Is Contrast-related Vasodilatation after Intra-coronary Iodixanol and Iopromide In Vivo Endothelium-dependent?

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Aims: Goals of the study were the assessment of the correlation between flow-dependent and contrast-related vasodilatation, comparison of iodixanol to iopromide and evaluation of the impact of plaque on vasodilatation in coronary arteries.

Methods and Results: A controlled randomized paired cross-over comparison between iodixanol (320 mg I.ml⁻¹) and iopromide (300 mg I.ml⁻¹) was performed in 10 consecutive patients. Vessel area (Visions Five-64 F/X intra-vascular ultrasound-catheter, Endosonics and blood flow velocity measurements (0.014 inches Doppler guide wire, Cardiometrics) were recorded simultaneously at an identical position, at baseline, after i.c. bolus injection of 10 ml physiologic saline (flow-dependent vasodilatation), and after application of contrast agent 1 and contrast agent 2 as randomized.

The action of iodixanol and iopromide on the vascular wall did not differ and was equal to local flow-dependent vasodilatation induced by a saline bolus (correlation 0.95–0.98). The increase in local luminal area after injection of saline, iodixanol and iopromide in morphologically normal vessels (~2.5 mm²) was absent in atherosclerotic segments. Both contrast agents and saline demonstrated a nearly identical flow increase.

Conclusion: If iodixanol or iopromide are used as contrast agents, contrast-related vessel area increase in vivo seems to be endothelium-dependent.

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Key Words: Intra-vascular ultrasound; Doppler; endothelium; vasodilatation; contrast agents.

Introduction

Endothelial function is commonly tested by assessing diameter changes after application of endothelium-dependent vasoactive substances or flow increase[11]. The resulting local changes of diameter or area are assessed by intra-vascular ultrasound or more often quantitative coronary angiography[2,3]. Quantitative coronary angiography allows the evaluation of several different vascular segments. For quantitative coronary angiography, however, contrast agents have to be used and these are known to act on the vascular wall by themselves[4–7]. Isotonic iodixanol is a recently developed contrast agent that demonstrated a reduced effect on blood flow in peripheral vessels as compared to other contrast agents[8–10]. A recent angiographic study in coronary arteries demonstrated a minor endothelium-dependent effect of isotonic iodixanol and iopromide on large coronary arteries[11]. The study was not intra-vascular ultrasound controlled, however. In a small additional methodological intra-vascular ultrasound study presented in this paper to assess the time course of vasodilatation following application of iodixanol, an immediate increase in luminal diameter in normal coronary segments with a peak at 40 s could be demonstrated[11]. These time kinetics are identical to those found for flow-dependent vasodilatation[3]. As a result the current study had several related aims:

(1) A first target was to compare the impact of the flow-dependent vasodilatation induced by an
equivalent bolus of saline to the effect related to the application of the contrast agents.

(2) A further question was whether isotonic iodixanol is superior to iopromide as contrast agent when coronary function is tested by quantitative coronary angiography.

(3) A goal methodologically related to these aims was to control the impact of atherosclerotic wall thickening on these measurements.

Methods

Study Design

The study was performed as a controlled randomized paired cross-over comparison between isotonic iodixanol (320 mg I.ml\(^{-1}\), Visipaque\((\text{*)})\), Nycomed\((\text{*)})\) and iopromide (300 mg I.ml\(^{-1}\), Ultravist\((\text{*)})\), Schering\((\text{*)})\). Iodixanol is a hydrophilic electrolyte balanced isotonic dimer of a nonionic tri-iodinated aromatic compound (osmolality 290 mosm.kg\(^{-1}\) H\(_2\)O, dynamic viscosity 1.4·mPa.s\(^{-1}\) at 37°C, iodine 320 mg.ml\(^{-1}\)). Iopromide is a hydrophilic low-osmolar nonionic tri-iodinated aromatic compound without added electrolytes (osmolality 610 mosm.kg\(^{-1}\) H\(_2\)O, dynamic viscosity 5.4·mPa.s\(^{-1}\) at 37°C, iodine 300 mg.ml\(^{-1}\))\((12)\). For comparison the respective values for whole blood: osmolality 282–294 mosm.kg\(^{-1}\) H\(_2\)O, dynamic viscosity 3.95–5.5·mPa.s\(^{-1}\) at 37°C at a shear rate of 230 s\(^{-1}\))\((13)\).

