Intramural Coronary Arterial Course Is Associated With Coronary Arterial Stenosis and Prognosis of Major Cardiac Events


Objective—The clinical significance of an intramural course (or bridging) of the coronary artery remains controversial. We investigated the relationship between intramural coronary arteries (ICAs) and coronary stenosis and prognosis of subjects with ICA.

Methods and Results—ICA and coronary stenosis were assessed by multidetector computed tomography coronary angiography. ICAs in the left anterior descending artery were studied, which were further classified as superficial (≤2 mm) or deep type (>2 mm). Coronary stenosis was classified as nonstenosis, insignificant stenosis (<50%), and significant stenosis (≥50%). A total of 261 subjects with ICA in left anterior descending artery were identified from 2318 enrolled subjects. Most of the ICAs (66.3%) were superficial. ICA was positively associated with insignificant stenosis, and the odds ratios were 2.055 (95% confidence interval, 1.405–3.007), 3.314 (1.818–6.039), and 1.640 (1.036–2.597) for overall, deep, and superficial ICA (all P<0.05), respectively. In the case of significant stenosis, ICA was negatively associated, and the odds ratios were 0.555 (0.416–0.739) and 0.413 (0.288–0.590) for overall and superficial ICA (both P<0.05), respectively, and 0.985 (0.611–1.588; P>0.05) for deep ICA type. The depth and location of ICA correlated with stenosis. The major cardiac events, including cardiovascular death, myocardial infarction, and revascularization, were recorded during 3-year follow-up. ICA predicted a lower incidence of major cardiac events, especially superficial type: the adjusted hazard ratios were 0.585 (0.375–0.911; P=0.018) and 0.535 (0.300–0.954; P=0.034) for total and superficial type, respectively.

Conclusion—ICA, especially deep type, is positively associated with insignificant stenosis proximal to ICA. Meanwhile, ICA, especially superficial type, is negatively associated with significant stenosis proximal to ICA and predicts a better prognosis not only in normal subjects but also in patients with coronary artery disease. (Arterioscler Thromb Vasc Biol. 2013;33:000-000.)

Key Words: coronary artery stenosis ■ intramural coronary artery ■ major cardiac event ■ multidetector computed tomography ■ myocardial bridging

Intramural coronary artery (ICA) is a congenital anatomic variant of main coronary arterial course, which exists almost exclusively in the left anterior descending coronary artery (LAD).1 Coronary arteries normally traverse in the subepicardial fat surrounded by fat all along the course. ICA is defined as a segment of a major coronary artery that runs through the myocardium beneath a muscle bridge, and subsequently, the artery coursing within the myocardium is called a tunneled or bridging artery. In the literature, myocardial bridging (MB) is also frequently used to refer to intramyocardial systolic compression of a segment of bridged coronary artery. The prevalence of ICA varies substantially in literature. The variation has been attributed mainly to the variation in definition, detection techniques, sample selection, and size. The true prevalence in different geographic areas and races is not available at present.

The clinical significance of an ICA remains controversial. Some follow-up studies support that this anatomic variant is a benign condition with good prognosis.2,3 Some other studies found that the LAD segments proximal to ICA exhibit eccentric4 and severe atherosclerotic lesions.1 The presence of an ICA and the characteristics of atherosclerotic evolution may signify the occurrence of myocardial infarction (MI).3 MB muscle index (the length of ICA multiplied by thickness) has been associated

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with a shift to coronary disease more proximally and the risk of MI. These authors suggested that ICA is not a benign condition but an anatomic risk factor of coronary artery disease (CAD).

Although ICA is considered as a common anatomic variant of coronary artery and the maximal prevalence has been reported to be 85% on autopsy, so far no convincing evidence is available to conclude that the variant is a benign or pathological condition or a risk factor for CAD. Previous prospective studies mainly focused on the significance of isolated ICA in the absence of atherosclerosis in the nonbridging arteries or with small sample sizes. The results were quite discordant; some showed that ICA is a benign anatomic variation, and others showed it as an anatomic risk factor for CAD.

