Non-Invasive Assessment of Coronary Arterial Tone Using Trans-Thoracic Doppler Echocardiography

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Background  As coronary flow velocity (CFV) is inversely related to the luminal size that exists for the myocardial bed, the elevated arterial tone can be assessed as the higher flow velocity in the epicardial artery. We examined the usefulness of transthoracic Doppler echocardiography (TTDE) for the assessment of coronary arterial tone.

Methods and Results  A total of 32 patients underwent TTDE and angiography. The luminal diameter (LD) in the left anterior descending artery (LAD) was measured by using quantitative coronary angiography before and after nitroglycerin (NTG) administration. The ratio of post NTG LD to the control (LDNTG/Pre) was assessed as a standard parameter of coronary arterial tone. We also measured CFV and CFV reserve (CFVR) at the LAD by TTDE. We evaluated the change of CFV (CFVNTG/Pre) and CFVR (CFVRNTG/Pre) following NTG administration. The LD increased from 1.98±0.46 to 2.51±0.34 mm (p<0.001), while the CFV decreased from 23.9±10.0 to 16.3±5.6 cm/s (p<0.03), and the CFVR increased from 2.39±0.65 to 3.56±1.12 (p<0.001). There were significant correlations between CFVNTG/Pre and LDNTG/Pre (p<0.0001, R2=0.532), and between the CFVRNTG/Pre and LDNTG/Pre (p<0.0001, R2=0.715).

Conclusion  TTDE can assess the coronary arterial tone by measuring the responses of CFV and CFVR to NTG administration.  (Circ J 2006; 70: 459–462)

Key Words: Coronary flow; Transthoracic Doppler echocardiography; Vascular tone
ratio of the hyperemic CFV to the basal CFV. Ten minutes later, 0.3 mg of NTG was administrated to patients by an oral spray. Thereafter, another Doppler measurement was performed 3 min after NTG administration.

To assess the coronary vascular tone, 2 parameters were calculated as follows:

\[
CFV_{\text{NTG/Pre}} = \frac{CFV \text{ after NTG}}{\text{Baseline CFV}}
\]

\[
CFVR_{\text{NTG/Pre}} = \frac{CFVR \text{ after NTG}}{\text{Baseline CFVR}}
\]

Coronary Angiographies

A coronary angiography was taken from the right anterior oblique view both at the baseline and after the administration of NTG by an oral spray. To avoid the variation in the time of angiography, regarding the circadian changes of vascular tone, all angiograms were taken before 10.00h. An offline quantitative coronary angiography (QCA) was performed, and the luminal diameters (LD) of angiographically normal segments in the mid LAD were analyzed by an automated edge detection system (CMS, MEDIS, Leiden, Netherlands) both at the baseline and after the administration of NTG by an experienced observer who was blinded to the echocardiographic analysis. To quantify the coronary vascular tone, the dilatation of LAD diameter was calculated as follows:

\[
LD_{\text{NTG/Pre}} = \frac{\text{Diameter after NTG}}{\text{Baseline diameter}}
\]

Statistical Analysis

Data were expressed as mean ± SD. Differences in all the measurements were analyzed by the repeated ANOVA and a post hoc test where appropriate. Statistical significance was defined as a p value < 0.05. In the scattergrams, the relationship and variability between coronary flow parameters and angiographic luminal change were analyzed by using a polynomial regression test.

Results

Patients

The characteristics of the 30 studied patients are summarized in Table 1. All patients complained of chest pain at rest. Five out of 30 patients had diabetes. Fourteen patients were clinically diagnosed as having CSA.

Angiographic and Hemodynamic Findings

By administrating NTG orally, the patient heart rate tended to increase, however, the fall of blood pressure was not significant (Table 2). QCA demonstrated the significant increase of LD of the LAD from 1.98±0.46 to 2.51±0.34 mm, p<0.001. The mean LD_{NTG/Pre} was 1.32±0.30.

Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.8±9.3</td>
</tr>
<tr>
<td>M/F</td>
<td>21/9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td>Smoking habits (%)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>161.8±8.8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.7±9.8</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or n (%).

Table 2 Angiographic and Hemodynamic Findings

<table>
<thead>
<tr>
<th>Pre</th>
<th>NTG</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal diameter of LAD (mm)</td>
<td>1.98±0.46</td>
<td>2.51±0.34</td>
</tr>
<tr>
<td>LD_{NTG/Pre}</td>
<td>1.32±0.30</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systole (mmHg)</td>
<td>135.5±19.0</td>
<td>122.4±17.1</td>
</tr>
<tr>
<td>Diastole (mmHg)</td>
<td>75.1±14.1</td>
<td>69.6±13.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.7±8.9</td>
<td>70.2±8.5</td>
</tr>
</tbody>
</table>

NTG, nitroglycerin; LAD, left anterior descending artery; LD, luminal diameters.

Table 3 CFV Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>NTG</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFV (cm/s)</td>
<td>23.9±10.0</td>
<td>16.3±5.6</td>
<td>0.033</td>
</tr>
<tr>
<td>Hyperemia (cm/s)</td>
<td>53.3±19.1</td>
<td>54.9±19.0</td>
<td>0.941</td>
</tr>
<tr>
<td>CFVR</td>
<td>2.39±0.65</td>
<td>3.56±1.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFVR_{NTG/Pre}</td>
<td></td>
<td>1.57±0.56</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±SD.

CFV, coronary flow velocity; NTG, nitroglycerin; CFVR, CFV reserve; CFVR_{NTG/Pre}, CFV by nitroglycerin.