Area (intra-vascular ultrasound) and blood flow velocity measurements (Doppler) were recorded four times at an identical position, at baseline, after i.c. bolus injection of 10 ml physiologic saline (flow-dependent vasodilatation), and after application of contrast agent 1 and contrast agent 2 as randomized with a time interval of at least 2 min between each injection.

Patients

Ten patients were investigated from 20 June to 7 July 2000. Data on gender, age, diagnoses, sites of quantitative coronary angiography and intra-vascular ultrasound measurements and local vascular morphology are given in Table 1.

General Procedures

Written informed consent was obtained from all patients prior to examination. The study was approved by the local institutional review committee. Vasodepressor medication was discontinued 24 hours prior to catheterization.

Diagnostic right and left heart catheterization and coronary angiography were performed according to standard clinical practice using the transfemoral approach. Biplane angiograms of coronary arteries were acquired using standard angiographic X-ray equipment (INTEGRIS\((\text{*)})/LARC system, Philips\((\text{*)})\).

At the end of routine catheterization after administration of 5000 IU of heparin i.v., a 3 F Visions Five-64 F/X\((\text{*)}) catheter (Endosonic\((\text{*)})\) and a 0.014 Doppler guide wire (Cardiometrics\((\text{*)})\)\((14)\) were positioned at an easily accessible non-stenotic site in a proximal coronary artery through a 7 or 8 F guiding catheter.

Documentation

Volume of injected contrast agent, blood pressure, heart rate and procedure-related data were recorded by

Table 1. Data on gender, age, diagnoses, sites of quantitative coronary angiography and intra-vascular ultrasound measurements and local vascular morphology.

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Diagnoses</th>
<th>QCA</th>
<th>IVUS</th>
<th>Morphology</th>
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<tr>
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<td>64</td>
<td>Mitral insufficiency</td>
<td>Cx prox.</td>
<td>Cx prox.</td>
<td>Plaque</td>
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<td>2</td>
<td>F</td>
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<td>Normal</td>
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<td>3</td>
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<td>47</td>
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<td>Cx dist.</td>
<td>LAD prox.</td>
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<td>F</td>
<td>60</td>
<td>Three vessel disease</td>
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<td>Cx prox.</td>
<td>Circumferential plaque</td>
</tr>
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<td>M</td>
<td>59</td>
<td>Aortic insufficiency</td>
<td>LAD</td>
<td>LAD prox.</td>
<td>Normal</td>
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<tr>
<td>6</td>
<td>M</td>
<td>61</td>
<td>Single vessel disease</td>
<td>Cx dist.</td>
<td>Cx prox.</td>
<td>Circumferential plaque</td>
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<tr>
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<td>M</td>
<td>43</td>
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<td>Normal</td>
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<tr>
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<td>M</td>
<td>37</td>
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<td>Cx prox.</td>
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<td>Circumferential plaque</td>
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<tr>
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<td>Cx</td>
<td>LAD prox.</td>
<td>Normal</td>
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<tr>
<td>10</td>
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<td>56</td>
<td>Three vessel disease</td>
<td>LAD med.</td>
<td>Cx prox.</td>
<td>Plaque</td>
</tr>
</tbody>
</table>

*Chest pain and ECG or stress echo changes suggestive of ischaemia and normal coronary angiogram.
written protocol. Average peak flow velocity (APV) was documented on SVHS video and on hard copies. An example of a series of measurements in a patient with a normal coronary artery segment is given in Fig. 1.

Angiograms were stored on CD-ROM in DICOM format. Intra-vascular ultrasound recordings were stored on SVHS video and on CD-ROM. Evaluation was performed off-line from CD-ROM and documented on hard copies.

Intra-coronary Ultrasound

Luminal areas (A) were determined from CD-ROM by the use of resident software. Calibration was performed using a grid. At least three measurements were averaged. An example of a series of intra-vascular ultrasound frames in a patient with a normal coronary artery segment is given in Fig. 2.

Quantitative Coronary Angiography

Diameters of a clearly visible segment of the investigated coronary artery delimited by defined landmarks and with minimal foreshortening were measured by QANSAD\textsuperscript{\ref{b}}, a state-of-the-art second generation quantitative coronary angiography system with an accuracy of within ±0.028 mm\textsuperscript{\ref{b}}. Calibration was performed with guiding catheters. Pin-cushion distortion was corrected.