Recently, multidetector computed tomography (MDCT) has been used noninvasively to examine coronary arteries directly, and surprisingly, the wide use of MDCT also increased the detection rate for ICA. MDCT could follow the whole journey of tunneled artery and define the precise location and depth of ICA. Compared with intravascular ultrasound, a sensitivity of 93% and specificity of 100% were reported in 30 patients with and in 21 patients without MB. This advancement in technique provides us an opportunity to perform a cross-sectional and longitudinal study to obtain the prevalence of ICA close to its clinical reality and relationship between ICA and coronary stenosis and to prospectively follow up the incidence of major cardiac events in subjects with ICA to establish the connection between the morphological characteristics of ICA and clinical implications.

**Materials and Methods**

**Study Population**

We enrolled 2318 consecutive adult subjects who underwent MDCT as a result of chest pain or chest distress for suspected CAD from a single center. The subjects were of Han nationality and lived in north China. All subjects provided written informed consent between April 2007 and June 2008 for participation in the study. Major exclusion criteria included chronic kidney disease, hypertrophic cardiomyopathy, valvular or congenital heart disease, and non-sinus rhythm. The study was approved by the ethics committee of Fuwai Hospital.

**ICA and Coronary Stenosis Evaluation**

The scanning protocol was as described previously. The schematic drawing for characterizing individual ICA is shown in Figure I in the online-only Data Supplement. The data were independently reviewed by 2 radiologists blinded to subjects’ identity and clinical characteristics. According to a previous study, the covering tissue, with the same threshold as myocardial tissue and thickness over 1.0 mm, was regarded as bridging. Because ICAs are almost exclusively located in LAD that features prominently in coronary circulation, only ICAs located in LAD were studied. ICAs located in left circumflex artery or right coronary arteries were excluded from this study, and ICAs in coronary branches were not recorded. ICA was further classified into 1 of the 2 types according to the depth of the tunneled segment beneath the epicardial surface, which is ≤2 mm in superficial type and >2 mm in deep type. The length of the ICA, regarded as the distance of the covering myocardial tissue between the entrance and the exit of the tunneled artery, was also determined in the vertical long-axis plane. Stenosis meant a significant reduction in the diameter of the arterial lumen at the site of the lesion compared with that in the segment distal to the lesion. According to coronary artery images, participants were divided into 3 groups: (1) nonstenosis group, which is defined as no coronary stenosis in the 3 major coronary arteries; (2) insignificant stenosis group, in which coronary artery stenosis exists but <50% in at least one of the major coronary arteries, except for ≥50% stenosis at any coronary arteries, and (3) significant stenosis group, in which coronary artery stenosis ≥50% exists in at least one of the major coronary arteries. Stenosis was classified as significant or insignificant after consensus was concluded by 2 experienced radiologists. The detailed methods for cardiac image analysis and risk factor determination are found in the online-only Data Supplement.

**Follow-Up Information**

Follow-up was carried out for a mean duration of 3 years. Experienced major cardiac events were recorded from hospital records, direct telephone contact, and computer records. Supplemental information was obtained from the patient’s family and their physicians. Review of all available medical records was performed by 2 physicians for in-hospital and later outcomes. The major cardiac events were defined as cardiac death, nonfatal MI, and revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Deaths were further classified as cardiac or noncardiac. In the present study, β-blockers and calcium channel blockers were used as the medical treatment for ICA because they prolong the diastolic time and decrease the contraction force above the coronary artery, whereas none of the patients underwent percutaneous transluminal coronary angioplasty or surgical treatment for isolated ICA. Revascularization was carried out as a result of significant stenosis in their coronary arteries.

**Statistical Analysis**

Quantitative variables were compared with the Student t test or 1-way ANOVA test. A χ² test was used to test for qualitative variables. The odds ratio (OR) was analyzed with 2×2 cross tabulation to evaluate the association between ICA and coronary arterial stenosis. The Pearson correlation test was used to assess the correlation among ICA types, the distance from the left coronary ostium to the first intramural segment, and coronary arterial stenosis. Cox proportional hazards models were used to examine the association between ICA and the incidence of major cardiac events after adjustment for conventional risk factors. SPSS 13.0 software (SPSS, Chicago, IL) was used.

