Noninvasive Prediction of Angiographic Spasm Provocation Using Trans-Thoracic Doppler Echocardiography in Patients With Coronary Spastic Angina

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Background  In the present study it was examined whether transthoracic Doppler echocardiography (TTDE) would be useful for noninvasive diagnosis of coronary spastic angina (CSA) by assessing coronary arterial tone in the morning.

Methods and Results  The study population comprised 21 CSA patients and 27 control subjects. All diagnoses were angiographically confirmed by provocation test using acetylcholine. Coronary flow velocity reserve (CFVR) was measured at the distal left anterior descending artery with a frequency of 5.0 MHz ultrasound at baseline and after sublingual administration of nitroglycerin (NTG). Coronary arterial tone was assessed by obtaining the change of CFVR induced by NTG administration (CFVRNTG/Pre). Basal CFVR tended to be lower in CSA patients (2.13±0.63, 2.71±0.67, respectively, p=0.05). CFVR after NTG was significantly higher in CSA patients (3.91±1.10, 3.07±0.74, p=0.003). The CFVRNTG/Pre was significantly higher in CSA patients than in the control subjects (1.90±0.49, 1.15±0.22, p<0.0001). Using a cut-off value of 1.4 in CFVRNTG/Pre, the sensitivity and specificity for the diagnosis of CSA were 91% and 90%, respectively.

Conclusion  TTDE appeared to be useful for the noninvasive diagnosis of CSA by assessing the coronary arterial tone. 

Key Words:  Coronary flow; Coronary spastic angina; Trans-thoracic Doppler echocardiography

Coronary spastic angina (CSA) causes myocardial ischemia at rest by abnormal contraction of epicardial coronary arteries without organic stenosis, which often occurs between midnight and early in the morning. The diagnostic accuracy of noninvasive modalities for CSA, such as the cold pressor test or hyperventilation test, has been low, so angiographic assessment in conjunction with spasm-provocation by intracoronary injection of acetylcholine has been the most standard, albeit an invasive, method of diagnosis. However, it may sometimes lead to a serious adverse outcome.

The basal coronary arterial tone is increased in patients with CSA. Because coronary flow velocity (CFV) is inversely related to lumen size in the distal myocardial bed, elevated basal arterial tone can be assessed as higher flow velocity in the coronary artery. Transthoracic Doppler echocardiography (TTDE) enables reliable measurement of CFV and its reserve (CFVR) in the human left anterior descending artery. We have previously reported that measuring the change of CFVR following nitroglycerin (NTG) administration is useful for assessing basal coronary arterial tone.

Accordingly, we evaluated the usefulness of TTDE for noninvasive diagnosis of CSA by assessing coronary arterial tone in the morning.

Methods

Study Patients and Study Design

We studied 50 consecutive patients with chest pain at rest who underwent planned coronary angiography and had no significant stenoses. Two patients were excluded because of suboptimal TTDE measurements. A total of 48 patients (age 40–77 years, mean 59.8±9.1; 28 males, 20 females) were included for further analysis.

The Institutional Review Board approved the study, and the patients provided written informed consent. Vasodilators were withdrawn at least 72 h before the study, except sublingual NTG, which was withdrawn at least 2 h before the study. The patients fasted overnight and did not smoke within 2 h prior to the study. All foods or drinks containing flavonoids, catechins or caffeine were withheld during the study. The Doppler examinations were performed prior to the cardiac catheterization in the morning.

CFV Measurements

TTDE was performed with 5-MHz transducer connected to Vivid 7 echocardiographic machine (GE-Vingmed Ultrasound, Horten, Norway), by an experienced investigator. The distal left anterior descending artery was examined using color Doppler mapping with a velocity ranging from −15 to +15 cm/s. After positioning a sample volume where the ultrasonic beam was as parallel to the direction of the distal part of the left anterior descending artery as possible,
the spectral Doppler signal was recorded as the baseline measurement. Thereafter, Doppler signals were obtained under maximal hyperemic conditions during intravenous infusion of adenosine 5'-triphosphate (ATP: 0.14 mg·kg⁻¹·min⁻¹) for 2 min. The mean diastolic flow velocity was traced for the CFV measurements. The measurements were averaged over 3 cardiac cycles. The CFVR was calculated as the ratio of the hyperemic CFV to the basal CFV. After 10 min, 0.3 mg of NTG was administrated by oral spray and 3 min later another Doppler measurement at both baseline and during hyperemia was performed as before (Fig 1). To assess the coronary vascular tone, a parameter was calculated as follows:

$$\text{CFVR}_{\text{NTG/Pre}} = \frac{\text{CFVR after NTG}}{\text{CFVR before NTG}}$$

To avoid variation in the time of TTDE, with regard to circadian changes of vascular tone, we performed all TTDE before 9 o’clock in the morning.

**Quantitative Coronary Angiography**

As in a previous report, we infused either graded doses of acetylcholine (Daiichi-Sankyo, 20, 50, and 100 μg into the left coronary artery or 20 and 50 μg into the right coronary artery). Patients were carefully monitored with 12-lead ECG and serial coronary angiography at 2-min intervals. Coronary artery spasm was defined as >90% diameter stenosis in 1 or more epicardial segments accompanied by either clinical symptoms or ischemic ST deviation. Patients who had severe chest pain, hypotension or both were immediately treated with intracoronary NTG. Patients with negative provocation for CSA were designated as the control group.

