Acute endothelin$_A$ receptor antagonism improves coronary artery compliance in coronary artery disease patients

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ABSTRACT

Endothelin (ET) exerts a tonic, stiffening effect on the common carotid artery in rats in vitro. This effect is mediated via the ET$_A$ receptor. The aim of this study was to examine the acute effects of ET$_A$ receptor antagonism on coronary artery compliance in humans. We examined 22 patients with stable angina after diagnostic coronary arteriography. Intracoronary BQ-123 (6 µmol), an ET$_A$ receptor antagonist (14 patients), or saline (8 patients), was infused in an artery without significant lesion over 20 min. The artery lumen area in the proximal arterial segment was measured at end diastole and end systole before and after BQ-123 or saline administration using an intravascular ultrasound catheter. Calculations were made of absolute (in mm$^2$/mmHg$^{-1}$) and normalized compliance index (in mmHg$^{-1}$). Pulse pressure decreased from 64±21 to 61±17 mmHg after BQ-123 administration and increased from 59±16 to 68±20 mmHg after saline administration ($F = 9.54$, $P = 0.006$). The respective changes in absolute compliance index were from 24±18 to 39±25 and from 19±15 to 14±17 ($F = 6.43$, $P = 0.02$). Normalized compliance index changed from 2.5±2.0 to 3.6±2.4 and from 2.7±2.6 to 1.6±1.8 ($F = 11.92$, $P = 0.002$) respectively, in the two groups. Acute ET$_A$ receptor antagonism improves coronary artery compliance in coronary artery disease patients.

INTRODUCTION

The mechanical properties of large arteries have been studied extensively in animals and human beings. Recent attention has been given to the possibility that changes in vasomotor tone, due to an imbalance in the release of vasoconstrictor and vasodilator substances from the endothelium, significantly contribute to the mechanical behaviour, not only of small size resistance arteries, but also of larger arterial conduits [1,2]. Recently, it has been demonstrated that endothelin (ET) exerts a tonic, stiffening effect on the in vitro common carotid artery in rats and that this effect is mediated via the ET$_A$ receptor [3].

The ETs are a family of 21-amino-acid peptides with potent and characteristically sustained vasoconstrictor and vasopressor actions [4]. ET-1 is the predominant isopeptide generated by the vascular endothelium [5]. ET-1 binds to at least two receptors [6]: the ET$_A$ receptor appears to be the major receptor causing vasoconstriction in arteries [7]; the ET$_B$ receptor mediates release of endothelium-dependent vasodilator substances and is also present in some resistance and capacitance arteries, where it contributes to vasoconstriction. Endogenous production of ET-1 contributes to the maintenance of peripheral and coronary vascular tone in coronary artery disease patients and healthy controls [8,9].

We thus hypothesize that ET may influence the mechanical properties of large epicardial coronary arterial segments. However, to the best of our knowledge,
this issue has not so far been directly investigated in humans.

The aim of this study was to examine the acute effects of ETα receptor antagonists on coronary artery compliance in patients with coronary artery disease by analysing the pressured-cross-sectional area relationship.

PATIENTS AND METHODS

The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The Hospital Ethics Committee approved the study and all patients gave written informed consent.

Study group

Twenty two patients with stable angina, on the waiting list for coronary angiography, were selected prospectively on the basis of the following inclusion criteria: (1) atherosclerotic coronary vessels with or without single-vessel coronary artery disease, (2) normal left ventricular ejection fraction, and (3) coronary arteries eligible for intravascular ultrasound studies. Nine patients with atherosclerosis but no significant coronary artery stenoses were included. Patients were considered eligible for intravascular ultrasound imaging when the proximal segment of the artery to be examined was large on angiography (> 2.5 mm) and nontortuous. Exclusion criteria: patients with diabetes mellitus, acute or old myocardial infarction, unstable angina, additional cardiac disease and severe non-cardiac disease. All medications, except aspirin, were discontinued at least 12 h before the procedure. The patients were randomly assigned to receive, in proportions of 2:1, ETα receptor antagonism or saline infusion.

Protocol

After the end of diagnostic coronary arteriography, 2000 units of heparin were administered.

Intravascular ultrasound catheter

Intravascular ultrasound studies were performed with an Avanar 2.9 French catheter from Endosonics (Rijswijk, The Netherlands). The catheter was connected to an image console, and intravascular ultrasound images were displayed in real time during the procedure and were also stored on a compact disk.

Image protocol

No patients received nitroglycerin before the study. Intravascular ultrasound catheters were advanced through large lumen guiding catheters, 7 French, to facilitate the advancement of the system and to allow the injection of contrast material to monitor the location of the transducer in relation to angiographic landmarks.