**Results**

**Characteristics of the Participants**

A total of 2318 subjects who underwent MDCT angiography were enrolled. The clinical characteristics are shown in Table 1. The main complaints and signs of these patients were angina

![Figure](http://atvb.ahajournals.org/)
Wang et al. ICA and Coronary Arterial Stenosis, Prognosis

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(n=935), atypical chest pain (n=471), and chest distress with multiple risk factors (n=912). No significant differences were identified between subjects with and without ICA in LAD in conventional cardiovascular risk factors, including age, sex, smoking, alcohol use, blood pressure, body mass index, family history of stroke, and CAD, as well as comorbidity, including hypertension, diabetes mellitus, and hyperlipidemia. The typical examples of the 2 types of ICA and concomitant stenosis are shown in Figure II in the online-only Data Supplement.

A total of 261 (11.3%) subjects were found to have ICA in LAD, of which 183 (70.1%) were men and 155 (59.4%) had atherosclerotic plaque. Only 1 patient had plaques located in both the segments proximal to and distal to ICA. All other plaques were exclusively located in the segment proximal to ICA. No plaque was found in the segment beneath the myocardial bridge. Among these ICAs, 21 occurred in the proximal LAD, 233 in middle LAD, and 17 in distal LAD. The most frequently involved segment was the middle LAD in our study population (223 patients, 85.4%). Most ICAs were of superficial type (174/261, 66.7%; Table 2). The length of the tunneled artery was 17.89±9.22 mm in superficial type and 19.02±9.74 mm in deep type. No significant difference was found in the length of the tunneled artery between the 2 types of ICA (P=0.117).

ICA Was Positively Associated With Insignificant Stenosis But Negatively With Significant Stenosis in LAD

ICA was positively associated with insignificant LAD stenosis (OR, 2.055; 95% confidence interval [CI], 1.405–3.007; P<0.001) but negatively associated with significant LAD stenosis (OR, 0.555; 95% CI, 0.416–0.739; P<0.001). A total of 261 (11.3%) subjects were found to have ICA in LAD, of which 183 (70.1%) were men and 155 (59.4%) had atherosclerotic plaque. Only 1 patient had plaques located in both the segments proximal to and distal to ICA. All other plaques were exclusively located in the segment proximal to ICA. No plaque was found in the segment beneath the myocardial bridge. Among these ICAs, 21 occurred in the proximal LAD, 233 in middle LAD, and 17 in distal LAD. The most frequently involved segment was the middle LAD in our study population (223 patients, 85.4%). Most ICAs were of superficial type (174/261, 66.7%; Table 2). The length of the tunneled artery was 17.89±9.22 mm in superficial type and 19.02±9.74 mm in deep type. No significant difference was found in the length of the tunneled artery between the 2 types of ICA (P=0.117).

Table 1. Characteristics of Enrolled Subjects Grouped by ICA

<table>
<thead>
<tr>
<th>ICA(−)</th>
<th>ICA(+)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2057</td>
<td>261</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.3±10.0</td>
<td>55.8±9.8</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>124.7±13.4</td>
<td>124.4±14.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.2±9.6</td>
<td>77.9±10.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7±3.4</td>
<td>25.7±3.1</td>
</tr>
<tr>
<td>Men</td>
<td>72.2%</td>
<td>69.7%</td>
</tr>
<tr>
<td>Smoke</td>
<td>54.2%</td>
<td>51.7%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>55.2%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>72.6%</td>
<td>72.0%</td>
</tr>
<tr>
<td>DM</td>
<td>33.4%</td>
<td>31.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.9%</td>
<td>55.9%</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; ICA, intramural coronary arteries; and SBP, systolic blood pressure. P values are from Student t test or χ² test.

