Role of Transthoracic Doppler-Determined Coronary Flow Reserve in Patients With Chest Pain

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Background The assessment of patients with chest pain is an important step to make a diagnosis and clinical decision. Coronary flow reserve (CFR) can be used for the screening of significant coronary stenosis. However, the feasibility and limitation of CFR in those patients remains unknown.

Methods and Results A total of 100 patients with chest pain were examined. CFR was measured in all 3 major coronary arteries by using transthoracic Doppler echocardiography (TTDE). Coronary angiography was performed 1 to 3 days after TTDE. CFR in all 3 major coronary arteries could be measured in 83 (83%) of 100 patients. The echo-contrast agent was useful in 32 of 49 patients who had unclear color Doppler images. When CFR <2.0 was regarded as the cut-off point, the overall agreement rate between CFR and the results of coronary angiography was 83% (69 of the 83 patients). In addition, CFR could predict the presence of coronary artery disease satisfactorily (sensitivity 85%, specificity 81%, positive predictive value 89%, negative predictive value 93%).

Conclusions TTDE seems to be a promising tool for screening patients with chest pain. Moreover, an echo-contrast agent seems to be an effective and supportive tool for patients who have poor visualization of coronary flow. (*Circ J* 2007; **71:** 891 – 896)

Key Words: Chest pain; Coronary artery disease; Coronary flow reserve

Chest pain is one of the key symptoms of coronary artery disease (CAD). Because this symptom is associated with not only the heart but also the other non-cardiac organs, it is important in patients with chest pain to differentiate CAD from the other diseases correctly. Although coronary angiography is the gold standard for the diagnosis of CAD, this is an invasive method. There are various non-invasive modalities such as exercise electrocardiography, stress echocardiography or myocardial scintigraphy. However, each of these modalities has some limitations such as cost, time or low reliability in some cases with a bundle-branch block or multivessel disease. Thus, a less-invasive, simpler and more useful modality seems to be ideal for these patients.

Coronary flow reserve (CFR) measurement is a useful method of assessing a significant functional coronary artery stenosis and coronary microvascular circulation.[1–3] Recent studies have shown that it is possible to measure CFR by transthoracic Doppler echocardiography (TTDE) in not only the left anterior descending artery (LAD),[4] but also the left circumflex artery (LCX) and the right coronary artery (RCA).[5,6] Thus, TTDE seems to be valuable as a diagnostic tool for CAD. Furthermore, TTDE might enable us to distinguish patients who should undergo further invasive tests such as coronary angiography from those who should not. However, there is not enough data on the feasibility and limitations of CFR measurement in all 3 major coronary arteries by TTDE as a non-invasive screening tool for patients with chest pain. In the present study, we measured CFR in all 3 major coronary arteries in 100 consecutive patients with chest pain, and investigated the diagnostic value and limitations of this method.

Methods

Study Population

Between June 2004 and January 2005, 100 consecutive patients who were hospitalized in our facility because of clinically suspected CAD were enrolled in the present study. Both coronary angiography and CFR measurement by using TTDE were performed. The reasons for hospitalization were to assess the presence of CAD due to chest pain, which suggested stable angina pectoris or to investigate the origin of chest pain. We excluded those patients suspected of having unstable angina pectoris, who had chest pain at rest, a new onset chest symptom within 1 month, or chest symptoms with a crescendo pattern. Moreover, the following patients were excluded from the present study: patients who had previously undergone a coronary angiography, percutaneous coronary intervention, coronary artery bypass graft surgery, patients with congestive heart failure, severe valvular heart disease, atrial fibrillation or flutter, any of the contraindications of CFR measurement by TTDE, such as bronchial asthma or a more than second degree atrioventricular block. All patients continued taking their anti-ischemic medications (eg, nitrates, β-blockers, calcium antagonists and nicorandil) and antiplatelet agents

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No conflict of interest is existed in this study.

