The Impact of Coronary Artery Disease on the Coronary Vasomotor Response to Nonionic Contrast Media

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Background—Coronary artery disease (CAD) alters the vasomotor response to a variety of pharmacological agents. We tested the hypothesis that CAD also has an impact on the coronary vasomotor response to radiologic contrast media.

Methods and Results—We performed quantitative coronary angiography in 42 patients without angiographic evidence of CAD and 38 patients with CAD in the left coronary artery. Angiographically smooth coronary segments (n=235) were analyzed for changes on luminal diameters and coronary venous oxygen saturation in response to 3 media: the nonionic dimer iodixanol, the nonionic monomer iopromide, and the ionic agent ioxaglate. In subjects without CAD, we assessed the effects of intracoronary administration of the nitric oxide synthase inhibitor N\textsuperscript{G}-monomethyl-L-arginine and of the cyclooxygenase inhibitor indomethacin on such changes. Iodixanol induced coronary vasodilation in subjects without CAD (8.8±8.6%, P<0.001). Patients with CAD exhibited no significant diameter changes in segments ≥20 mm apart from a stenosis (4.7±9.4%, P=NS) and significant constriction in segments <20 mm from a stenosis (−3.8±4.6%, P<0.05). Similar results were obtained with iopromide, but no changes were found with ioxaglate. All contrast media induced transient (<35 seconds) increases in coronary venous oxygen saturation in all subjects. Indomethacin, but not N\textsuperscript{G}-monomethyl-L-arginine, blunted the vasodilating effect of iodixanol and iopromide (by 80% and 76%, respectively; P<0.001).

Conclusions—Nonionic contrast media induce a vasodilatory response in normal vessels not by a mechanism involving increased flow or endothelial nitric oxide synthesis, but rather by depending on preserved vascular cyclooxygenase activity. CAD changes normal epicardial vasodilatory response into vasoconstriction. (Circulation. 2000;101:491-497.)

Key Words: contrast media ◆ coronary disease ◆ vasoconstriction ◆ vasodilation ◆ endothelium-derived factors

A change in vessel tone is a well known side effect of angiographic contrast media. Most often a vasoconstriction is seen, but sometimes a vasospasm occurs. Vasoconstriction has been attributed to hyperosmolality, chemotoxicity, ion content of the medium, and flow-mediated changes in vascular tone.1-5 Coronary vasoconstriction has been observed after injection of both ionic and nonionic contrast agents.6-8 In experimental studies on isolated arteries, vasoconstriction has been related to chemotoxicity and/or depolarization of smooth muscle cells.5,10 It is conceivable that coronary artery disease (CAD) might interfere with the vasomotor reaction of coronary arteries to contrast agents. In fact, low concentrations of diatrizoate, a high-osmolar ionic agent, induced vasoconstriction in normal rabbit aortas but vasoconstriction in atherosclerotic aortas.11 Jost et al12 have shown no uniform vasomotor responses to diatrizoate in stenosed coronary segments.

We tested the hypothesis that CAD is associated with an altered vasomotor response to contrast media. Our objectives were to evaluate: (1) the effect of 3 iodinated contrast media: iodixanol (nonionic, dimeric), iopromide (nonionic, monomeric), and ioxaglate (ionic) on the dimensions of angiographically normal epicardial coronary segments in patients with normal coronary arteries and patients with CAD; (2) the relationship between the effects of contrast media on epicardial coronary artery dimensions and changes in coronary blood flow; and (3) the role of endothelial nitric oxide and cyclooxygenase in the vasomotor effect of contrast agents.

Methods

Patient Selection

We enrolled 92 patients undergoing diagnostic cardiac catheterization and coronary angiography for chest pain syndrome. Forty-seven patients had entirely smooth coronary arteriograms and 45 had significant CAD, as defined by the presence of a stenosis ≥50% in at least 1 segment of the left coronary artery. Patients with unstable angina, previous myocardial infarction, left ventricular hypertrophy or dysfunction, valvular disease, or renal insufficiency, as well as patients with isolated right CAD, occlusive or subocclusive coronary
stenoses, or diffuse disease were excluded from the study. All medications were discontinued 48 hours before the study with the exception of low-dose (50 mg/d) aspirin. The study was approved by the Institutional Review Committee at Pisa University. Informed consent was obtained from each patient.