The Depth of ICA and the Distance From the Left Coronary Ostium to the First Segment of ICA Were Positively Associated With Stenosis in LAD

The Pearson correlation coefficient was 0.189 for the relationship between the type (superficial or deep) and stenosis in LAD (P<0.01). The distance from the left coronary ostium to the first segment of ICA was positively associated with stenosis in LAD (OR, 2.055; 95% CI, 1.405–3.007; P<0.001) but negatively associated with significant LAD stenosis (OR, 0.555; 95% CI, 0.416–0.739; P<0.001). In the case of ICA type, both deep and superficial types were positively associated with insignificant LAD stenosis (OR, 3.314; 95% CI, 1.818–6.039; P<0.001 and OR, 1.640; 95% CI, 1.036–2.597; P<0.05), respectively. In contrast, the superficial type was negatively associated with significant LAD stenosis (OR, 0.413; 95% CI, 0.288–0.590; P<0.001), but the deep type was not (OR, 0.985; 95% CI, 0.611–1.588; Table 3). The coronary artery stenosis in LAD was significantly less frequently identified in subjects with ICA than in subjects without ICA (72.1% versus 84.7%; OR, 0.477; 95% CI, 0.326–0.699; P<0.001).

Table 2. Subjects Grouped by ICA Status and Coronary Arterial Stenosis, and the Number of Subjects With Major Cardiac Events in the Corresponding Groups

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Location of Stenosis</th>
<th>MI Status</th>
<th>ICA(−)</th>
<th>Total</th>
<th>Superficial</th>
<th>Deep</th>
<th>Proximal</th>
<th>Middle</th>
<th>Distal</th>
<th>Type</th>
<th>Location in LAD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5/730‡</td>
<td>0/107</td>
<td>0/79</td>
<td>0/28</td>
<td>0/13</td>
<td>0/88</td>
<td>0/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% stenosis Total</td>
<td>1/126</td>
<td>0/30</td>
<td>0/19</td>
<td>0/11</td>
<td>0/2</td>
<td>0/26</td>
<td>0/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stenosis in LAD</td>
<td>1/103</td>
<td>0/27</td>
<td>0/16</td>
<td>0/11</td>
<td>0/2</td>
<td>0/24</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stenosis not in LAD</td>
<td>0/23</td>
<td>0/3</td>
<td>0/3</td>
<td>0/0</td>
<td>0/0</td>
<td>0/2</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50% stenosis Total</td>
<td>278/1201</td>
<td>21/124</td>
<td>12/75</td>
<td>9/49</td>
<td>0/6</td>
<td>20/109</td>
<td>1/9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stenosis in LAD</td>
<td>252/1017</td>
<td>15/84</td>
<td>8/47</td>
<td>7/37</td>
<td>0/3</td>
<td>14/73</td>
<td>1/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI(−)*</td>
<td>166/655</td>
<td>10/56</td>
<td>6/27</td>
<td>4/29</td>
<td>0/2</td>
<td>10/51</td>
<td>0/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI(+)</td>
<td>86/362</td>
<td>5/28</td>
<td>2/20</td>
<td>3/8</td>
<td>0/1</td>
<td>4/22</td>
<td>1/5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major stenosis not in LAD</td>
<td>26/184</td>
<td>6/40</td>
<td>4/28</td>
<td>2/12</td>
<td>0/3</td>
<td>6/36</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI(−)</td>
<td>14/103</td>
<td>4/27</td>
<td>2/18</td>
<td>2/9</td>
<td>0/2</td>
<td>4/25</td>
<td>0/0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI(+)</td>
<td>12/81</td>
<td>2/13</td>
<td>2/10</td>
<td>0/3</td>
<td>0/1</td>
<td>2/11</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>284/2057</td>
<td>21/261</td>
<td>12/173</td>
<td>9/88</td>
<td>0/21</td>
<td>20/223</td>
<td>1/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICA indicates intramural coronary arteries; LAD, left anterior descending coronary artery; and MI, myocardial infarction.

*ICA(+) indicates subjects with ICA, ICA(−) indicates subjects without ICA, MI(−) indicates subjects without MI, and MI(+) indicates subjects with MI.†Location in LAD means the location of ICA in proximal, middle, or distal segment of LAD.