Intravascular ultrasound catheters were advanced under continuous fluoroscopic monitoring during imaging and subsequently slowly pulled back manually in order to study the target angiographic lesion. At sites where a relatively central catheter position was obtained and optimal visualization of the entire lumen wall interface was achieved, the movement of the catheter was stopped. Sites near the takeoff of the side branches and where the imaging catheter was wedged into the plaque, resulting in a small residual lumen, were excluded.

Drug administration

After baseline recordings, while the catheter was in the same site of the coronary artery, the ETα receptor antagonist BQ-123 [cyclo(-D-Asp-L-Pro-D-Val-L-Leu-D-Trp-)]; Clinalfa] (14 patients) or saline (8 patients) was administered. The substance was dissolved in 0.9 % saline and was infused intracoronary at a constant rate of 1 ml/min (300 nmol/min) for 20 min using an infusion pump. Before the initiation of BQ-123 infusion, normal saline 0.9 % was infused at a rate of 1 ml/min for 5 min and then the first baseline recordings were performed (heart rate and arterial blood pressure synchronously with intravascular ultrasound recordings). The second recordings were taken immediately at the end of the 20 min infusion of saline or BQ-123.

Compliance indices

Quantitative analysis of intravascular ultrasound images was performed off-line with specific software (Endosonics). Maximal and minimal lumen areas at the selected sites were identified during frame-by-frame playback analysis and were defined as the areas circumscribed by the ultrasound leading-edge interface between lumen and plaque or lumen and intima. All reported measurements represent the average of three consecutive beats obtained by two independent observers.

Vascular pulsatility was determined as both the absolute change in area in mm² and also as a percentage [10]:

\[
\text{Percentage} = \frac{\text{difference between planimetered large and small areas}}{\text{small area}} \times 100
\]

Absolute compliance was determined from systolic–diastolic changes in area resulting from pressure changes:

\[
\text{Absolute compliance (mm}^2/\text{mmHg} \times 10^3) = \text{change in area/change in pressure.}
\]

Subsequently, compliance was also normalized to reference vessel area:

\[
\text{Normalized compliance (mmHg}^{-1} \times 10^3) = \text{(change in area/vessel area)/change in pressure.}
\]

Because artery compliance estimated by the above rules could be influenced by a change in blood pressure, the stiffness index (β), which is considered to be independent
Table 1 Clinical and angiographic characteristics of the patients studied

There was no statistically significant difference between the two groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BQ-123 group</th>
<th>Saline group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 12</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/3</td>
<td>7/1</td>
</tr>
<tr>
<td>Baseline heart rate (beats/min)</td>
<td>74 ± 13</td>
<td>72 ± 18</td>
</tr>
<tr>
<td>Baseline mean blood pressure (mmHg)</td>
<td>109 ± 11</td>
<td>107 ± 11</td>
</tr>
<tr>
<td>History of systemic hypertension (n)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Total cholesterol (mg%)</td>
<td>221 ± 48</td>
<td>208 ± 51</td>
</tr>
</tbody>
</table>

Studied artery (n)
- Left anterior descending artery 5 3
- Right coronary artery 7 5
- Left circumflex artery 2 0
- Patients without significant stenotic lesions (n) 6 3

of the changes in blood pressure, was obtained, essentially by normalizing dimension change to the diastolic mean diameter according to the following formula:

$$\beta = \frac{\ln(\text{systolic intracoronary pressure}/\text{diastolic intracoronary pressure})}{(\text{difference between systolic and diastolic mean diameters}/(\text{diastolic mean diameter})))}$$

The systolic and diastolic mean diameters were calculated from those areas with the assumption that the cross-section was circular \([\text{diameter} = 2(\text{area}/\pi)^{1/2}, \text{where } \pi = 3.14]\).

Interobserver and intraobserver variability
The cross-sectional lumen areas of 14 randomly selected sites were measured by two independent observers and by one observer two separate times. These data were used to obtain the interobserver and intraobserver variability. An excellent correlation between the two measurements was found: \((r = 0.95, P < 0.001)\) and \((r = 0.96, P < 0.0001)\) respectively.

Statistical analysis
All data were expressed as mean ± S.D. ANOVA with repeated measures was used for the statistical evaluation of the results, followed by Tukey’s honest significant difference test for post-hoc comparisons. A P value of < 0.05 was considered as statistically significant.

RESULTS
Clinical and angiographic characteristics were similar in the two groups (Table 1).

