Coronary Flow Reserve by Contrast Enhanced Transesophageal Coronary Sinus Doppler Measurements Can Evaluate Diabetic Microvascular Dysfunction

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Background This study was undertaken to investigate whether coronary flow reserve (CFR) using coronary sinus flow (CSF), which can be measured by transesophageal Doppler echocardiography (TEDE), especially when contrast enhanced, is useful in evaluating microvascular dysfunction in patients with diabetes mellitus (DM).

Methods and Results CSF recordings using contrast enhanced TEDE were performed before and after adenosine triphosphate infusion (0.15 mg·kg⁻¹·min⁻¹) in 16 patients with type 2 DM and diabetic retinopathy and in 13 non-DM patients (control). Coronary angiography revealed normal epicardial coronary arteries. CFR was defined as the ratio of the antegrade flow velocity time integral in hyperemic conditions and basal levels. Clear envelopes of CSF were obtained in all DM patients using contrast-enhanced TEDE. CFR using CSF in the DM group was significantly decreased compared with the control group (1.4±0.4 vs 2.1±0.5, p<0.01), but there were no significant differences of age, ejection fraction, rate of hypertension and hypercholesterolemia between the 2 groups. Using 1.7 of CFR as the cut-off value, diabetic microvascular dysfunction could be detected with 82% sensitivity and 83% specificity.

Conclusions CFR calculated by CSF using contrast-enhanced TEDE may be useful for evaluating diabetic microvascular dysfunction. (Circ J 2006; 70: 1415 – 1420)

Key Words: Contrast echocardiography; Coronary flow reserve; Coronary sinus; Diabetes mellitus; Transthoracic echocardiography

Diabetes mellitus (DM) is a major coronary risk factor that affects not only epicardial coronary atherosclerosis but also microvascular dysfunction. In fact, it has been reported that coronary flow reserve (CFR) in patients with DM is impaired because of diabetic microvascular dysfunction even when there is no evidence of epicardial coronary atherosclerosis.¹² There is increasing evidence that coronary microvascular dysfunction may be an underlying mechanism in patients with symptoms and signs of myocardial ischemia without angiographically detectable coronary artery disease, and even in asymptomatic patients with cardiovascular risk factors.²³ Microvascular processes have also been implicated in left ventricular dysfunction and subsequent heart failure,⁵⁶ particularly in patients with DM.⁷⁸ Thus, CFR measurement offers important diagnostic information about microvascular dysfunction in patients with DM and may be useful for the clinical management and prediction of prognosis for patients with DM. However, most methods of CFR calculation are based on invasive methods and thus do not apply to the general diabetic population. Transthoracic echocardiography (TTE) can be used to evaluate the CFR of the left anterior descending artery (LAD), the left circumflex artery (LCX)⁹ and right coronary artery (RCA)¹⁰ but the detection rate is not satisfactory. Moreover, to measure the CFR of the LAD, LCX and RCA simultaneously is time consuming and thus not suitable in the clinical setting. Recently, noninvasive assessment of CFR using transesophageal Doppler echocardiography (TEDE) evaluation of coronary sinus flow (CSF) has been reported and the calculations based on CSF may better represent CFR of the entire coronary artery system compared with individual CFR of the LAD, LCX or RCA.¹²¹³ Thus, in this study, we investigated whether CFR using CSF is useful for evaluating diabetic microvascular dysfunction.

Methods

Study Patients

Sixteen patients (10 males, mean age: 64±8 years old) with diabetic retinopathy who had a positive exercise stress test, including treadmill, dobutamine stress echocardiography or thallium-201 exercise scintigraphy, and angiographi-
cally normal coronary arteries were designated as the DM group. All 16 patients were taking sulfonylurea, but none was being treated with insulin. Diabetic retinopathy was diagnosed by 2 ophthalmologists in the hospital who were unaware of the coronary artery data. Thirteen non-DM neurosurgical patients with angiographically normal coronary arteries who underwent coronary angiography (CAG) for atypical chest pain, and who were referred for TEDE for preoperative exclusion of a patent foramen ovale comprised the control group. Selective CAG was performed by the Judkins technique (transradial approach) using a 4F CAG catheter (FansacIV, Clinical Supply Co, Ltd), and stenosis severity was judged by 2 experienced investigators from multiple projections stored on cineangiograms. Exclusion criteria were: history of myocardial infarction, valvular disease, left ventricular hypertrophy (wall thickness >11 mm), and reduced left ventricular function (ejection fraction (EF) <50%). The study protocol was in accordance with the guidelines of the institutional ethics committee and all patients gave written informed consent.

Echocardiography

Before CAG, TTE was performed in all patients to evaluate EF, wall thickness and left ventricular end-diastolic diameter. Within 1 week of CAG, all patients underwent TEDE performed after local anesthesia of the oropharynx with lidocaine, and using routine sedation (intravenous injection of 2–3 mg propofol (AstraZeneca Pharmacy)). An intravenous cannula was placed into an antecubital vein to inject the contrast agent (Leovist; Schering and Tanabe Pharmacy), which was prepared at a microbubble concentration of 200 mg/ml. The surface ECG was monitored, and noninvasive blood pressure measurements were performed during echocardiography.