**Statistical Analysis**

Data are expressed as mean±SD. Differences in all the measurements were analyzed by repeated ANOVA and post hoc test where appropriate. Statistical significance was defined as p<0.05.

**Results**

**Patients**

The characteristics of the patients are summarized in Table 1 and a representative case is shown in Fig 2. Acetylcholine provoked coronary artery spasm in 21 patients. Despite the higher incidence of hypertensive patients in the coronary spastic group, there were no significant differences in the incidence of diabetes or hypercholesterolemia between the coronary spasm group and control group. However, females were more predominant in the control group. In 14 patients with CSA, spasm was induced in the left anterior descending artery, and in 7, the spasm provocation was positive only in the right coronary or circumflex artery.

**Hemodynamic Change**

There were no differences in blood pressure or heart rate between the CSA and control groups (Table 2). Following oral administration of NTG, both systolic and diastolic blood pressures significantly decreased, but there were no differences between the 2 groups.

**Doppler Echocardiographic Findings**

The basal CFV in the patients with CSA was significantly higher than that of the control group (p=0.033; Table 3). However, hyperemic CFV tended to be lower in the CSA patients than in the control patients (2.13±0.63 vs 2.71±0.67, p=0.05; Fig 3).

In the group with CSA, the baseline CFV significantly decreased following NTG administration (p=0.01; Table 3), but in the in the control group the change of baseline CFV was not significant after NTG.

Fig 3 demonstrates the change of CFVR in both groups. In
Fig 2. Representative case of coronary spastic angina. (Upper) Serial change of coronary flow velocity (CFV) in the left anterior descending artery (LAD) obtained by transthoracic Doppler echocardiography. After nitroglycerin (NTG), baseline CFV decreased and hyperemic CFV did not change. Consequently, the CFV reserve increased from 2.6 to 5.1. (Lower) Coronary angiography. After acetylcholine infusion, distal LAD (white arrow) shows diffuse and tight narrowing, indicating coronary spastic angina. ATP, adenosine 5‘-triphosphate.

**Table 2 Hemodynamics During Transthoracic Doppler Echocardiography**

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>Control</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline BP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systole</td>
<td>134.6±8.5</td>
<td>131.3±20.9</td>
<td>0.529</td>
</tr>
<tr>
<td>Diastole</td>
<td>78.0±11.7</td>
<td>70.7±12.9</td>
<td>0.059</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65.0±9.6</td>
<td>63.6±8.2</td>
<td>0.575</td>
</tr>
<tr>
<td><strong>After nitroglycerin BP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systole</td>
<td>118.4±16.2</td>
<td>120.1±17.0</td>
<td>0.736</td>
</tr>
<tr>
<td>Diastole</td>
<td>69.1±12.4</td>
<td>66.4±12.6</td>
<td>0.455</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68.0±7.6</td>
<td>69.1±12.3</td>
<td>0.699</td>
</tr>
</tbody>
</table>

Values are mean±SD.
BP, blood pressure; HR, heart rate. Other abbreviation see in Table 1.

**Table 3 Coronary Flow Velocity Measurements**

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline (cm/s)</td>
<td>26.7±11.0</td>
<td>20.9±7.1</td>
<td>0.033</td>
</tr>
<tr>
<td>Hyperemia (cm/s)</td>
<td>53.7±21.0</td>
<td>54.1±16.0</td>
<td>0.941</td>
</tr>
<tr>
<td><strong>NTG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (cm/s)</td>
<td>15.3±5.9*</td>
<td>17.9±6.4</td>
<td>0.161</td>
</tr>
<tr>
<td>Hyperemia (cm/s)</td>
<td>52.8±18.8</td>
<td>57.1±19.9</td>
<td>0.452</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*p=0.03, compared with baseline flow velocity before NTG.
NTG, nitroglycerin. Other abbreviation see in Table 1.
the control group, CFVR did not significantly improve after NTG administration, whereas it was significantly higher in the patients with CSA (3.91±1.10 vs 3.07±0.74, p=0.04; Fig 3), resulting in greater improvement of the CFVR in the group with CSA than in the control group (Fig 3).

Diagnostic Significance
Calculating the CFVRNTG/Pre significantly distinguished the distribution of the value between patients with CSA and the control group (1.90±0.40 vs 1.15±0.22, respectively, p<0.0001; Fig 4). Receiver-operating characteristic analysis revealed that a cut-off value of 1.40 in CFVRNTG/Pre was significant for distinguishing patients with CSA from control patients, with an area under the curve of 0.96 (p<0.0001). The sensitivity and specificity in distinguishing CSA were 91% and 90%, respectively.