Protocol A
This protocol was designed to evaluate the effects of contrast media on epicardial coronary artery dimensions and on coronary venous oxygen saturation (Figure 1A). Patients were randomly assigned to the iso-osmolar, nonionic, dimeric agent iodixanol (Visipaque 320, Nycomed Imaging AS; osmolality: 290 mOsm/kg)(n = 28); the low-osmolar, nonionic, monomeric agent iopromide (Ultravist 370, Schering AG; osmolality: 770 mOsm/kg)(n = 14); or the low-osmolar, ionic agent ioxaglate (Hexabrix 320, Guerbet; osmolality: 608 mOsm/kg)(n = 18). No significant differences in the prevalence of the main cardiovascular risk factors were observed among the different contrast groups (Table 1). Total cholesterol showed a trend, within each contrast agent comparison, to be higher in the CAD group and was significantly higher in the entire CAD group of this protocol compared with the no CAD group (200 ± 37 versus 178 ± 46 mg/dl, P < 0.05).

The first quantitative coronary angiogram (QCA-0) was performed in the 30° right anterior oblique projection and served as reference. At 50-second intervals, subsequent diagnostic or QCA angiograms were performed in standard conditions and used for quantitative coronary angiography. INDO indicates intracoronary indomethacin 3 μmol/min; L-NMMA, intracoronary Nω-monomethyl-l-arginine 50 μmol/min; NTG, intracoronary nitroglycerin 200 μg; O₂ sat., coronary venous blood oxygen saturation measurement; RAO 30°, right anterior oblique 30° projection; and SALINE, saline intracoronary infusion at 1 mL/min.

Protocol B
This protocol, summarized in Figure 1B, was designed to examine the role of endothelial nitric oxide and vascular cyclooxygenase in the changes induced by nonionic agents on epicardial coronary
dimensions. Twenty patients with angiographically normal coronary arteries were enrolled according to the same inclusion/exclusion criteria described above. Sixty-nine segments (all segments A) were analyzed (Table 2). After completion of diagnostic coronary arteriography, intracoronary infusion of isotonic saline at 1 mL/min was started. Two quantitative left coronary angiograms, QCA-0 and QCA-1, were performed as described in protocol A. Thereafter, the arginine analogue N\textsuperscript{\textmu}N-monomethyl-L-arginine, a competitive inhibitor, were infused into the left coronary artery at 50 μmol/min and 3 μmol/min, respectively, for the rest of the protocol (infusion rate 1 mL/min). QCA-0 and QCA-1 were then repeated. A final quantitative angiogram was performed after intracoronary administration of 200 μg nitroglycerin (QCA-3). Differences in epicardial coronary dimensions between QCA-0 and QCA-1 were assumed to be contrast-induced. Patients were randomly assigned to ioxaglate or iopromide. Within each contrast group, indomethacin or N\textsuperscript{\textmu}N-monomethyl-L-arginine were used in an alternate fashion.

**Protocol C**

This protocol was designed to evaluate the time course of nonionic contrast-induced changes in coronary luminal diameters. Five patients (2 female, 3 male, age 60±11 years) with angiographically normal coronary arteries and 7 patients (2 female, 5 male, age 64±13 years) with left CAD were enrolled according to the same inclusion/exclusion criteria as above. After completion of the diagnostic coronary angiography, additional heparin (2500 U) was administered and a 2.6F, 40-MHz SCIMED intravascular ultrasound catheter was introduced over a 0.014-inch guidewire and positioned in an angiographically normal left coronary segment. In patients with CAD, only segments >5 mm and <20 mm apart from a significant stenosis were evaluated. Luminal cross-sectional area, defined as the integrated area central to the intimal leading-edge echo, was measured in basal conditions and at various times after intracoronary injection of 8 mL ioxaglate. One or 2 segments were evaluated in each patient.

