Effects of Amiodarone on Cardiac and Coronary Hemodynamics and on Myocardial Metabolism in Patients with Coronary Artery Disease

Pierre Côté, M.D., Martial G. Bourassa, M.D., Jacques Delaye, M.D., André Janin, M.D., Roger Froment, M.D., and Paul David, M.D.

SUMMARY While the antiarrhythmic effects of amiodarone are well-documented, its hemodynamic effects are not. We injected 5 mg/kg amiodarone i.v. in 16 patients undergoing coronary arteriography. Heart rate did not change. Aortic (systolic, diastolic and mean) and left ventricular (systolic and end-diastolic) pressures decreased significantly \( (p < 0.01) \) at 5 and 15 minutes; systemic vascular resistance also fell significantly \( (p < 0.05) \), while cardiac index increased slightly but significantly \( (p < 0.05) \). Coronary vascular resistance decreased significantly \( (p < 0.01) \) and coronary sinus blood flow rose in most patients, from a mean of 138 ml/min to 153 ml/min at 5 minutes \( (p < 0.02) \); it then returned toward the control value at 15 minutes (mean 145 ml/min). Myocardial metabolism of \( O_2 \) was normal and unchanged. Metabolism of lactate improved in five patients, remained unchanged in seven and deteriorated transiently in four. No undesirable hemodynamic and clinical side effects occurred when the drug was administered slowly. We conclude that amiodarone is a powerful systemic and coronary vasodilator. In addition to its present indications in the treatment of angina pectoris and arrhythmias, the drug might be very useful as an afterload-reducing agent.

AMIODARONE (L3428*, 2 butyl-3-(3,5-diido-4β-diethylaminethoxybenzoyl)-benzofuran) was introduced as an antianginal drug in 1967 and as an antiarrhythmic drug in 1970. The oral form of this non-nitrate coronary vasodilator has been extensively used in Europe to treat patients with chronic angina. A recent report suggests that amiodarone administered intravenously is extremely effective in relieving not only the acute and severe pain which occurs in patients with variant angina, but also the accompanying ventricular arrhythmias. This class III antiarrhythmic agent was recently introduced in Argentina and in Canada, and was also found very effective in preventing and treating arrhythmias, particularly when associated with the Wolff-Parkinson-White syndrome. More recently, amiodarone was reported to be very effective as an antiarrhythmic agent during cardiac surgery.

To our knowledge, only two reports in the literature have discussed the hemodynamic effects of amiodarone after intravenous administration in man. Only one of them dealt with its effects on the coronary circulation. These studies indicate that amiodarone injected in a dosage known to produce therapeutic antiarrhythmic effects decreases myocardial \( O_2 \) requirements without a decrease in myocardial blood flow. This decrease in myocardial \( O_2 \) demand is the result of reduced heart rate, contractility, and afterload from systemic vasodilatation.

Material and Methods

Subjects

Sixteen subjects premedicated with a Nembutal suppository (200 mg) who were undergoing coronary angiography for chest pain were studied after an overnight fast. Exclusion criteria were as follows: presence of valvular heart disease, unstable angina, heart failure, recent myocardial infarction, uncontrolled diabetes and significant systemic hypertension. Table 1 details the clinical and angiographic characteristics of the patients. Two patients had normal coronary arteries with anginal pain and are included because of a response similar to that of patients with coronary heart disease.

Techniques

With the patient under local anesthesia, we inserted a #8 French Sones catheter into the right or left brachial artery to measure left ventricular and aortic pressures. We inserted a #8 French Ganz thermodilution catheter* from a right or left basilic vein into the coronary sinus to determine coronary sinus blood flow (CSBF), to take blood samples and to inject dye for measurement of cardiac output (CO).

Catheters were connected to Statham P23Db transducers, which were adjusted so that the zero pressure was at the mid-chest position. Pressures were

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*Amiodarone (Cordarone), manufactured by Labaz, Brussels, Belgium. Its structural formula is shown in figure 1.