CSF Using Contrast-Enhanced TEDE

To obtain CSF recordings, the transesophageal probe was advanced to the gastric level and then, with dorsal angulation of the transducer, the probe was cautiously withdrawn until a modified 4-chamber view with visualization of the coronary sinus near its ostium into the right atrium was achieved. The transducer position was then optimized to

![Fig 1. Placement of Doppler sample point (arrow) for measuring coronary sinus flow by contrast-enhanced transesophageal Doppler echocardiography. CS, coronary sinus; RA, right atrium.](image)

![Fig 2. Examples of coronary sinus flow velocity recordings at baseline and during hyperemia in the DM and control groups. In 1 patient with DM (Left panels), S, D, and AVTI at baseline were 21 cm/s, 18 cm/s and 98 mm, respectively and 26 cm/s, 26 cm/s and 139 mm, respectively, during hyperemia. In 1 patient from the control group (Right panels), S, D, and AVTI at baseline were 18 cm/s, 22 cm/s and 90 mm, respectively, and 22 cm/s, 53 cm/s and 216 mm during hyperemia. Thus, the CFR of the patient from the DM group was 1.4, and that of the control patient was 2.2. AVTI, antegrade flow velocity time integral; CFR, coronary flow reserve; D, maximum antegrade diastolic flow velocity; DM, diabetes mellitus; S, maximum antegrade systolic flow velocity.)](image)
obtain an angle of <30° between the Doppler beam and the long axis of the coronary sinus, and to achieve continuous visualization of the vessel throughout the cardiac cycle. Flow recordings were performed after placement of a sample volume into the coronary sinus no more than 1.5 cm from its ostium (Fig 1). Up to 5 consecutive attempts were undertaken to obtain optimal flow recordings. Recordings were repeated until at least 3 consecutive flow velocity curves of similar appearance were achieved. After baseline recordings, adenosine triphosphate (ATP) (0.15 mg·kg⁻¹·min⁻¹) was continuously infused for 5 min, during which time the CSF velocity recordings were repeated. Doppler velocity curves of optimal signal quality were evaluated, and measurements obtained from 3 cardiac cycles were averaged after bolus injection of Levovist (200 mg/ml, 2 ml). One experienced investigator who was unaware of the other patient’s data analyzed each study. Measurements included maximum antegrade flow velocity (Systolic (S) and diastolic phase (D), respectively) and antegrade flow velocity time integral (AVTI), and maximal coronary sinus dimension. For all measurements, 2 different methods with or without Levovist for the calculation of CFR were used to evaluate the usefulness of contrast. CFR was determined by dividing AVTI after ATP administration by AVTI at baseline (Fig 2).

Reproducibility of CFR Data

We determined intraobserver and interobserver variabilities for measuring CFR by measuring the 2 variables in 10 randomly selected records twice by the same observer and by 2 independent observers, respectively. Intraobserver and interobserver variabilities of CFR were 6.1±6.3% and 7.0±6.0% (absolute difference), respectively.

Statistical Analysis

Results are expressed as mean values±SD. An analysis of variance with subsequent Scheffe’s F test and Fisher’s exact probability test was performed to compare the Doppler parameters and clinical data of the DM group and control group. Two-way ANOVA was used to compare data before and after ATP administration. To analyze the predictive value of detecting diabetic microvascular dysfunction using the CFR of CSF, we constructed receiver-operating characteristic (ROC) curves and determined that a suitable cutoff point would be when sensitivity was as nearly equal to specificity as possible. A p-value <0.05 was considered statistically significant.

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Using a ROC curve, we considered the optimal cut-off point of CFR for detecting diabetic microvascular dysfunction to be around 1.7, because it had a sensitivity of 82% and specificity of 83% to detect diabetic microvascular dysfunction.

Various Hemodynamic and Echocardiographic Parameters of CSF

Fig 2 shows representative cases of CSF velocity recordings in the DM and control groups. CFR using CSF in DM was lower than that in the controls. Table 2 shows the effects of ATP administration on various hemodynamic and echocardiographic parameters during CSF measurements using contrast-enhanced TEDE. ATP significantly increased the heart rate in both groups while blood pressure remained unchanged. The maximal diameter of the coronary sinus remained unchanged after ATP infusion. ATP significantly increased D and AVTI in both groups but did not affect the other CSF parameters. D and AVTI after ATP infusion in DM group were significantly lower than in the control group. As a result, CFR in the DM group was significantly lower than in the control group (Fig 4: 1.4±0.4 vs 2.1±0.5; *p<0.01 vs Baseline, ‡p<0.01 vs Control group).