**Quantitative Angiography**

Study angiograms were examined by 2 investigators, and angiographically smooth coronary segments not overlapping with other branches and running parallel to the image plane were selected by a consensus decision before the analysis. The analysis of each angiogram was performed on 2 end-diastolic frames of different cardiac cycles, and the results were averaged. Digitally recorded frames were then analyzed with a software allowing an automated edge-detection technique.\textsuperscript{12} One-centimeter segments of the coronary artery were selected for measurements. Anatomic landmarks were used to reproduce the regions of interest in different angiograms. The angiographic catheter in the field of view served as a scaling device and this, together with correction for pincushion distortion, allowed the diameters to be measured as absolute values (in millimeters). Analyzed segments were classified according to the presence of, and distance from, a ≥50% diameter stenosis in another coronary segment: (1) segments A: angiographically normal segments without stenoses in other coronary segments; (2) segments B: angiographically normal segments located ≥20 mm from the closest stenosis; and (3) segments C: angiographically normal segments located >5 mm and <20 mm from the closest stenosis. Differences between QCA-1 and QCA-2 provided an evaluation of both spontaneous short-term variability of coronary segment dimensions and the intraobserver variability associated with repeated measurements. Single-segment diameter changes were considered significant with a >95% probability if they were ≥1 mean ±1.96SD of the difference between QCA-1 and QCA-2. The mean change in coronary dimensions between QCA-1 and QCA-2 was 0.050±0.039 mm (n=166). Thus, a single segment change was considered significant if ≥0.13 mm.

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**TABLE 1. Clinical and Angiographic Characteristics of the Study Population (Protocol A)**

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol</th>
<th>Iopromide</th>
<th>Ioxaglate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>10</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±13</td>
<td>61±11</td>
<td>64±8</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>60</td>
<td>72</td>
<td>60</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td>173±44</td>
<td>196±36</td>
<td>183±39</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>38±16</td>
<td>42±11</td>
<td>35±5</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>127±90</td>
<td>143±75</td>
<td>144±71</td>
</tr>
<tr>
<td>Current/recent smoker, %</td>
<td>30</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>10</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>1-Vessel disease, n</td>
<td>...</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>2-Vessel disease, n</td>
<td>...</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>3-Vessel disease, n</td>
<td>...</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>Analyzed segments, n</td>
<td>29</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>O\textsubscript{2} sat, n</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Iodixanol indicates patients subjected to coronary venous blood oxygen saturation measurement. No significant differences in comparisons of clinical characteristics in patients with CAD or noCAD within each group were found.

**TABLE 2. Characteristics of the Study Population (Protocol B)**

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol</th>
<th>Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
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<td>6</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±11</td>
<td>63±4</td>
</tr>
<tr>
<td>Male sex, %</td>
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<td>3</td>
</tr>
<tr>
<td>Analyzed segments*, n</td>
<td>18</td>
<td>19</td>
</tr>
</tbody>
</table>

I-NMMA indicates N\textsuperscript{\textmu}N-monomethyl-L-arginine; Indo, indomethacin.

*All segments A (for definition, see Methods). No significant differences existed among groups.
Statistical Analysis

Data were expressed as mean±SD. The significance of changes with respect to baseline values was tested by ANOVA for repeated measures followed by the Bonferroni correction. The significance of differences among groups was tested by the ANOVA followed by the Newman-Keuls test. Comparisons between groups of CAD versus non-CAD patients were analyzed by unpaired Student’s t test. For dichotomous variables χ² analysis was used (unless the expected value for a cell was <5, in which case Fisher’s exact test was performed). Statistical significance was assumed if a null hypothesis (2-tailed) could be rejected at P<0.05.13