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*Supplied through Wilton Webster Company, Altadena, California.
AMIODARONE (CORDARONE)

\[
\begin{align*}
\text{C}_{2}H_{5} & \cdot HCl \\
\text{C}_{2}H_{5} & \cdot \text{O}-\text{CH}_{2}-\text{CH}_{2}-\text{N} \\
& \text{(CH}_{3}\text{)}_{3}\text{-CH}_{3}
\end{align*}
\]

FIGURE 1. Chemical structure of amiodarone.

amplified and recorded on high and normal sensitivity and at a paper speed of 100 mm/sec on a multichannel Philips photographic recorder.

At prescribed intervals, we took aortic and coronary sinus blood specimens simultaneously to determine hemoglobin, hematocrit, pH and blood gases, sodium and potassium, SMA 12/60,* lactate and the following enzymes: creatine phosphokinase (CPK), oxaloacetic transaminase (GOT), and total lactic dehydrogenase (LDH) and its five isoenzymes.

CSBF was measured by thermodilution.14 Location of the coronary sinus ostium was confirmed by a small hand injection of contrast material and the external thermistor or distal pacing electrode of the Ganz catheter was positioned just inside the coronary sinus ostium and maintained in that position throughout the study. A physiologic saline solution at 22-25°C was injected into the coronary sinus, using a calibrated Harvard pump and twin syringes of 20 ml, at a constant rate of about 35-40 ml/min for 20-30 seconds. This relatively high injection rate allows adequate mixing of the injectate with blood. CSBF was obtained twice at rest in most patients, and did not vary more than 5%. CSBF in ml/min was obtained using the formula:

\[
\text{CSBF} = \text{Fi} \left( \frac{Tb - Ti}{Tb - Tm} - 1 \right) 1.08
\]

where Fi represents the volume of injectate (ml/min), Tb, Ti and Tm are temperatures of blood, injectate and mixture of blood and injectate (°C); 1.08 is a constant derived from the density and specific heat of the saline solution and blood.

CO was measured after rapid injection in the coronary sinus of 5 mg of indocyanine green, followed immediately by a saline flush. Central aortic blood was withdrawn by a Harvard infusion pump at a rate of 20 ml/min through a cuvette dye densitometer. Computation of CO was performed with the use of the Williams formula.14

Treatments

The study was undertaken after left-heart and coronary sinus catheterization, and before left ventriculography and coronary arteriography. The control measurements described below were not carried out until at least 10 minutes after catheter manipulations to achieve a stable basal state. The following procedures were accomplished in close temporal sequence: pressure recordings, blood sampling and determination of CSBF and CO.

After completing basal measurements, we injected an amiodarone dosage of 5 mg/kg of body weight into the coronary sinus over a 1-minute period. The patient was unaware that a drug was being administered. Measurements were repeated at 5-10 minutes and 15-20 minutes, and the drug study was completed within 30 minutes. In addition, heart rate (HR), left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) were continuously monitored during the first 5 minutes of amiodarone administration. Left ventriculography and selective coronary arteriography were then carried out.18

Statistical Analysis

Pressure readings were always the mean of 10 beats. Calculations of cardiac index (CI) and stroke index were made according to standard formulas. The following calculations were obtained:

Systemic vascular resistance (SVR) in units = MAP / CO

where MAP indicates mean aortic pressure in mm Hg and CO is cardiac output (1/min);

Left ventricular stroke work index (LVSWI) in g-m/beat/m² =

\[
\frac{\text{SI} \times (\text{MSAP} - \text{LVEDP})}{1000}
\]

where SI indicates stroke-volume index in ml/beat/m², MSAP is mean systolic aortic pressure and LVEDP is left ventricular end-diastolic pressure, both in mm Hg.