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Table 1 Patients Characteristics

Number of patients, n	*100*
Age (years)	*68±9*
Male, n	*77*
Height (cm)	*162±8*
Weight (kg)	*62±9*
Body mass index (kg/m²)	*22.5±5.9*
Angina pectoris, n	*63*
Vasospastic angina pectoris, n	*10*
Coronary risk factors	
Hypertension, n	*78*
Hyperlipidemia, n	*73*
Diabetes mellitus, n	*37*
Smoking, n	*64*
Previous myocardial infarction, n	*11*
Left ventricular hypertrophy, n	*27*

Table 2 Coronary Angiography Results

Single vessel disease, n	*26*
Double vessel disease, n	*24*
Triple vessel disease, n	*12*
Left main disease, n	*3*
Left anterior descending artery stenosis, n	*23*
Left circumflex artery stenosis, n	*38*
Right coronary artery stenosis, n	*35*
Significant stenosis (–), n	*37*

on the day of the echocardiographic study. We obtained informed consent from all patients.

Transthoracic Doppler Echocardiography

Echocardiographic examinations were performed using a commercially available high-resolution ultrasound system (ACUSON Sequoia 512, Siemens Medical Solutions USA, Inc) with a 7V2C probe for the LAD and a 3V2C probe for the LCX and RCA. For color Doppler echocardiography, the velocity range was set at 12–24 cm/s. Color and pulsed-wave Doppler studies were performed in the fundamental imaging mode at 2.5 and 2.0 MHz, respectively.

Coronary flow in the 3 major coronary arteries was measured with patients mostly in the left lateral decubitus position. However, in some patients who produced poor color Doppler image, the degree of decubitus was changed to obtain clear and evaluable color Doppler images. Because details of the detection of coronary artery flows by TTDE have been previously reported elsewhere,[4–6] they are only summarized here. To image the mid-distal LAD, the transducer (7V2C) was placed at either the cardiac apex or 1 intercostal space above, along the interventricular groove, focusing on the proximal field. Once an optimal 2-dimensional image was obtained, the transducer was rotated and tilted until a coronary segment could be visualized by color Doppler imaging.[4] Doppler flow signals in the LCX were identified as linear color signals persisting during diastole on the base to mid portion of the left ventricular lateral region in the apical 4-chamber view. When Doppler flow signals in the LCX could not be detected, the transducer (3V2C) was rotated and tilted until adequate Doppler flow was acquired.[5] To record the Doppler flow signals in the RCA, we searched the posterior descending coronary artery. A modified apical 2-chamber view including the posterior interventricular sulcus was obtained by rotating the transducer counterclockwise from the apical 4-chamber view to the apical 2-chamber view. The ultrasound beam was angled posteriorly to obtain the best long axis of coronary flow signals. The posterior descending coronary artery flow was identified as a linear color signal continuing during diastole, directed from the base to the apex of the left ventricle.[6]

CFR Measurements by TTDE

Doppler spectral signal recordings were obtained by TTDE. First, we recorded baseline Doppler signals in the 3 major coronary arteries. Next, adenosine triphosphate (0.14 $mg \cdot kg^{-1} \cdot min^{-1}$) was infused intravenously for 2 min. All patients had a continuous heart rate and electrocardiographic monitoring. Blood pressure was recorded at the baseline, during adenosine triphosphate infusion at 1-min intervals, and at recovery.

Spectral Doppler signals in each major coronary artery were continuously recorded at the baseline over 3 cycles and during hyperemia. The position of the transducer was not changed during the administration of adenosine. Blood flow velocity was measured from the spectral Doppler signals, using the integrated evaluation program in the ultrasound system. Peak diastolic flow velocity was measured at the baseline, and at peak hyperemic conditions. When visualization of diastolic flow velocity by color Doppler echocardiography was unsuccessful or not clear enough to measure CFR, 1–2 ml of an echo-contrast agent (Levovist, Schering, Berlin, Germany, 300 mg/ml) was administered by an intravenous bolus infusion. The average of the measurements in 3 cardiac cycles was obtained. CFR was calculated as the ratio of peak hyperemic to baseline average diastolic peak velocity. Normal CFR was defined as ≥2.0 according to previous studies.[7,8]

Coronary Angiography

Selective coronary angiography was performed 1–3 days after CFR measurements. Before angiography, all of the patients received an intracoronary bolus injection of nitroglycerin (0.125–0.25 mg). Left ventriculography was performed at the 30° right anterior oblique projection, and the left ventricular ejection fraction was calculated using the area-length method. Coronary stenosis was evaluated using computer-assisted quantitative analysis system (CMS-QCA ver.4.0 MEDIS, Netherlands) based on multiple projections by an experienced investigator unaware of the echocardiographic data. A percent diameter stenosis of more than 70% was defined as a significant stenosis.

