time demonstrate normal echocardiograms at rest.

In conclusion, we have developed a novel modality by using tissue Doppler derived displacement timing analysis:

detection of diastolic abnormality by dyssynchrony imaging (DADI), which readily portrays the presence of PSS on 2-D echocardiograms. Detection of PSS by DADI showed a significant correlation with the presence of CAD among patients presenting with chest pain and visibly normal wall motion.

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