Tension-time index (TTI) in mm Hg/sec/min = HR × SEP × MSAP, where HR represents heart rate in beats/min and SEP is systolic ejection period in sec/beat;

Mean systolic ejection rate (MSER) in

\[
\text{ml/sec/m²} = \frac{\text{SI}}{\text{SEP}}
\]

 Coronary vascular resistance (CVR) in units

\[
= \frac{\text{MAP}}{\text{CSBF}}
\]

Left ventricular O₂ consumption (LVVO₂) in

\[
\text{ml/min} =
\]

*Technicon Corporation, Ardsley, New York (calcium, inorganic phosphate, glucose, urea nitrogen, uric acid, cholesterol, proteins, albumin, total bilirubin, alkaline phosphatase, total lactic dehydrogenase and creatinine).
TABLE 1. Clinical and Angiographic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Angina*</th>
<th>Old MI</th>
<th>Medication at angiography</th>
<th>Rest ECG</th>
<th>CAD</th>
<th>Abnormal LV angiogram</th>
</tr>
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<tbody>
<tr>
<td>MB†</td>
<td>55</td>
<td>IV</td>
<td>+</td>
<td>Anticoagulants</td>
<td>LBBB</td>
<td>1V</td>
<td>+</td>
</tr>
<tr>
<td>FV</td>
<td>58</td>
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<td>Normal</td>
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<td>+</td>
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<td>None</td>
<td>Ischemia</td>
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<td>+</td>
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<td>+</td>
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<td>2V</td>
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<td>+</td>
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<td>3V</td>
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<td>+</td>
<td>None</td>
<td>MI</td>
<td>2V</td>
<td>No</td>
</tr>
<tr>
<td>MC</td>
<td>57</td>
<td>IV</td>
<td>+</td>
<td>None</td>
<td>MI</td>
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<td>Ischemia</td>
<td>2V</td>
<td>+</td>
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<tr>
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<td>62</td>
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<td>−</td>
<td>Pexid</td>
<td>Normal</td>
<td>2V</td>
<td>No</td>
</tr>
</tbody>
</table>

*Classification of effort angina of the Canadian Cardiovascular Society.12
†Female patient.

Abbreviations: MI = myocardial infarction; CAD = significant coronary artery disease ≥ 50% stenosis of a vessel (V) on coronary angiogram; LV = left ventricular; pexid = perhexiline maleate; LBBB = left bundle branch block.

[Arterial-coronary sinus O₂ content in ml/100 ml] × CSBF × 10⁻²;
Left ventricular O₂ (LVO₂E) or lactate (LVLE) extraction in % =
Arterial - coronary sinus O₂ or lactate × 100
Arterial

All calculations were performed with an electronic calculator using the same program (Hewlett-Packard calculator 9830A with digitizer). Statistical analysis was performed with a paired t test and amiodarone data obtained at 3, 5 and 15 minutes were compared with control values.

Results

Systemic Hemodynamic Effects of Amiodarone (table 2)

Heart Rate and ECG

All patients were in normal sinus rhythm and free of arrhythmia. Injection of amiodarone caused no effect on cardiac conduction or morphology of the ECG. HR was 69 beats/min at rest and unchanged at 5 (69 beats/min) and 15 minutes (67 beats/min). However, HR was significantly (p < 0.001) increased to 79 beats/min at 3 minutes of the injection, which probably represents a reflexly induced acceleration in cardiac rhythm after maximal systemic vasodilatation.

Aortic and Left Ventricular Pressures

Left ventricular pressures were continuously monitored during the first 5 minutes of the injection of amiodarone. Peak effects occurred at 3 minutes: LVSP decreased from a control value of 132 mm Hg to 109 mm Hg at 3 minutes (p < 0.001), to 119 mm Hg (p < 0.01) at 5 minutes and to 122 mm Hg (p < 0.01) at 15 minutes. Hypotension of brief duration (systolic pressure < 90 mm Hg) occurred in two patients who received the drug rapidly as a bolus, and in a third patient. LVEDP decreased in the eight patients with resting values > 12 mm Hg. A control mean LVEDP of 12.6 mm Hg fell to 9.8 mm Hg at 3 minutes (p < 0.001), to 10.2 mm Hg at 5 minutes (p < 0.001) and to 9.7 mm Hg at 15 minutes (p < 0.01). Aortic diastolic pressure decreased slightly but significantly, from a mean resting value of 77 mm Hg to 71 mm Hg at 5 minutes (p < 0.01) and to 73 mm Hg at 15 minutes (p < 0.02). Mean aortic pressure was also significantly decreased at 5 and 15 minutes (p < 0.001).