Study Design

All patients underwent history taking and assessment of coronary risk factors (ie, hypertension, hyperlipidemia, diabetes mellitus, smoking habits and family history). Body mass index was calculated. CFR measured by TTDE was compared with the results of coronary angiography to determine the screening and diagnostic feasibility of CFR measurement by TTDE for significant stenoses.

Statistical Analysis

Continuous data are expressed as mean ± SD. Sensitivity, specificity, positive predictive value and negative predictive value for CFR as a predictor of significant LAD, LCX and RCA stenosis were calculated. Differences in correct agreement rate among patients with single-, double-, and triple-vessel diseases were tested by ANOVA. A p value <0.05 was considered to indicate statistical significance. All analyses were performed using Stat-View software (version 5.0, SAS Institute Inc, NC, USA).

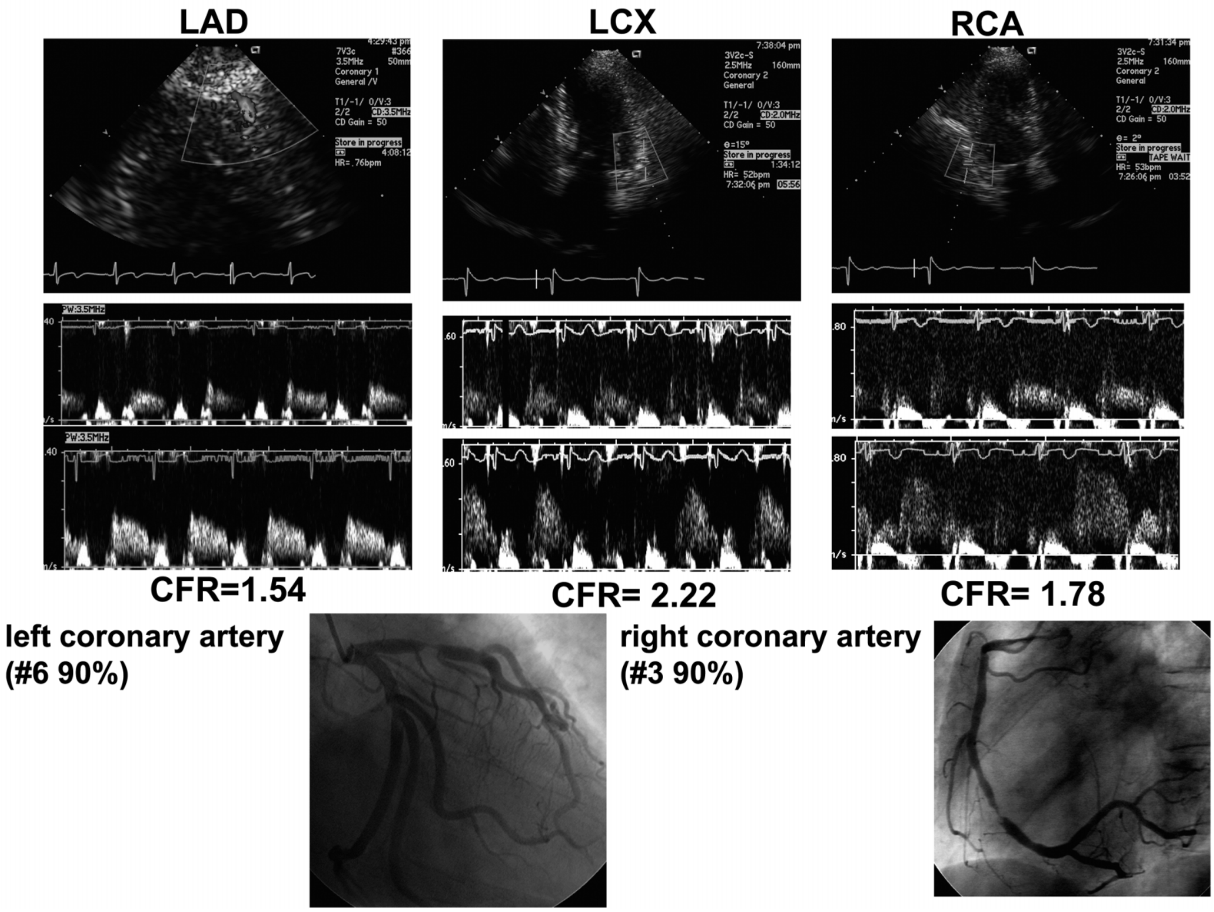

Fig 1. A representative case of a 67-year-old male who had suspected angina pectoris. All 3 major coronary arteries could be obtained clearly. Coronary flow reserve (CFR) in the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) was 1.54, 2.22, 1.78, respectively. Coronary angiography showed a significant stenosis in the LAD and RCA.