Assessment of impact on perfusion of distal coronary vascular bed:

mean velocity (V) was taken as:

\[
V = \frac{APV}{2} \text{ (cm.s}^{-1})\text{[14]}
\]

Volume flow (F) was calculated as:

\[
F = V \times A \text{ (mm}^2\text{.cm.s}^{-1}) = V \times A \times (0.01 \times 60) \text{ (ml.min}^{-1})\text{[14,16]}
\]

Flow reserve (F_res) was calculated as

\[
F_{\text{res}} = \frac{F_{\text{after injection}}}{F_{\text{at baseline}}} \text{ for injection of saline, and both contrast agents.}
\]

Statistics

For description of data, mean and standard deviations are given. Paired differences were assessed by the paired

\textbf{Figure 1.} Average peak flow velocity documented on hard copies. An example of a series of measurements in a patient with a normal coronary artery segment.
Inter-group differences between the group with normal vascular wall as assessed by intra-vascular ultrasound and the group with local atherosclerosis were calculated using the unpaired Student’s $t$-test and the non-parametric Mann–Whitney $U$-test. Significance was assumed at $P \leq 0.05$. Pearson’s correlation was used to test trends.

**Results**

**Methodological Aspects**

There were no complications and no lost data in this study. A total of $18.3 \pm 5.9$ ml of ioxianol and of $19.6 \pm 5.6$ ml of iopromide per injection were used. The difference is not significant. The volume in the lines (including contrast infusion system) and the catheter was $12.3$ ml. Thus the average amount of contrast volume injected into a coronary artery was about $8$ ml, comparable to the volume of the saline injection ($10$ ml).

The variation between repeated area determinations from intra-vascular ultrasound was $0.2 \pm 0.1 \text{mm}^2$. Repeated diameter determinations by quantitative coronary angiography agreed within $0.1 \pm 0.1$ mm. Area measurements of the same segment from intra-vascular ultrasound varied by $0.15 \pm 0.1 \text{mm}^2$. Diameter determinations by quantitative coronary angiography in the same segment agreed within $0.09 \pm 0.1$ mm.

**Local Vessel Morphology**

Of 10 patients, six were without angiographically visible coronary disease. Five of these patients (group N) had a morphologically normal vascular wall as assessed by intra-vascular ultrasound. Of the remaining five patients (group A) three had circumferential plaque and two focal non-circumferential wall thickening.
Total Group Analysis (see Table 2)

Mean baseline luminal area was $11.9 \pm 5.7 \text{mm}^2$. Luminal area and area increase after saline injection ($13.2 \pm 8.1 \text{mm}^2$, $7 \pm 11\%$) demonstrated no statistical difference as compared to iodixanol ($13.4 \pm 7.5 \text{mm}^2$, $9 \pm 9\%$) and iopromide ($13.2 \pm 7.7 \text{mm}^2$, $7 \pm 10\%$).

Area increases after iodixanol ($r=0.952$) and iopamidol ($r=0.986$) were strongly correlated with saline-induced flow-dependent area increase.

Diameters evaluated by quantitative coronary angiography were nearly identical for iodixanol ($2.65 \pm 0.65 \text{mm}$) and iopromide ($2.66 \pm 0.65 \text{mm}$) with a mean difference of paired values of $-0.02 \pm 0.07 \text{mm}$. There was no significant difference in absolute flow or flow reserve between saline and either of the contrast agents. Area values were minimally higher $0.25 \pm 1.04 \text{mm}^2$ after iodixanol than after iopamidol. This difference was not significant.

There was no significant difference in flow or flow reserve between saline and either of the contrast agents.

Subgroup Analysis

Comparison of the group without plaque (group N) and the group with local atherosclerosis (group A) demonstrated a significant difference with respect to flow-dependent local area increase as shown in Fig. 3. There was no significant group-related difference of local vasodilatation between saline and either of the contrast agents. Area values were minimally higher $0.25 \pm 1.04 \text{mm}^2$ after iodixanol than after iopamidol. This difference was not significant.

There was no group-related difference of flow or flow reserve between saline and either of the contrast agents.