Vascular Resistance, Cardiac Index and Performance

SVR decreased significantly from a mean of 20.2 units at rest to 16 at 5 minutes (p < 0.001) and to 17.5 at 15 min (p < 0.05), (fig. 2). CI was normal at rest (mean 2.97 l/min/m²), and increased significantly in most patients to a mean of 3.3 l/min/m² at 5 minutes (p < 0.05) and to 3.23 l/min/m² at 15 minutes (NS). Since HR was unchanged at 5 and 15 minutes, the increase in CI may have been due to an increase in stroke volume; however, the increases in SI from 60 ml/beat/m² to 65 and 64 ml/beat/m² at 5 and 15 minutes, respectively, were not statistically significant (p > 0.05) (table 2). SEP was augmented significantly, from 341 msec at rest to 355 msec at 5 minutes (p < 0.05) and 350 msec at 15 minutes (NS). This prolonged SEP without a change in HR could
Table 2. Systemic Hemodynamic Effects of Amiodarone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>3 min</th>
<th>5 min</th>
<th>15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>69 ± 9</td>
<td>79 ± 13</td>
<td>69 ± 11</td>
<td>67 ± 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic, systolic</td>
<td>132 ± 16</td>
<td>109 ± 18†</td>
<td>119 ± 17</td>
<td>122 ± 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.01</em></td>
<td><em>p &lt; 0.01</em></td>
</tr>
<tr>
<td>Aortic, diastolic</td>
<td>77 ± 8</td>
<td>71 ± 11</td>
<td>73 ± 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.01</em></td>
<td><em>p &lt; 0.02</em></td>
<td></td>
</tr>
<tr>
<td>Aortic, mean</td>
<td>99 ± 11</td>
<td>89 ± 12</td>
<td>90 ± 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.001</em></td>
<td></td>
</tr>
<tr>
<td>LVED</td>
<td>12.6 ± 6.6</td>
<td>9.8 ± 5.7</td>
<td>10.2 ± 5.7</td>
<td>9.7 ± 5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.01</em></td>
<td></td>
</tr>
<tr>
<td>CI (15)</td>
<td>2.97 ± 0.9</td>
<td>3.30 ± 0.9</td>
<td>3.23 ± 1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.05</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR (15)</td>
<td>20.2 ± 5</td>
<td>16 ± 4</td>
<td>17.5 ± 3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.05</em></td>
<td></td>
</tr>
<tr>
<td>SI (15)</td>
<td>60 ± 29</td>
<td>65 ± 24</td>
<td>64 ± 26</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEP (15)</td>
<td>341 ± 44</td>
<td>355 ± 47</td>
<td>350 ± 49</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td><em>p &lt; 0.05</em></td>
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<td></td>
</tr>
<tr>
<td>TTI</td>
<td>2645 ± 458</td>
<td>2515 ± 559</td>
<td>2402 ± 460</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>p &lt; 0.05</em></td>
</tr>
<tr>
<td>LVSWI (15)</td>
<td>82 ± 43</td>
<td>80 ± 30</td>
<td>83 ± 33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSER (15)</td>
<td>171 ± 61</td>
<td>181 ± 51</td>
<td>179 ± 54</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Values are mean ± sd.

*Paired t test: difference from control values (NS indicates not significant).
†Left ventricular systolic pressure.

Abbreviations: LVED = left ventricular end-diastolic; CI = cardiac index (l/min/m²); SVR = systemic vascular resistance (units); SI = stroke-volume index (ml/beat/m²); SEP = systolic ejection period (msec/beat); TTI = tension-time index (mm Hg/sec/min); LVSWI = left ventricular stroke-work index (g/beat/m²); MSER = mean systolic ejection rate (ml/sec/m²).

reflect the increase in stroke volume. TTI was decreased significantly at 15 minutes (2645 mm Hg/sec/min at rest to 2402 mm Hg/sec/min) (p < 0.05). LVSWI and mean systolic ejection rate were not affected by amiodarone.