Results

Effect of Contrast Media on Coronary Artery Dimensions

The average changes in the luminal diameters of segments A, B, and C after iodixanol injection are illustrated in Figure 2A. Iodixanol induced significant dilation of segments A (8.8±8.6%, P<0.001), no significant changes of segments B (4.7±9.4%, P=NS), and a slight but significant constriction of segments C (−3.8±4.6%, P<0.05). The average increase in luminal diameter of segments A was significantly greater than that of segments B and C, and the increase in luminal diameter of segments B was significantly greater than that of segments C (P<0.05 in all cases). A vasodilatory capacity was preserved in all groups because nitroglycerin resulted in similar dilation of segments A, B, and C (Figure 2A).

Iopromide induced changes in epicardial coronary dimensions similar to iodixanol, ie, significant dilation of segments A (P<0.001), no significant changes in segments B, and significant constriction of segments C (P<0.05)(Figure 2B). Ioxaglate injection did not induce significant luminal diameter changes in any segment group (Figure 2C).

The percent of segments reacting with a significant (≥0.13 mm) dilation after iodixanol or iopromide injection showed a highly significant decreasing trend from segments A to segments C (from 69% to 7%, P<0.001 for trend after iodixanol, and from 67% to 6%, P<0.001 for trend after iopromide), whereas a specular trend toward increase was observed for the constrictive reactions (from 0% to 32%, P<0.01 for trend after iodixanol, and from 0% to 31%, P=NS for trend after iopromide). On the contrary, <10% of segments A, B, or C reacted to ioxaglate with a significant dilation or constriction, and no evident trends were observed from group A to C. Defining the range of normal vasomotor reactions to iodixanol or iopromide as the mean±1.96SD of diameter changes of segments A, 20% of segments B, and 42% of segments C showed vasomotor responses below that range (Figure 3).

Effect of Contrast Media on Coronary Venous Oxygen Saturation

Iodixanol, iopromide, and ioxaglate injection resulted in a transient increase in coronary venous oxygen saturation from 27±6% to 37±5% (n=11, P<0.01), from 28±5% to 39±7% (n=9, P<0.01), and from 31±7% to 49±8% (n=10, P<0.001), respectively, without significant differences between patients with and without CAD (Figure 4). The peak increase in oxygen saturation was significantly greater after injection of ioxaglate than after iodixanol (P<0.05) or iopromide (P<0.05). The time course of the increase in oxygen saturation was similar for the 3 agents.
Effect of N\textsuperscript{G}-Monomethyl-L-Arginine and Indomethacin on Contrast-Induced Changes in Coronary Artery Dimensions

In patients with angiographically normal coronary arteries, N\textsuperscript{G}-monomethyl-L-arginine at 50 μmol/min significantly reduced coronary artery diameters by 27.7±6.5% (P<0.001).

Iodixanol and iopromide increased coronary luminal diameters to a similar extent with or without N\textsuperscript{G}-monomethyl-L-arginine (iodixanol: 7.8±4.9% versus 10.8±6.9%, P=NS; iopromide: 8.4±6.1% versus 9.4±7.0%, P=NS)(Figures 5A and 5B).

Indomethacin infusion at 3 μmol/min did not induce coronary luminal diameter changes (Figures 5A and 5B).

Iodixanol increased coronary luminal diameters by 9.4±6.4% (P=0.001) and by 2.5±4.7% (P=NS) in the absence and presence, respectively, of indomethacin (Figure 5A). Similarly, iopromide increased coronary luminal diameters by 6.8±5.2% (P<0.001) and 1.7±2.5% (P=NS) in the absence and presence of indomethacin, respectively (Figure 5B). Therefore, indomethacin significantly reduced the vasodilating effect of iodixanol and iopromide by 80% (P<0.001) and 76% (P<0.001), respectively.