‡Number of subjects with major cardiac event in this group/the number of subjects enrolled in this group.
ICAs, Especially Superficial Type, Was Negatively Associated With Incidence of Major Cardiac Events Not Only in Normal Subjects But Also in CAD Patients

During the 3-year follow-up, a total of 14 subjects died of noncardiac disease and 305 experienced major cardiac events. Ten subjects died of acute MI, 34 had an MI, 230 underwent drug-eluting stents, and 31 underwent coronary artery bypass grafting surgery. The details of the follow-up are shown in Table 2. In the nonstenosis group, no major cardiac events occurred in subjects with ICA, whereas 0.7% of subjects without ICA suffered from major cardiac events. In subjects with insignificant stenosis, no major cardiac events were found in subjects with ICA, whereas it was 0.8% in subjects without ICA. In patients with significant coronary stenosis, the incidence of major cardiac events was 17.8% in subjects with ICA and 24.8% in subjects without ICA. In patients with their stenosis located in non-MB arteries, no significant difference was found in the incidence of major cardiac events between patients with (15.0%) and without (14.1%) ICA. Overall, ICA predicted a lower incidence of major cardiac events during a 3-year follow-up, with a relative risk of 0.569 (95% CI, 0.365–0.886; P=0.013); the relative risk remained significant after adjustment for age, sex, body mass index, and other conventional risk factors (0.585; 95% CI, 0.375–0.911; P=0.018).

The incidence of major cardiac events was 6.9% in superficial type and 10.2% in deep type. The distance from the left coronary ostium to the first MB segment also influenced the incidence. No cardiac events were noted in those who had ICA located in the proximal segment of LAD, whereas 8.8% of the patients with ICA located in mid-distal LAD segments suffered major cardiac events. For superficial type, the relative risk was 0.490 (95% CI, 0.275–0.874; P=0.016) and remained 0.535 (95% CI, 0.300–0.954; P=0.034) after adjustment for conventional risk factors. For deep type, the adjusted relative risk was 0.667 (95% CI, 0.343–1.296; P=0.232; Figure).

ICAs, Especially Superficial Type, Was Negatively Associated With Significant Stenosis in Nonbridging Coronary Arteries

In patients with significant stenosis in their nonbridging coronary arteries, ICA was marginally associated with stenosis (OR, 1.469; 95% CI, 0.988–2.186; P=0.056). This kind of positive association was also identified in patients with their ICA located in mid LAD (OR, 1.623; 95% CI, 1.066–2.470; P<0.05). The association of ICA with significant stenosis in nonbridging arteries was found in both deep (OR, 1.700; 95% CI, 0.848–3.408) and superficial types (OR, 1.389; 95% CI, 0.877–2.199), but did not reach statistical significance (Table 5).

Discussion

Our major findings were that ICA, especially deep type, was positively associated with insignificant stenosis proximal to ICA. ICA in the middle LAD is positively associated with significant stenosis in non-MB arteries. Meanwhile, ICA, especially superficial type, was negatively associated with significant stenosis proximal to ICA and predicted a better prognosis not only in normal subjects but also in patients with CAD. So ICA may play a Janus-faced role in the development of atherosclerosis. To our knowledge, this is the first clinical investigation clearly demonstrating that ICA, especially superficial type, is a benign anatomic variant of coronary artery both in normal controls and in CAD patients.

The present study demonstrated that ICA in LAD was a relative common anatomic variation (11.3%) in this group of Chinese population. More than half of the ICA subjects had atherosclerotic plaque. The prevalence of ICA in our study was in concordance with some previous reports by MDCT and higher than that in angiographic series. The frequency of superficial type was 66.3% in our study, which was similar to that in other populations (71.1% in a Korean population).16

In patients with significant stenosis in coronary arteries, ICA could induce angina by promoting atherosclerosis in the segment proximal to ICA. However, the majority of such patients exhibit no considerable atherosclerosis in the LAD; their symptoms could be caused by the hemodynamic alterations brought about by MB contraction. ICA may predispose to myocardial ischemia in systole and diastole in the absence