Coronary and Metabolic Effects of Amiodarone (table 3)

Coronary Hemodynamics

CSBF was determined in 15 patients. It increased from 138 ml/min at rest to 153 ml/min at 5 minutes (p < 0.02) and returned toward control value at 15 minutes (mean 145 ml/min) (NS). Twelve patients had an increase in CSBF, one a decrease and two had no change. CVR decreased significantly, from 0.75 units to 0.59 units at 5 minutes (p < 0.01) and to 0.65 units at 15 minutes (NS) (fig. 3).

Metabolic Data

Oxygen, Substrates and Enzymes. There was no change in the arterial and coronary sinus O₂ concentrations after amiodarone, so myocardial O₂ extraction was unchanged. The increase in myocardial O₂ consumption from 13.8 ml/min at rest to 16.8 ml/min at 5 minutes (p < 0.05) was therefore secondary to the

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Individual values and mean ± sem are shown (n = 15). Systemic vascular resistance (SVR) decreased significantly at 5 (p < 0.001) and 15 minutes (p < 0.05).
TABLE 3. Coronary and Metabolic Effects of Amiodarone

<table>
<thead>
<tr>
<th>Parameter (n = 16 or as indicated)</th>
<th>Control</th>
<th>Amiodarone 5 min</th>
<th>Amiodarone 15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBF (15)</td>
<td>138 ± 31</td>
<td>153 ± 28</td>
<td>145 ± 23</td>
</tr>
<tr>
<td>CVR (15)</td>
<td>0.75 ± 0.17</td>
<td>0.59 ± 0.12</td>
<td>0.65 ± 0.12</td>
</tr>
<tr>
<td>LVVO2 (15)</td>
<td>13.8 ± 3.4</td>
<td>16.8 ± 5.3</td>
<td>14.7 ± 3</td>
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<tr>
<td>LVO2E</td>
<td>57 ± 6</td>
<td>59 ± 7</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>LVLE</td>
<td>6.1 ± 23</td>
<td>9.3 ± 25</td>
<td>11.2 ± 19</td>
</tr>
<tr>
<td>Glucose (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>108 ± 24</td>
<td>120 ± 23</td>
<td>118 ± 23</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>104 ± 29</td>
<td>107 ± 29</td>
<td>109 ± 30</td>
</tr>
<tr>
<td>LDH1 (% total LDH)</td>
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</tr>
<tr>
<td>Arterial</td>
<td>27 ± 6</td>
<td>26 ± 8</td>
<td>25 ± 8</td>
</tr>
<tr>
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<td>22 ± 7</td>
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<tr>
<td>LDH4 (% total)</td>
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<tr>
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<td>4.9 ± 2.3</td>
<td>8.6 ± 5</td>
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<tr>
<td>Coronary sinus</td>
<td>4.7 ± 1.4</td>
<td>7.1 ± 3.5</td>
<td>9.9 ± 5.0</td>
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</tbody>
</table>

Values are mean ± sd.
Paired t test: difference from control values (NS indicated no significance).
Abbreviations: CSBF = coronary sinus blood flow (ml/min); CVR = coronary vascular resistance (units); LVVO2 = left ventricular O2 consumption (ml/min); LVO2E and LVLE = left ventricular O2 or lactate extraction (%); LDH = lactic dehydrogenase; LDH1 = cardiac fraction (European system of nomenclature).

Concomitant simultaneous and equivalent increase in CSBF.

Mean myocardial extraction of lactate did not change significantly: 6.1% in the control state, 9.3% at 5 minutes (NS) and 11.2% at 15 minutes (NS). However, five of the eight patients with lactate production at rest improved, shifting to extraction at 5 and 15 minutes of amiodarone, one patient had no change and lactate production further increased in two. Of the eight patients with lactate extraction, six were unchanged and in two patients, extraction shifted to production. Thus, in the 16 patients, lactate metabolism was unchanged in seven, improved in five and deteriorated in four, possibly indicating myocardial ischemia in the last four patients.