**Discussion**

The present study results indicate that contrast-enhanced TEDE measurements of CFR using CSF can be evaluated easily and noninvasively, and that global CFR is significantly reduced in patients with type 2 DM and retinopathy. The retinal circulation provides an opportunity to noninvasively explore the relationship of systemic microvascular disorders. Signs of retinopathy are structural markers of microvascular dysfunction caused by various processes, including diabetes, and have been found to predict incident coronary heart disease. Thus, in this study, we defined the patients with diabetic microvascular dysfunction as those with diabetic retinopathy but without significant epipardial coronary artery stenosis.

Compared with previous studies of the CFR of patients with DM using either a Doppler guide wire or pressure-wire, contrast-enhanced TEDE measurements can be done noninvasively. TEDE can make some patients uncomfortable, but this can be relieved by sedation. We evaluated the CFR of the entire coronary artery system, whereas in the previous study the CFR of only the LAD was evaluated using an invasive Doppler guidewire or TTE. In cardiac disease with diffuse reduction of CFR (eg, diabetic microvascular dysfunction), evaluation of the global flow reserve by coronary sinus techniques may be more appropriate. There are reports that noninvasive measurement of flow-mediated dilation (FMD) of the brachial arteries can detect diabetic cardiovascular dysfunction. However, the CFR of CSF is superior to FMD for evaluation of diabetic cardiovascular dysfunction because it directly reflects cardiac function directly as compared with FMD and moreover the measurement of FMD can be difficult.

One of the major factors causing reduced CFR in DM is microvascular dysfunction and left ventricular dysfunction and heart failure as well as being related to coronary atherosclerosis. DM is a major coronary risk factor so early detection of coronary arterial abnormality and preventing coronary atherosclerosis are important in the management of DM. Thus, we believe that contrast-enhanced TEDE measurements of CFR in patients with DM is useful for preventing heart failure and coronary artery disease.

Compared with previous data about CFR, the present values were lower, possibly because of differences between the CFR of CSF and that of each coronary artery, as well as differences in methodology. In fact, the other report of CFR using CSF also had lower values as compared with CFR measured using Doppler guidewire. Moreover, Kornzon et al have shown that the coronary sinus cross-sectional area varies in size and shape during the cardiac cycle, which may also explain why our CFR values were lower than the previous reports.

Recently, various conditions, including hypertension, left ventricular hypertrophy, hypercholesterolemia,
valvular disease\textsuperscript{28} and the postmenopausal state\textsuperscript{31,32} have been reported to reduce CFR. As shown in Table 1, in the present study there were no significant differences in the rates of hypertension and hypercholesterolemia, or left ventricular wall thickness measured by echocardiography between patients with and without DM. Moreover, we excluded left ventricular hypertrophy >11 mm, which included cases of hypertrophic cardiomyopathy, and all of the female study subjects were postmenopausal. Thus, the direct effects of these various factors on CFR can be considered as negligible in this study.

As shown in Fig 3, before injection of Levovist, in approximately 10% of patients, we could not clearly evaluate the Doppler envelope of CSF. However, after injection of Levovist, thorough and accurate evaluation of CFR was achieved in all patients. With respect to coronary artery flow, some studies have demonstrated that Levovist increases the feasibility and quality of transesophageal Doppler recordings\textsuperscript{33,34}. Thus, evaluation of CFR using TEDE can be considerably improved by injecting a small amount of Levovist.

\textbf{Study Limitations}

First, this study had a small sample size and moreover, as shown in Fig 4, there was a relative overlap of the DM and control groups. However, CFR of 1.7 in this study was a useful cut-off value for detecting diabetic microvascular dysfunction. Thus, we believe that this method can be used in the clinical setting. Second, TEDE can be an uncomfortable and semi-invasive examination; however, by sedating all patients who underwent TEDE there were no complaints of discomfort during the procedure. Although there are potential negative inotropic effects of propofol, it clearly did not affect blood pressure or systolic cardiac function as evaluated by TEDE. Thus, the influence of the sedative on CFR in this study can be discounted. Third, a change in the coronary sinus dimensions throughout the cardiac cycle can affect the measurements of CFR, but in our study, there were no significant differences between the 2 groups in the maximal coronary sinus dimension at baseline and during ATP administration (Table 2). Therefore, that effect on the measurements was weak in this study. Finally, we did not compare our data with that obtained using the nuclear method\textsuperscript{35,36} that is widely used to noninvasively determine the functional severity of coronary lesions. However, the nuclear methods are usually used as regional cardiac assessments with some underestimation. CFR using CSF may be better for a global cardiac evaluation, such as for assessing diabetic microvascular dysfunction.

\textbf{Conclusions}

Contrast-enhanced TEDE measurement of CFR using CSF was able to evaluate diabetic microvascular dysfunction noninvasively. This technique can be used to identify patients with DM who may have a worse prognosis despite having normal left ventricular function and a normal epicardial coronary artery.

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\textbf{References}