Fig 1. Changes of coronary flow indices demonstrated significant correlation with the luminal diameter changes after nitroglycerin administration. CFV_{NTG/Pre}, change of coronary flow velocity by nitroglycerin; CFVR_{NTG/Pre}, coronary flow velocity reserve by nitroglycerin.
**Doppler Echocardiographic Findings**

As shown in Table 3, baseline CFV significantly decreased from 23.9±10.0 to 16.3±5.6 cm/s following NTG administration, p=0.033. However, the hyperemic CFV did not change significantly from 53.3±19.1 to 54.9±19.0 cm/s. This resulted in the significant increase of CFVR from 2.39±0.65 to 3.56±1.12 (p<0.001) by NTG administration. The mean change of CFVR (CFVRNTG/Pre) was 1.57±0.56.

**CFVR in Patients With CSA**

In 14 patients with CSA, the mean CFVR at baseline tended to be lower than those in patients without CSA (2.19±0.69 vs 2.6±0.69, p=0.07). In 8 patients with CSA, the baseline CFVR was less than 2.0, a criterion for diagnosis of inducible ischemia. After the administration of NTG, CFVR was significantly higher in patients with CSA than those without (4.09±1.18 vs 2.97±0.69, p=0.004).

**Correlation Between LDNTG/Pre and CFVNTG/Pre, CFVRNTG/Pre**

The change of basal CFV (CFVNTG/Pre) by NTG administration inversely correlated with the LDNTG/Pre, an angiographic parameter of coronary tone with statistical significance (p<0.001, r²=0.539, Fig 1). Moreover, the CFVRNTG/Pre demonstrated the stronger correlation with LDNTG/Pre (p<0.001, r²=0.715).

**Discussion**

To the best of our knowledge, this is the first study that demonstrated the clinical potential of TTDE in assessing coronary vascular tone. Exactly how the coronary flow is altered during the changes of coronary tone or in the patients with coronary spasm has not been well addressed. This has been partially because of the invasive methods with Doppler guide-wire in measuring the coronary physiology during cardiac catheterization.10,11 Inserting the guide-wire into the coronary artery may cause spastic response, and requires pre-medication of nitrates. Morita et al also reported that measuring the diameter of the left main trunk using trans-esophageal echocardiography was also helpful to assess the coronary spasm.12 In the present study, we measured the CFV and CFVR using TTDE, which was more ‘non-invasive’ and feasible for the daily practice, compared with their methods.

In the present study, the basal CFV significantly decreased after NTG administration. The homodynamic change was considered to be minimum by giving NTG to the patients; therefore, the driving pressure of coronary circulation might have been relatively constant. As Anderson et al demonstrated, the CFV is inversely related to the lumen size that exists for the distal myocardial bed; the decrease in basal CFV indicated the dilation of the coronary artery.6 We observed this phenomenon both in echocardiographic and angiographic results in the present study. The basal CFV significantly decreased after NTG administration. Regarding the change of luminal area, the measured decrease of CFV of 26.3±22.7% seemed to be lower than expected. As we only measured one segment of the whole LAD, the variation in the dilation of coronary arteries by NTG may respond to the difference in the magnitude of velocity reduction and luminal increase.12 However, the present study significantly demonstrated the inverse relationship between flow parameters and LD in the patients, as previously shown in the animal study.5 As NTG has been thought to dilate the larger coronary vessels and mostly have an impact on the epicardial artery, the NTG-induced decrease of the baseline CFV suggested the significant dilatation of the epicardial arteries. While the baseline CFV varied, hyperemic CFV was relatively constant among the circumstances, before and after NTG administration. As the angiography demonstrated, the vessels were minimally diseased and might be able to dilate almost completely by flow-mediated dilatation during hyperemia. However, we assessed the coronary artery tone by obtaining the change of CFVR induced by NTG administration. The advantages of measuring CFVR over CFV include distinguishing organic stenoses from coronary spasm. CFVR following NTG administration represents epicardial disease and microcirculatory function. Moreover, in the present study, the change of CFVR showed a stronger correlation to the diameter change in the LAD induced by NTG administration than the change of basal CF did. Several explanations can be related to the results. First, not only the epicardial coronary artery but also the microvascular spasm might contribute to the myocardial ischemia as it does in patients with CSA.14 The spasm of perforators could be released by NTG administration, and this could affect the change in CFVR. In the present study, the mean CFVR tended to be lower in patients with CSA. However, there was no statistical significance in CFV before NTG administration comparing those with and without CSA. Further prospective analysis with larger numbers of patients is necessary. The second explanation is the elapsed time between measurements and NTG administration. Angiography was taken only once after NTG administration, which could be conducted at different times from the TTDE study in terms of elapsed time after NTG administration. If patients had coronary spasm before the study, this kind of difference in the elapsed time might impact on the results.

**Limitations**

The present study had several limitations. First, the number of the enrolled patients was relatively low. A prospective study with larger numbers of patients is warranted. Second, the factors influencing the CFV should be considered, such as aortic stenosis, left ventricular hypertrophy, hemodialysis or old myocardial infarction. However, in the present study, none of the patients had any of the diseases listed above; only 5 patients had diabetes. Third, all the patients had a history of chest pain, which might suggest some degree of microvascular impairment but were not able to perform stress-thallium-scntigraphy to exclude microvascular angina;15 however, the fact that all patients were found to have a normal CFVR value after NTG administration indicated minimum impairment of the microvasculature.

**Clinical Implications**

Despite those limitations, our methods have some clinical implications. Our methods can be performed repeatedly even for outward patients, thus avoiding invasive angiography to assess the implications of vasodilators for the patients complaining of angina at rest. This simple examination to measure the basal coronary artery tone can be also applied to assess the impact of diets, lifestyle and medications on coronary circulation. Moreover, there is a possible indication to diagnose CSA by using our method.
In conclusion, TTDE appeared to be useful for the non-invasive assessment of the coronary artery tone.

References