Arterial glucose concentration increased in 13 of the 14 patients in whom it was measured, from a mean of 108 mg/100 ml at rest to 120 mg/100 ml at 5 minutes (p < 0.01) and to 118 mg/100 ml at 15 minutes (p < 0.001). Since coronary sinus glucose concentration increased proportionally less than arterial glucose concentration, arterial-coronary sinus glucose difference rose significantly from a mean of 3.1 mg/100 ml at rest to 12.7 mg/100 ml at 5 minutes (p < 0.05) and 8.1 mg/100 ml at 15 minutes (NS), as well as the percentage of myocardial glucose extraction from 3.8% at rest to 9.3% at 5 minutes (p < 0.05) and to 7.8% at 15 minutes (NS).

One of the cardiac LDH isoenzymes, fraction 1, was significantly decreased in the coronary sinus 15 minutes after amiodarone, from 27% of total LDH to 22% (p < 0.05), while arterial concentration was unchanged at 26%; therefore, myocardial production of LDH1 at rest, mean of −2.5%, reversed to extraction at 15 min, +3.8%; this change is slight and not significant. Arterial and coronary sinus concentrations of LDH4 significantly increased at 5 and 15 minutes after the drug (p < 0.05); both changes were of the same magnitude, so no change in myocardial extraction or production occurred. The drug had no effect on other isoenzymes of LDH and on enzymes GOT and total CPK.

Other Substances. Amiodarone had no effect on the myocardial metabolism of Hb, Ht, Pco2, Po2, Na-K, calcium, inorganic phosphate, urea nitrogen, uric acid, cholesterol, proteins, albumin, total bilirubin, alkaline phosphatase and creatinine.

Clinical Effects

No complication occurred during the drug study and the angiographic procedures. Six patients ex-
Electrophysiologic Effects

Electrophysiologic effects were recently summarized by Rosenbaum et al. The drug increases the refractory period of atrial and ventricular muscle and is therefore useful in the treatment of atrial and ventricular premature depolarizations; it also increases refractoriness of the atioventricular node and His-Purkinje system, as well as in the anomalous pathways of patients with the Wolf-Parkinson-White syndrome, creating the most favorable conditions for prevention and interruption of any reentry mechanism in this and other types of tachycardia.

Experimental Hemodynamic Studies

Initial and more recent hemodynamic observations in laboratory animals reveal that amiodarone has intrinsic and extrinsic (anti-adrenergic) pharmacologic properties. Direct effects of amiodarone are a slowing in heart rate, a decrease in pressure work of the heart without a decrease in flow, a fall in peripheral resistance, a modest decrease in contractility and an increase in coronary blood flow. These effects on systemic and coronary hemodynamics permit a favorable influence on the balance of oxygen supply and demand in myocardial ischemia. Indirect effects of amiodarone have also been documented in experimental studies. This agent shows marked but partial antagonistic effects on various α- and β-adrenergic cardiovascular phenomena, such as hypertension and tachycardia induced by noradrenaline and adrenaline. However, amiodarone is not an α- or β-blocking agent.

Human Hemodynamic Studies

Few hemodynamic studies of amiodarone are available. Ourbak injected intravenously 5 mg/kg of amiodarone in six patients with coronary artery disease and noted a decrease in HR of only 2–5 beats/min. This is similar to the results of the present study. Sicart injected the drug, using the same dosage, in six patients catheterized because of heart murmur, but without significant hemodynamic lesion. He also observed no change in HR after 5–30 minutes, but then noted an acceleration at the end of the injection from 78 to 97 beats/min (69 to 79 beats/min in the present study). This reflexely mediated acceleration in HR is transient and probably related to the drop in blood pressure.

The predominant effect of amiodarone is a marked systemic vasodilatation and a hot feeling like that frequently experienced with the injection of contrast material during angiographic procedures. This dilatation is maximal at 2–3 minutes of the injection and, at that time, all arterial pressures are decreased. Left ventricular systolic and end-diastolic pressures decrease at 3 and 5 minutes and remain lower than resting values at 15 minutes. These effects on arterial pressure do not represent a negative effect of the drug, since should this have occurred, LVEDP would have increased and CI would have diminished.