Results

Clinical Characteristics

Baseline demographics of the patients in the present study are presented in Table 1. Thirty patients had obesity (BMI ≥25 kg/m^2). Roughly 70% of the patients had more than 2 coronary risk factors. Table 2 shows the results of coronary angiography. A significant stenosis in the LAD was found in 23 patients, in the LCX in 38 patients and in the RCA in 37 patients. Thirty-six patients had multivessel disease and 3 patients had left main trunk stenosis. In the present study, 10 patients had chronic total occlusion and 4 patients had a hypoplastic LCX or RCA without a significant stenosis. The left ventricular ejection fraction was 54±6%. Left ventricular wall motion abnormalities could be seen in 29 patients.

Coronary Flow Imaging by TTDE

Adequate spectral Doppler recording of coronary flow was obtained in 94 patients (94%) in the LAD, in 83 patients (83%) in the LCX and in 88 patients (88%) in the RCA. Finally, the coronary flow in all 3 major coronary arteries could be detected in 83 (83%) of 100 patients. The total time required to obtain adequate coronary artery flows in all 3 major coronary arteries was 25±9 min (range from 9 to 56 min).

The echo-contrast agent was used in 49 patients (10 for LAD, 43 for LCX and 31 for RCA) because the color Doppler signal could not be detected in 48 patients and the diastolic flow was not clear enough to measure CFR in 1 patient. By using the echo-contrast agent, an adequate colored Doppler signal or clear diastolic flow could be obtained. Finally, all 3 major coronary artery flows were successfully obtained in 32 of these 49 patients after using the echo-contrast agent. Thus, contrast enhancement increased the success rate of optimal imaging and recording of the Doppler signals in all 3 major coronary arteries from 51% to 83%. There was no major complication such as angina, atrioventricular block, bradycardia, nausea or flushing during the administration of adenosine triphosphate or the echocardiographic contrast agent.

Feasibility of TTDE for Screening of CAD

The sensitivity and specificity for the detection of a significant coronary artery stenosis in the LAD was 96% and 94%, respectively. The positive predictive value and negative predictive value for the LAD was 87% and 99%, respectively. The sensitivities and specificities were 90% and 92% for the LCX, and 97% and 94% for the RCA, respectively. The positive predictive values and negative predictive values were 88% and 94% for the LCX, and 92% and 98% for the RCA, respectively.

After 17 patients were excluded because of the inability to detect the coronary flow in more than 1 major coronary

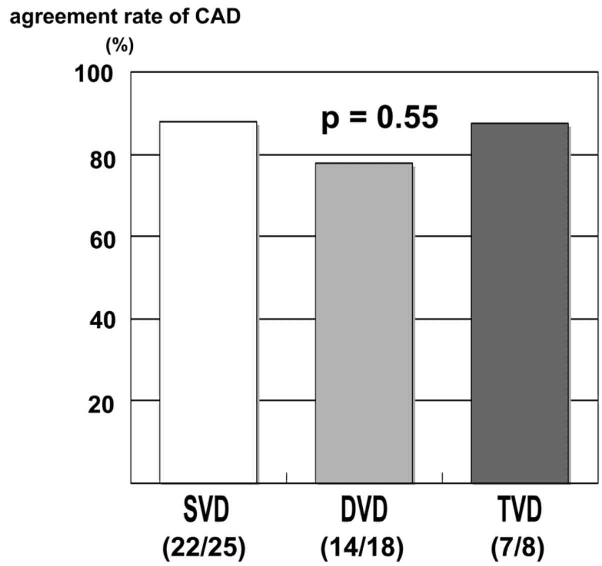

Fig 2. Comparison of the stenosis detection rate by transthoracic Doppler echocardiography among single-, double- and triple-vessel diseases (SVD, DVD and TVD). CAD, coronary artery disease.