Intracoronary ultrasound and blood pressure measurements
Heart rate was not affected by BQ-123 or saline administration in the two groups. Systolic blood pressure and pulse pressure showed a tendency to increase after

Table 2 Variables before and after BQ-123 or saline infusion

*P < 0.05 versus before; BQ-123 group \((n = 14)\); saline group \((n = 8)\).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Before</th>
<th>After</th>
<th>(F)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>BQ-123</td>
<td>74 ± 13</td>
<td>72 ± 13</td>
<td>1.15</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>72 ± 18</td>
<td>67 ± 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>BQ-123</td>
<td>148 ± 21</td>
<td>141 ± 16</td>
<td>7.23</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>141 ± 16</td>
<td>152 ± 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>BQ-123</td>
<td>64 ± 21</td>
<td>61 ± 17</td>
<td>9.54</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>59 ± 16</td>
<td>68 ± 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic area (mm²)</td>
<td>BQ-123</td>
<td>10.3 ± 3.5</td>
<td>11.2 ± 3.8</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>8.2 ± 4.1</td>
<td>9.1 ± 4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic area (mm²)</td>
<td>BQ-123</td>
<td>11.6 ± 3.9</td>
<td>13.4 ± 4.3</td>
<td>2.11</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>9.2 ± 4.0</td>
<td>9.9 ± 4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic — diastolic area (mm²)</td>
<td>BQ-123</td>
<td>1.37 ± 0.79</td>
<td>2.12 ± 1.16*</td>
<td>5.53</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>1.0 ± 0.78</td>
<td>0.85 ± 0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatility (%)</td>
<td>BQ-123</td>
<td>14 ± 7</td>
<td>20 ± 10*</td>
<td>10.07</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>15 ± 14</td>
<td>10 ± 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute compliance index (mm²/mmHg x 10⁶)</td>
<td>BQ-123</td>
<td>24 ± 18</td>
<td>39 ± 25*</td>
<td>6.43</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>19 ± 15</td>
<td>14 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized compliance index (mmHg⁻¹ x 10⁴)</td>
<td>BQ-123</td>
<td>2.5 ± 2.0</td>
<td>3.6 ± 2.4*</td>
<td>11.92</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>2.7 ± 2.6</td>
<td>1.6 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β Index</td>
<td>BQ-123</td>
<td>1.60 ± 0.59</td>
<td>1.50 ± 0.72</td>
<td>9.16</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>1.71 ± 0.77</td>
<td>2.42 ± 0.99*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
saline administration, but a tendency to decrease after BQ-123 infusion (Table 2). There was no differential response of diastolic and systolic cross-sectional areas in the two groups after saline or BQ-123 administration (Table 2).

**Coronary distensibility**
Pulsatility, as well as the other indexes of coronary artery compliance, showed a differential response in the two groups after saline or BQ-123 administration. In the BQ-123 group pulsatility increased by 42%, absolute compliance by 62%, normalized compliance by 44% and the $\beta$ index decreased by 6%. In the control group pulsatility decreased by 20%, absolute compliance by 26%, normalized compliance by 41% and $\beta$ index increased by 42% (Table 2 and Figure 1).

**DISCUSSION**

In animal models it has been demonstrated that ET affects not only small resistance arteries but also much larger, conduit-functioning arterial vessels [3]. These effects are mediated via $ET_\alpha$ receptors. This study extended these results to patients with coronary artery disease. Our findings provide evidence for augmentation of coronary artery distensibility after acute $ET_\alpha$ receptor antagonism in patients with coronary artery disease.

In the control group it was demonstrated that during saline infusion the arterial systolic blood and pulse pressures showed a tendency to increase in parallel with a tendency to decrease for pulsatility and artery compliance. However, taking into account that pressure and stretch release ET from endothelial cells [11], and that the pulsatility and artery compliance obtained after saline and BQ-123 administration were divergent, it is reasonable to hypothesize that increases in pressure can be associated with a significant release of ET, which could be the cause of the deterioration of the compliance indices after saline in the control group.

A consideration arising from our findings relates to their possible clinical implications. It has been suggested that ET contributes to the regulation of vasomotor tone in healthy subjects as well as in patients with cardiovascular disease. Our current finding that the action of ET extends to the functional behaviour of large arteries further enhances the potential pathophysiological relevance of ET in terms of circulatory homoeostasis and of the progression of cardiovascular structural and functional alterations. It has recently been shown that ET contributes to the worsening of atherosclerosis of the vessels themselves [12]. These considerations may become of practical significance as a result of the recent introduction of non-peptidic ET receptor antagonists as cardiovascular therapeutic agents.

![Figure 1](image_url) Line plots of the normalized compliance index at baseline and after 20 min of infusion of BQ-123 (left panel) or saline (right panel)

* $P < 0.05$ versus baseline.
In conclusion, acute ETₐ receptor antagonism improves coronary artery compliance in coronary artery disease patients, and this may have important implications with respect to the progression of arterial atherosclerosis.

REFERENCES