Table 4. The Relationship Between ICA Location in LAD and ICA Depth

<table>
<thead>
<tr>
<th>Location in LAD</th>
<th>Proximal LAD</th>
<th>Middle LAD</th>
<th>Distal LAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial, n (%)</td>
<td>7 (33.3)</td>
<td>153 (68.6)</td>
<td>13 (76.5)</td>
</tr>
<tr>
<td>Deep, n (%)</td>
<td>14 (66.7)</td>
<td>70 (31.4)</td>
<td>4 (23.6)</td>
</tr>
<tr>
<td>Total, n</td>
<td>21</td>
<td>223</td>
<td>17</td>
</tr>
</tbody>
</table>

In subjects with ICA in LAD, the location correlated with its depth. The Pearson correlation coefficient was −0.184 (P=0.003). ICA indicates intramural coronary arteries; and LAD, left anterior descending coronary artery.

Table 3. The Relationship Between ICA and LAD Stenosis

<table>
<thead>
<tr>
<th>Location in LAD</th>
<th>Total</th>
<th>Superficial</th>
<th>Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>&lt;50% stenosis</td>
<td>2.055 (1.405–3.007)‡</td>
<td>1.640 (1.036–2.597)*</td>
<td>3.314 (1.818–6.039)‡</td>
</tr>
<tr>
<td>&gt;50% stenosis</td>
<td>0.555 (0.416–0.739)‡</td>
<td>0.413 (0.288–0.590)‡</td>
<td>0.985 (0.611–1.588)</td>
</tr>
</tbody>
</table>

The relationship between ICA and stenosis in LAD was expressed as the odds ratio (95% CI) (ICA[+] or different types of ICA vs ICA[−]), and no stenosis was used as reference. ICA indicates intramural coronary arteries; and LAD, left anterior descending coronary artery.

*P<0.05, ‡P<0.001.
of atheroma because of the degree of systolic compression. Vasoplastic coronary constriction, as an alternative mechanism, may be associated with ICA. In our population with chest pain or chest distress, 41.6% (856/2057) showed normal or insignificant stenosis of coronary arteries in the group without ICA, whereas it was 52.5% (137/261) in the group with ICA; the OR was 1.55 (95% CI, 1.197–2.007; P < 0.01). We speculated that the weakly resumptive blood flow in the diastolic phase could not get normal circulation because of the stronger retrograde blood flow, which means that ICA may play a role in chest pain or chest distress.

The degree of systolic compression of MB correlates well with the depth of ICA.17 In our study, the superficial type ICA was positively associated with significant stenosis and negatively associated with significant stenosis proximal to ICA. Traditionally, the area under the MB has been considered to be spared from atherosclerosis, and the area just proximal to MB causes the compression of the tunneled segment during systole.5,22 Indeed, areas of low mean shear stress and areas where blood flow departs from a laminar unidirectional pattern, including areas of oscillatory flow and flow reversal, seem to be prone to the development of atherosclerotic plaques, preceded by the development of endothelial dysfunction.19,23–25 In the coronary artery with superficial ICA, the forward blood flow is much more than the retrograde blood flow from the MB squeezing at systole. When the atherosclerotic plaque in the segments proximal to ICA developed to medium size, the rapidly resumptive blood flow in diastolic phase would inhibit the development of plaque.

It has been known that deep type ICA causes relative severe systolic narrowing and coronary vasospasm, then a higher risk for local wall stress, flow and shear stress, and stronger predisposition to proximal atherosclerosis. The severe systolic compression would result in an increase in pressure gradients in the segments proximal to ICA, which ultimately enhances the progression of atherosclerosis in the proximal LAD. Correspondingly, the retrograde blood flow from the MB squeezing at systole in segments proximal to deep type ICA would be more than that in segments proximal to superficial type ICA. When the resumptive blood flow in diastolic phase could not get normal circulation because of the stronger retrograde blood flow, the new round of systole would come again. We speculated that the weakly resumptive blood flow in the diastolic phase could not inhibit the development of plaque. So we observed that deep type ICA was more strongly associated with significant stenosis proximal to ICA than showed no association with significant stenosis proximal to ICA.