artery, the data of CFR obtained by TTDE were compared with the results of coronary angiography and the overall agreement of CFR with the presence of CAD was investigated. In the assessment of all 3 major coronary arteries, 44 patients with CAD and 25 patients without significant stenosis could have been assessed by using CFR, and an overall agreement between CFR and the results of coronary angiography was 83% (69 of the 83 patients). Thus, CFR measured by TTDE could predict the presence of CAD satisfactorily (sensitivity 85%, specificity 81%, positive predictive value 89%, negative predictive value 93%). The representative case is shown in Fig 1.

CFR measured by TTDE was useful for both in single-vessel and multivessel diseases with a high overall agreement (88% vs 82%, p=0.152). The rate of overall agreement for triple-vessel disease was higher than that for double-vessel disease, but the difference was not statistically significant (88% vs 78%, p=0.55; Fig 2). Furthermore, although there were 11 patients with previous myocardial infarction in the present study, the feasibility of CFR for these patients was similar to that of patients without previous myocardial infarction (89% vs 92%, p=0.46).

In contrast, in patients with chronic total occlusion or a hypoplastic major coronary artery, the agreement between CFR measured by TTDE and the result of coronary angiography was not satisfactory. Among 10 patients with chronic total occlusion, coronary flow could not be detected in 4 patients and CFR was less than 2.0 in the remaining 6 patients. In the case of a hypoplastic LCX or RCA without a significant stenosis, although 2 patients had a CFR of more than 2.0, 1 had a CFR of less than 2.0 and the coronary artery flow could not be detected in the remaining patient.

Discussion

The major findings of the present study are that adequate coronary artery flow and CFR measurements in all 3 major coronary arteries were possible with high success rate (83%), sensitivity and specificity. In addition, for those patients who provided poor color Doppler images, the echo-contrast agent was useful and an important agent in providing clear images. Thus, the non-invasive screening of CAD by CFR using TTDE for the assessment of patients with chest pain seems to be feasible in the clinical setting.

Evaluation of Patients With Chest Pain

Chest pain is one of the important symptoms in patients with CAD. However, this symptom originates not only from the heart but also from a variety of non-cardiac intrathoracic structures, the tissues of the neck or thoracic wall and subdiaphragmatic organs. To investigate whether this chest symptom is derived from CAD, the diagnostic modality such as exercise electrocardiography, stress echocardiography or myocardial scintigraphy[9] are frequently used in clinical settings. In addition to these modalities, the feasibility of multidetector computed tomography or magnetic resonance coronary angiography are reported and performed in the emergency unit for the detection of acute coronary syndrome.[10–14] However, these modalities have some limitations such as cost, time, or low reliability. A less-invasive, simpler and more useful modality, which can be quickly performed at the bedside, seems to be ideal for the detection of CAD in patients with chest pain. The present study revealed that CFR is a non-invasive and promising tool for the assessment of patients with chest pain suggestive of stable angina pectoris. By using this modality, we can recognize those patients that are highly suspected of having CAD who should undergo further invasive tests such as coronary angiography, and it might enable us to avoid unnecessary diagnostic cardiac catheterization.

Assessment of Coronary Flow by TTDE

CFR is an important diagnostic index for functional severity of coronary artery stenosis.[1–3] CFR has mainly been measured by an invasive intracoronary Doppler guidewire,[15] a semi-invasive transesophageal Doppler echocardiography,[16,17] and an expensive positron emission tomography.[18] Recent advances in TTDE have made it possible to measure CFR in the LAD non-invasively.[4,19] Moreover, other recent studies have revealed that coronary artery flow can be detected by TTDE in not only the LAD but also the LCX and RCA.[5,6] However, CFR was measured in only 1 major coronary artery in those studies. Therefore, the feasibility of CFR measurement in all 3 major coronary arteries in an individual remains unknown. The present study demonstrated that it was possible to assess coronary flow by TTDE in all 3 major coronary arteries with a high success rate (83%). Moreover, the sensitivity and specificity for the detection of CAD were satisfactory for use in daily clinical practice. Although selective coronary angiography is the gold standard for assessing coronary artery stenoses, this modality is invasive, expensive and has the disadvantage of using contrast medium and exposing patients to radiation. Instead, TTDE might be an alternative tool for exploring coronary arteries in the screening of CAD in patients with not only typical but also atypical chest symptoms.