Time Course

There was a monophasic response to both contrast agents as well as to saline. Maximal diameter increase occurred about 40 s after injection. Maximal flow velocity was detected at 40–45 s after injection. Baseline levels of flow velocity and area change were attained about 2 min after injection.

Discussion

The action of both contrast agents, iodixanol and iopamidol, on the vascular wall was found to be equal to local flow-dependent vasodilatation induced by a saline bolus of equivalent volume. The increase of luminal area induced by these contrast agents correlated with flow-dependent vasodilatation. Flow-dependent vasodilatation is known to be endothelium-dependent and is mediated by several autocrine and/or paracrine mechanisms[17]. The increase in local luminal area after injection of saline, iodixanol and iopamidol was absent in atherosclerotic segments in agreement with findings of early endothelial dysfunction in atherosclerosis[18,19].

Table 2. Area increase and flow reserve with respect to baseline values.

<table>
<thead>
<tr>
<th>ID</th>
<th>Area increase (%)</th>
<th>Flow reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaCl</td>
<td>Iopromide</td>
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<tr>
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<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
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<td>10</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>−9</td>
<td>−4</td>
</tr>
</tbody>
</table>

P < 0.01 (t-test and U-test) for difference between group with normal morphology and group with atherosclerosis for all agents.

Figure 3. Absolute area increase after saline, iopamidol and iodixanol grouped with respect to presence or absence of local atherosclerosis. P<0.01 (t-test and U-test) for difference between group with normal morphology and group with atherosclerosis for all agents. ●: Normal morphology; ●: plaque, ± 95% confidence interval.
Thus, endothelial function is likely to mediate the correlation of local flow-dependent vasodilatation and vascular area increase after iodixanol and iopromide injection. It has been argued that the mechanism of vasodilatation is different, however. Inhibition of endothelial nitric oxide has been demonstrated to have no effect on dilatation after iodixanol and iopromide[11] in an angiographic study without control of flow-dependent vasodilatation. In isolated arterial preparations even an inhibitory effect of these contrast agents on nitric oxide could be demonstrated[20]. Flow-dependent vasodilatation is not mediated by nitric oxide alone. Cyclooxygenase products such as prostacyclin are known to partially mediate flow-dependent vasodilatation[21,22] and an inhibition of vasodilatation by iodixanol and iopromide was found after blocking cyclooxygenase[11]. Ion channels and endothelial hyperpolarizing factor may play a role in endothelium-dependent relaxation caused by these contrast agents[5,11,23]. More sophisticated studies will be necessary to verify the mechanisms of endothelium-dependent vasodilatation by iodixanol and iopromide.

Differences in vascular vasodilatory reaction to iodixanol as compared with iopromide were found to be not significant in agreement with a quantitative coronary angiography study by Limbruno et al.[11]. In experimental studies under no-flow conditions iopromide was a slightly more potent vasodilator than iodixanol and this effect was endothelium-independent for both contrast agents[24]. This potential endothelium-independent effect may not be relevant under flow conditions with short exposure times. A minor clinically irrelevant difference may not be excluded by this small study, however. The 95% confidence interval of the expected mean difference in area increase based on the presented data ranges from −0.08 to 0.58 mm² (SD of differences 1.04 mm²).

Flow-dependent flow reserve was not different between the group without local vessel abnormalities and the group with focal atherosclerosis. This may indicate preserved microvascular endothelial function. We intentionally selected patients without advanced angiographic coronary artery disease for this study. Atherosclerotic lesions have a predilection for larger vessel[25] and microvascular impairment reflects advanced disease. Contrast-related flow reserve did not differ between the two contrast agents and was equal to saline-induced flow-dependent flow reserve; this agrees with findings in the literature[26,27].

The study was conceived as a pilot study and is limited due to the small sample size. The major clinical implication of this study is that the error of quantitative coronary angiography due to contrast agent related local vasodilatation is small and may even be absent in segments with subclinical atherosclerosis. There may be negligible vasoconstriction in segments with stenosis or advanced atherosclerosis as demonstrated by others[11].

For studies in patients with preserved endothelial function a combined assessment of local vascular luminal area by intra-vascular ultrasound and intra-vascular flow velocity should be considered, which may help to differentiate between flow-mediated and other receptor-mediated endothelial responses[3].

Acknowledgement

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References