Time Course of Iodixanol-Induced Changes in Coronary Artery Dimensions

Dilation of segments A was maximal 40 seconds after iodixanol injection and still significant at 60 seconds. The vasoconstrictive response of segments C to iodixanol was slightly right-shifted with respect to the dilation of segments A (peak at 60 seconds, return to baseline at 180 seconds; Figure 6).

Discussion

The main findings of this study are that: (1) nonionic contrast media iodixanol and iopromide exert different vasomotor effects on angiographically normal coronary segments of patients with CAD and patients with normal coronary arteries; (2) the distance between the coronary segment and a stenosis has an impact on the segment’s vasomotor reaction to contrast, ie, the nearer the stenosis the more likely the vasoconstriction (and the more unlikely the dilation) of the segment; (3) the ionic agent ioxaglate has no effect on epicardial coronary dimensions; (4) the 3 media induce significant hyperemia regardless of the effect on the epicardial arteries; and (5) cyclooxygenase inhibition, but not inhibition of nitric oxide synthesis, markedly attenuates the vasodilating effect of the nonionic contrast agents on normal epicardial coronary arteries.

This is the first human study demonstrating that iodinated contrast agents elicit divergent vasomotor reactions in atherosclerotic and normal coronary arteries. Interestingly, the altered vasomotor response was present at the level of angiographically smooth-appearing coronary segments of patients with CAD.

The mechanism(s) responsible for the divergent vasomotor responses of normal and diseased coronary arteries to nonionic agents is (are) unknown. Iodixanol is an iso-osmolar (290 mOsm/kg), dimeric, nonionic contrast agent whereas iopromide is a low-osmolar (770 mOsm/kg), monomeric, nonionic agent. This suggests that the effects seen were not linked to a specific characteristic of a particular molecule or to hyperosmolality (iodixanol is actually iso-osmolar with plasma), but rather to more general properties of nonionic contrast media. Previous experimental and clinical studies
have shown that several stimuli, such as the intracoronary administration of acetylcholine or serotonin, the cold pressor test, dynamic exercise, and increased blood flow, may all cause quantitatively and/or qualitatively different vasomotor effects on epicardial coronary arteries in patients with CAD compared with control subjects.14–20 Vasoactive agents such as serotonin or acetylcholine elicit divergent vasomotor effects on normal and atherosclerotic coronary arteries through a direct vasoconstrictive effect on medial smooth muscle cells and an endothelium-mediated vasodilation.14,16,17,19 The endothelium-mediated effect predominates in normal coronary arteries, whereas it becomes blunted or absent in patients with CAD. Karstoft et al19 demonstrated that ioxaglate and iotrolan (both nonionic agents), but not ioxaglate, have a strong direct vasoconstrictive effect on isolated coronary arteries. The mechanism responsible for the vasoconstriction was found to be due to a depolarizing effect of the nonionic agent on smooth muscle cells.9,21 The direct vasoconstrictive effect of nonionic agents might be counteracted in normal coronary arteries by an endothelium-dependent, flow-mediated dilation. In fact, vasodilation of normal epicardial coronary arteries has been observed during increases in coronary blood flow and a loss of this flow-mediated, endothelium-dependent dilation occurs early in the development of coronary atherosclerosis.10,20 An increase in coronary blood flow immediately after the intracoronary injection of ionic or nonionic contrast agents has been documented in previous investigations1,2,22 and is confirmed in our study by the increase in coronary venous oxygen saturation (Figure 4). The short phase-lag between peak hyperemia and maximal epicardial vasodilation, occurring 15 seconds (Figure 4) and 40 seconds (Figure 6), respectively, after nonionic contrast injection, might be the time required for transduction of the flow signal into the activation of the epicardial vasodilatory mechanism(s).23 Nevertheless, ioxaglate induced changes in coronary venous oxygen saturation that were even greater than those induced by ioxixanol or iopromide (Figure 4) without effects on epicardial coronary dimensions. Therefore, changes in coronary blood flow are not likely to be involved in the differential effects of various contrast media.

