Coexistence and prognostic impacts of epicardial and microvascular coronary dysfunctions in patients with chest pain and unobstructive coronary artery disease - Involvement of Rho-kinase activation-

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Topic(s):
Coronary Microcirculation and Collaterals

Citation:
Background: Although the importance of coronary functional abnormalities has been emerging, including epicardial coronary spasm (vasospastic angina, VSA) and coronary microvascular dysfunction (CMD), comprehensive evaluation of the abnormalities in the same population remains to be examined.

Purpose: We examined the significance of coronary functional abnormalities in a comprehensive manner for both epicardial and microvascular coronary arteries in patients with chest pain and unobstructive coronary artery disease (CAD) as well as their prognostic impacts.

Methods and results: We prospectively enrolled 187 consecutive patients with suspected angina and unobstructive coronary arteries (M/F 113/74, 63.2±12.3 [SD] yrs.). We performed acetylcholine (ACh) provocation tests for coronary spasm, followed by functional tests for coronary microvascular function, including coronary flow reserve (CFR) and index of microcirculation resistance (IMR) during hyperemic state induced by intravenous adenosine. Among the 187 patients, ACh test identified 128 patients with VSA (68%). There was no significant difference in age, sex, or prevalence of traditional coronary risk factors between the non-VSA and the VSA groups. The median IMR value was significantly higher in the VSA group than in the non-VSA group [17.5 (12.0, 25.3) vs. 14.7 (10.7, 17.8), P=0.02], whereas CFR values were comparable between the 2 groups [2.51 (1.72, 3.35) vs. 2.66 (1.85, 3.64), P=0.34]. During the median follow-up period of 893 days, major adverse cardiac events (MACE), including cardiac death, non-fatal myocardial infarction, and hospitalization due to unstable angina pectoris, occurred in 10 patients (5.3%). Multivariable analysis revealed that IMR correlated with the incidence of MACE [hazard ratio (HR) (95% confidence interval), 1.05 (1.02-1.09), P=0.002] and receiver-operating characteristics curve analysis identified IMR of 18.0 as the optimal cut-off value for the incidence of cardiac events. When we divided the patients into the following 4 groups according to the cut-off value of IMR (>18) and the presence or absence of VSA; G1, IMR?18 without VSA (n=45); G2, IMR?18 without VSA (n=14); G3, IMR?18 with VSA (n=67); and G4, IMR=18 with VSA (n=61), the Kaplan-Meier survival analysis showed a significantly worse prognosis in G4 compared with other 3 groups (HR [95%CI] 6.23 [1.21-118.46], P=0.002) (Figure 1). Importantly, intracoronary administration of fasudil, a Rho-kinase inhibitor, significantly ameliorated IMR in G4 (P<0.0001) (Figure 2A), and %changes in IMR in response to intracoronary fasudil were more evident in G4 compared with other 3 groups (P<0.0001) (Figure 2B).

Conclusions: These results provide the first evidence that in patients with chest pain and unobstructive CAD, epicardial coronary spasm and increased microvascular resistance are frequently coexisted with worse long-term prognosis, for which Rho-kinase activation may be involved.
Abstract: P4156
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Figure 1

Log rank test for overall comparison P=0.002

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Follow-up (days)</th>
</tr>
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<tbody>
<tr>
<td>G1</td>
<td>45 43 42 36 25 19 8 1</td>
</tr>
<tr>
<td>G2</td>
<td>13 13 13 12 12 10 3 1</td>
</tr>
<tr>
<td>G3</td>
<td>67 67 67 54 36 29 10 1</td>
</tr>
<tr>
<td>G4</td>
<td>60 59 58 50 40 28 14 2</td>
</tr>
</tbody>
</table>

Figure 2

A  

<table>
<thead>
<tr>
<th>ATP</th>
<th>Fasudil</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMR</td>
<td>P=0.61</td>
</tr>
<tr>
<td>G1</td>
<td>n=45</td>
</tr>
</tbody>
</table>

B  

%change in IMR

P<0.0001