Usefulness of an Echo-Contrast Agent for the Detection of CAD

Although CFR measurement by TTDE is useful for the non-invasive assessment of major coronary arteries, it is difficult in some cases to obtain an adequate coronary artery flow image, especially in the LCX or RCA. Echo-contrast agents have been proven useful for increasing

Doppler signal-to-noise ratio in coronary arteries.[20,21] In the present study, contrast enhancement increased the success rate of optimal imaging and recording of Doppler signals in all 3 major coronary arteries from 51% to 83%. Visualizing color Doppler signals of coronary blood flow is of crucial importance because it allows for a more appropriate positioning of a pulsed-wave Doppler sample volume. Thus, although an additional cost is required, this agent is useful and important for CFR measurement by TTDE, especially in cases with unclear color Doppler signals.

Other Non-Invasive Screening Tools for CAD

Recently, there have been many reports showing that multidetector computed tomography or magnetic resonance coronary angiography are easily used for the detection of a significant coronary artery stenosis.[9–13] These modalities have high sensitivity and specificity, and can obtain clear images of the whole coronary arteries. However, multidetector computed tomography has the disadvantage of requiring contrast injection and exposing patients to radiation. Some studies reported that the sensitivity and specificity of magnetic resonance coronary angiography was ranging from 75% to 77%, and from 71% to 77% which is lower than those of TTDE in the present study (sensitivity 85%, specificity 81%).[22] Stress thallium-201 single photon emission computed tomography is more time-consuming than TTDE and is not reliable in patients with multivessel disease.[23] Stress echocardiography evaluates myocardial ischemia by detecting wall motion abnormalities. However, the accuracy of ischemia evaluation in each coronary artery territory is not sufficiently high.[24–26] In contrast, TTDE permits rapid and totally non-invasive assessment of coronary arteries. In particular, TTDE might be useful in patients with electrocardiographic abnormalities such as a left bundle-branch block, in those who are unable to exercise, or in those with multivessel disease, for which stress scintigraphy and echocardiography have a relatively high possibility of false-negative studies.

Limitations

First, for the assessment of a non-major coronary artery such as the diagnonal, obuse marginal or posterolateral branch, it is difficult to assess the presence of CAD correctly by using this modality. Second, there is a learning curve effect on the detection of the LCX and RCA coronary flow. In our preliminary analysis, the success rates of detection in the LCX and RCA were 72% and 78% in the first 20 patients. After these analyses, the success rate was improved and we could obtain the coronary flow signal more quickly than in the first 20 patients. Therefore, practice is required to obtain a clear visualization of coronary flow, especially in the LCX and RCA. Third, in patients with chronic total occlusion, distal stenosis or hypoplasty in a major coronary artery, there was no good agreement between CFR measured by TTDE and the results of coronary angiography. An erroneous sampling at a coronary artery branch or a prestenotic segment (in patients with distal stenosis) is a likely explanation. It is sometimes difficult to assess the CFR in patients who are obese. There were 17 patients with obesity in the present study and the coronary flow in more than 1 major coronary artery could not be detected in 12 of them. Finally, we did not discontinue any drugs on the day of the echocardiographic study because of ethical reasons. Although antianginal drugs might dilate coronary microcirculation,[27] it remains unknown how those drugs affect the CFR measurement in the present study.

Clinical Implications

This simple, non-invasive, and generally available method of assessing CFR has potentially important and interesting clinical applications. It seems useful for the patients with chest pain to detect CAD in particular situations, such as patients with a bundle-branch block or multivessel disease, and it might also be useful to differentiate other disorders with angina-like chest pain. In addition to this, CFR measured by TTDE has high negative and predictive values. Thus, by measuring CFR first, we can distinguish those patients who should have coronary angiography from those who should not.

Conclusions

CFR in all 3 major coronary arteries could be measured by TTDE with high success rate, sensitivity and specificity with the aid of a contrast agent. CFR measurement by TTDE is a simple and useful non-invasive diagnostic modality and seems to be a promising tool for screening patients with chest pain.

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