Endothelial control of vascular tone occurs through a host of vasodilators, including nitric oxide, prostacyclin, the endothelium-derived hyperpolarizing factor, or vasoconstrictors such as endothelins.24–27 Thus, the epicardial vasodilatory effect of nonionic media in subjects without CAD may occur through enhanced availability of vasodilators or decreased production of vasoconstrictors. We demonstrate that the infusion of Nω-monomethyl-L-arginine did not prevent the vasodilatory effect of nonionic agents on normal epicardial coronary arteries (Figures 5A and 5B), indicating the involvement of mechanism(s) other than the stimulation of nitric oxide synthesis and/or release. Conversely, a product of vascular cyclooxygenase activity, such as prostacyclin or the still elusive endothelium-derived hyperpolarizing factor, may play a role in the vasodilatory effect of nonionic contrast media because vascular cyclooxygenase inhibition by intracoronary indomethacin (likely more active than the weak baseline inhibition by oral low-dose aspirin) markedly attenuated the epicardial coronary vasodilation induced by ioxixanol or iopromide (Figures 5A and 5B).

Finally, the low-osmolar, ionic agent ioxaglate was surprisingly free of effects on epicardial coronary dimensions, although it was able to increase coronary blood flow. This result was unexpected because diatrizoate, another ionic agent, has a strong vasodilating effect on normal epicardial coronary arteries.1,2 The different vasomotor efficacy of ioxaglate (our findings) and diatrizoate (previous findings) does not seem simply attributable to the different osmolality of the 2 agents (608 mOsm/kg versus 2070 mOsm/kg) because ioxixanol, hypo-osmolar with respect to ioxaglate (290 mOsm/kg), still has a significant vasodilating effect on normal epicardial coronary arteries.

Study Limitations

A short attempt to obtain selective coronary sinus cannulation was performed in 48 consecutive patients of protocol A. Because the success rate of this procedure was only 63%, patient selection might have occurred, thus introducing a bias in the oxygen measurement data. No significant differences were observed in age, sex, and vascular risk factors distribution between patients with and without coronary venous oxygen measurements (data not shown).

The higher cholesterol levels in atherosclerotic patients of protocol A raises the possibility that the altered epicardial coronary vasomotor response to nonionic media reflects a direct effect of LDL cholesterol on the vascular vasomotility; alternatively, changes in vasomotility might represent the first signal of an atherosclerotic involvement of the vessel wall.

Clinical Implications

The vasoconstrictive response in atherosclerotic segments might contribute to the development of arterial thrombosis. There is an ongoing debate on whether nonionic contrast media may favor thrombosis, especially in the setting of PTCA, and this is mostly attributed to the lesser antplatelet and anticoagulant properties of nonionic versus ionic media. An additional vasoconstrictory effect on the site of exposure of highly thrombogenic material, such as on the vascular surface of a balloon-ruptured plaque, might favor this occur-
ence. Moreover, it is possible that the above mentioned vasoconstrictory effect might itself favor myocardial ischemia in the presence of severe stenoses. In our study, we did not observe symptoms or clear-cut electrocardiographic signs of ischemia after nonionic contrast injection, but this might be due to the exclusion of patients with subocclusive stenoses or diffuse disease, and this issue now deserves further attention.

Our findings suggest that contrast-induced vasoconstriction may last long enough to provide an erroneous impression of the severity of underlying CAD. This is likely to occur because the interval between 2 consecutive diagnostic angiograms is usually shorter than the 180 seconds required for a complete return to baseline dimensions (Figure 6). This also sheds some skepticism on the within- and between-study comparability of quantitative angiographic data obtained in different invasive laboratories not standardizing the use of contrast medium. Finally, this knowledge of the impact of atherosclerosis on the coronary vasodilatory effects of nonionic contrast media might allow for development of a tool for the assessment of concealed (ie, nonangiographically visible) coronary atherosclerosis in a somewhat more practical way than through the intracoronary administration of exogenous substances.

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References

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