MB causes the compression of the tunneled segment during systole, enhancing the lymph drainage of the vessel wall that is important for the prevention of lipid accumulation and disease development. Lujinović et al26 reported that there are no other histopathologic changes that would indicate an atherosclerotic process besides insignificant diffuse intima in ICA. So rather than causing proximal atherosclerosis, muscle bridging might have a more important role in the protection of the tunneled segment and distal segment from atherosclerosis. In concordance with the results from our study, the incidence of major cardiac event was less in ICA carriers than in non-ICA carriers in a mean follow-up of 3 years.

We also found that ICA was marginally associated with stenosis located in nonbridging coronary arteries, and a 1.4-fold risk was found in superficial type although it did not reach statistical significance. There was statistically significant association of ICA located in mid LAD (which was found to be the most common type) with significant stenosis in nonbridging coronary arteries. This is the first study that demonstrated ICA was associated with stenosis in nonbridging coronary arteries. We speculated that ICA may cause regional hemodynamic change not only in bridged arteries but also in nonbridging coronary arteries, resulting in predisposition to atherosclerosis in these nonbridging arteries. Further studies in other populations are needed to confirm the association.

Table 5. The Relationship Between ICA and Coronary Arterial Stenosis

<table>
<thead>
<tr>
<th>Stenosis Location</th>
<th>ICA(+), Total</th>
<th>ICA Type</th>
<th>MB Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50% stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.609 (1.030–2.515)*</td>
<td>0.772 (0.325–1.834)</td>
<td>2.276 (1.105–4.688)*</td>
</tr>
<tr>
<td>Major stenosis in LAD</td>
<td>1.772 (1.108–2.833)*</td>
<td>1.376 (0.806–2.349)</td>
<td>2.784 (1.345–5.762)</td>
</tr>
<tr>
<td>Major stenosis not in LAD</td>
<td>0.882 (0.260–2.986)</td>
<td>1.190 (0.350–4.052)</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;50% stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.698 (0.531–0.918)†</td>
<td>0.570 (0.410–0.791)†</td>
<td>1.064 (0.663–1.708)</td>
</tr>
<tr>
<td>Major stenosis in LAD</td>
<td>0.558 (0.413–0.754)†</td>
<td>0.422 (0.291–0.612)†</td>
<td>0.949 (0.575–1.564)</td>
</tr>
<tr>
<td>Major stenosis not in LAD</td>
<td>1.469 (0.988–2.186)</td>
<td>1.389 (0.877–2.199)</td>
<td>1.700 (0.848–3.408)</td>
</tr>
</tbody>
</table>

The relationship between ICA and coronary stenosis was expressed as the odds ratio (95% CI) ([ICA+] or different types of ICA vs ICA[−]), and no stenosis was used as reference. CI indicates confidence interval; ICA, intramural coronary arteries; LAD, left anterior descending coronary artery; MB, myocardial bridging; and NA, not applicable. *P < 0.05, †P < 0.01, ‡P < 0.001.
There are some limitations to this study. The first is that all subjects were recruited from a single center, thus the study sample may not be representative of the whole population. Also, the subjects were suspected to have CAD and so were not representative of the general population. However, the condition like ICA does not allow randomization. The present methods could not be used extensively in asymptomatic population as a result of the dose of radiation or the potentially life-threatening consequences. The frequency of ICA in our population referred for chest pain and chest distress would be higher than that in a group of asymptomatic patients. Second, MDCT techniques used in our study, including multiplanar reformation, could not provide dynamic information of the ICA during the cardiac cycle. Data on systolic compression of the tunneled artery were not included. Third, therapeutic approaches could definitely change the incidence of major cardiac events and prognosis. We could not get the therapeutic information on each participant in detail to adjust for confounding in the Cox regression analysis. We checked major conventional cardiovascular risk factors, and there were no significant difference between subjects with and without ICA. In addition, all patients who were diagnosed with CAD followed the standard care in our hospital, including β-blockers, angiotensin-converting enzyme inhibitors, statins, and aspirin unless contradicted, suggesting that these factors did not contribute much to our results.