Discussion
How the CFVR is altered in patients with CSA has been poorly researched, partly because of the invasive methods with Doppler guide-wire used to measure coronary physiology during cardiac catheterization.11,12 Inserting a guide-wire into the coronary artery may induce spasticity, requiring premedication with nitrates. In the present study, we measured the CFVR using TTDE, which is non-invasive and feasible for use at the bedside. Hirano et al demonstrated the usefulness of echocardiography to detect wall motion abnormalities induced by hyperventilation and cold pressor stress in CSA.13 However, assessing wall motion is qualitative and subjective, so there may be discordance between trained and untrained examiners. Morita et al also reported that measuring the diameter of the left main trunk using transesophageal echocardiography was helpful for assessing CSA.14 We believe that our method using TTDE is more “noninvasive and quantitative” than other methods.

NTG Induced Change of CFV
In the present study, the basal CFV of patients with CSA was higher than that of the control group. A significant decrease of CFV induced by NTG was only observed in the patients with CSA. Assuming that coronary flow is relatively constant, our results indicate that the coronary artery lumen is narrowed during the morning in patients with CSA.

As NTG is thought to dilate the larger coronary vessels, and mostly affect the epicardial arteries,15 the NTG-induced decrease of the baseline CFV suggests dilatation of the epicardial arteries. On the other hand, the control group did not show a significant change of the baseline CFV after NTG administration, which indicates that baseline coronary arterial tone was lower in the control group. In 10 patients with CSA, the CFV was less than 2.0 at baseline. These findings suggest that CSA may progress to silent myocardial ischemia in the morning. Although the baseline CFV varied among the groups and circumstances, hyperemic CFV was a constant among the groups, before and after NTG administration. This finding partially conflicts with the report by Akasaka et al,11 who found a decreased CFVR using a Doppler guidewire in patients with CSA. According to Akasaka et al, CFVR is reduced because of reduced hyperemic flow velocity; however, baseline flow is preserved. In the present study, CFVR was reduced mainly because of altered baseline flow velocity in CSA. In our previous study, CFVRNTG/Pre significantly correlated with angiographic luminal change in the epicardial arteries.8 We believe that our results are more rational because the epicardial coronary arteries of patients with CSA might have increased tone in the morning, resulting in an increased baseline CFV.
As the angiography demonstrated, the vessels were minimally diseased and therefore might be able to dilate almost completely by flow-mediated dilatation during hyperemia. We assessed coronary artery tone by obtaining the CFVRNTG/Pre values. The advantages of measuring CFV over CFV include distinguishing organic stenoses from coronary spasm. CFVR following NTG administration represents epicardial disease and microcirculatory function. We have already reported that CFVRNTG/Pre has a stronger relationship with coronary diameter change after NTG than represents epicardial disease and microcirculatory function. A change of CFV, which can be explained by the fact that not only the epicardial coronary artery, but also microvascular spasm contributes to myocardial ischemia in patients with CSA.

Recently, Park et al demonstrated that CFV in patients with CSA decreased during cold stimuli while the CFV in the control groups marginally increased. In their report, baseline CFV in both coronary spastic patients and control groups were higher than in the present study, and baseline CFV was equivalent between patients with CSA and the control groups. We believe that the time when TTDE is performed affects the flow measurements, because CSA is characterized by its circadian variation. Therefore, we performed all TTDE examinations before nine o’clock, whereas in Park’s study the time was not mentioned. Furthermore, our method is easier to perform and quantitative with a cut-off value for distinguishing patients with coronary spasm. The specificity and the sensitivity of measuring the increase in CFVR by NTG appeared to be satisfactory, suggesting the usefulness of TTDE in diagnosing CSA.

One question about the present study may relate to the fact that we only examined coronary flow in the left anterior descending artery, which might not correspond to the vessel in which the coronary spasm occurred. In the present study, the mean CFVRNTG/Pre in the patients in whom coronary spasm was observed in the left anterior descending artery was equivalent to that of patients whose left anterior artery demonstrated epicardial spasm during angiography. The frequent evidence of multivessel spasm or fluctuation of the spastic location also support that CSA is not merely a single-vessel disease, but a disease involving the entire coronary system.

Study Limitations
First, the number of the patients is relatively small; however, the clear difference between the 2 groups in the distribution of CFVRNTG/Pre suggests a strong trend that supports our results. Second, factors influencing CFV should be considered, such as aortic stenosis, left ventricular hypertrophy and hemodialysis; in the present study, none of the patients had these diseases and only 6 had diabetes. Third, we were unable to perform stress-thallium-scintigraphy to exclude vasodilators for patients complaining of angina while at rest. This may translate into a lower incidence of catheterization-provoked tests with an intracoronary injection of acetylcholine. Moreover, our method is easier to perform and quantitative compared to invasive angiography to assess the implications of CSA. It can be performed at the clinic, avoiding the use of invasive angiography to assess the implications of CSA.

Clinical Implications
Despite these limitations, our method has some clinical implications. It can be performed at the clinic, avoiding the use of invasive angiography to assess the implications of CSA. As the control patients all had a history of chest pain, they might have had some degree of lifestyle and pharmacological interventions.

In conclusion, TTDE appears to be useful for the non-invasive diagnosis of CSA by assessing the basal coronary artery tone in the left anterior descending artery.

References