In conclusion, we suggest that (1) ICA, especially deep type, is positively associated with insignificant stenosis in the segment proximal to ICA. (2) ICA in mid LAD is positively associated with significant stenosis in nonbridging arteries. (3) ICA, especially superficial ICA, is negatively associated with significant stenosis proximal to ICA and predicts a better prognosis not only in normal subjects but also in CAD patients. So ICA may play a Janus-faced role in the development of atherosclerosis.

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Disclosures
None.

References
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Supplement Material

Methods

Cardiac image analysis

Briefly, CT examination of coronary arteries was performed with a 64-row LightSpeed VCT scanner (GE Healthcare, Milwaukee, WI, USA). Patients with a prescanning heart rate of 70 beats per minute or higher received orally 25–50 mg of metoprolol (Selokeen; AstraZeneca, Zoetermeer, the Netherlands) 1 hour prior to the CT examination. A double-head power injector (Stellant D, Medrad, Pittsburgh, PA, USA) was used to inject contrast media through a 20-gauge trocar in an antecubital vein. Test bolus (10 ml contrast agent following 20 ml saline flush) with injection rate of 5 ml/sec was used to determine the timing of scan delay and image acquisition time.

In the retrospective ECG-gated scans, acquisition parameters include a detector collimation of 64×0.625 mm, a pitch of 0.16 and 0.22 depending upon the heart rate of the subject, gantry rotation speed of 350 ms per rotation, tube voltage of 120 kV, ECG modulated tube currents of 550 mA during 40–80% of an R-R interval for obtaining diagnostic image quality and of 200 mA during the other phase of an R-R interval, feed/rotation of 40 mm, a field of view of 250 mm within a transverse slice.

Images were reconstructed first from data acquired with a 75% R-R interval. When significant artifacts are observed in coronary artery images, images were reconstructed subsequently from data collected, respectively, at 40%, 50%, 60%, 70%, and 80% R-R intervals from which R-R interval images with better quality were selected.
The images were transferred to a stand-alone workstation (Deep Blue, ADW4.3, GE Healthcare, Milwaukee, WI, USA) for further analysis. The data were independently reviewed by two radiologists blinded to subjects’ identity and clinical characteristics. ICA was diagnosed when an intramural segment of a coronary artery was visualized on axial and multiplanar reconstruction images, usually by one of the two conditions or both: (1) the presence of the “step-down and step-up” appearance, a significant tortuosity of the segment beneath the muscle bridge at the entrance (step-down) and the exit (step-up) sites; and (2) soft tissues density covering the coronary artery, which had the same contrast enhancement as myocardial tissue.

Risk factors determination

Demographic and clinical characteristics were recorded, including age, sex, blood pressure, conventional cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking status. The disease was defined as a diagnosis or treatment for the corresponding disease. Hypertension was diagnosed with a mean of 3 independent measures of blood pressure >140/90 mmHg; DM, diabetes mellitus, was diagnosed when the subject had a fasting glucose >7.8 mmol/L, or >11.1mmol/L at 2 hours after oral glucose challenge, or both, hyperlipidemia was diagnosed with an elevation of one of more of the followings: >5.98 mmol/L for total cholesterol, >1.76 mmol/L for triglycerides, or >3.4 mmol/L for LDL-cholesterol. Age, systolic (SBP) and diastolic (DBP) blood pressure, and body mass index (BMI) are given as mean±SD, and other values as percentage.
Figures

Figure I. The schematic drawing showed the system for analyzing the individual ICA.
**Figure II, Visualization of ICA by MDCT.** Curved multiplanar reconstruction images showed the tunneled segment of the left anterior descending artery overlaid with myocardium (arrows) and calcified or soft plaque in the segment proximal to ICA (head of arrow). Superficial type was shown in panel A and B (A with an insignificant stenosis (<50%), and B with a significant stenosis (≥50%)), deep type was shown in C and D (C with an insignificant stenosis and D with an insignificant stenosis), and no stenosis was observed in the segment distal to ICA in the four samples. The axial images for them were shown in A1, B1, C1, and D1 respectively.