Discussion

Background

Although introduced as an antianginal agent, amiodarone hydrochloride might be more effective as an antiarrhythmic agent. Its efficacy has been demonstrated not only in the treatment of chronic cardiac conditions such as angina or arrhythmias, but also in the management of acute clinical situations such as variant angina and various severe ventricular arrhythmias sometimes resistant to the usual therapeutic measures. Besides its effectiveness, this relatively new cardioprotic drug meets the requirements for an ideal antiarrhythmic, as it is available orally and parenterally, does not depress the circulation in preliminary studies reported in humans, and is relatively well tolerated when administered for as long as 8 months. In this study we tried to determine the systemic and coronary hemodynamic effects of amiodarone and to investigate the mechanisms underlying its pharmacological actions.
In Sicart's study, LVSP decreased from 132 to 106 mm Hg at 5 minutes (132 mm Hg to 109 mm Hg in our study) and SVR decreased from 16 to 11 units (20 mm Hg to 16 mm Hg in our study). In the same study, LVEDP was also decreased at 5 minutes of 5 mg/kg of amiodarone. This fall in LVEDP at 5 minutes was more obvious when basal LVEDP was high. A decrease in venous return through venodilatation might explain this reduction of LVEDP. Unloading of the left ventricle through a decrease in afterload is probably responsible for this decrease in LVEDP as well as for the increase in CI. These effects of the drug on LVEDP, CI and stroke volume could also be related to both direct and indirect (increase in myocardial blood flow) increases in contractility. Contractility was not evaluated in this study.

CSBF increased in the patients with coronary artery disease, although perfusion pressure fell. Coronary vasodilatation occurred and explains the fall in CVR and the increase in CSBF. This mild increase in CSBF could also be due to coronary sinus blood reflux from the right atrium. Right atrial pressure was not routinely measured in this study, but we would suspect a fall instead of a rise after amiodarone since this drug caused a decrease in SVR. In the only available study of the effects of this drug on myocardial flow, CSBF was 138 ml/min at rest in six patients with coronary artery disease and was unchanged at 5, 15 and 30 minutes of the administration of 5 mg/kg of amiodarone.

This drug might also have effects on cardiac metabolism. Myocardial O2 extraction was unchanged; however, myocardial O2 consumption slightly increased, and this could be due to a sole increase in CSBF, since arterial-coronary sinus O2 difference was unchanged. This rise in myocardial O2 consumption and secondarily of CSBF could be due to enhancement of contractility.

Half of the patients we studied were ischemic at rest in terms of lactate metabolism, and many of them improved after amiodarone. Myocardial ischemia may have occurred in four patients with lactate production; when analyzing their clinical and hemodynamic data, we found the following explanations in one or more patients: absence of coronary and systemic vasodilatation, increase in TTI, or tachycardia. Arterial glucose concentration rose in these patients; since CSBF also increased, more glucose was available as a source of energy to the heart. This effect of the drug on the myocardial metabolism of glucose might be beneficial in ischemia during myocardial infarction or coronary artery bypass surgery. This remains controversial, although there is a recent interest in the administration of this substrate with K and insulin.

Isoenzyme I of LDH favors conversion of lactate to pyruvate, which is converted to acetyl-CoA to enter the citric acid cycle, the most important source of energy production. This enzyme was not increased in the coronary sinus. Since its arterial concentration was unchanged, there was some extraction by the myocardium. One may speculate that this increase in LDH extraction by the heart after amiodarone parallels the improvement in lactate metabolism.

This study demonstrates that amiodarone used in parenteral form is a powerful direct vasodilator of the systemic and coronary vessels, and therefore these beneficial effects of amiodarone should be further evaluated in patients with coronary artery disease. The drug probably should not be used orally for an extended time because of its side effects. Thus, it may have a limited application in chronic angina pectoris and could be useful orally to control refractory arrhythmias over relatively short periods.

Its main benefit may be when used acutely to control arrhythmias or, as suggested in this study, as an afterload-reducing agent.

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References

The Influence of Left Ventricular Volume and Wall Motion on Myocardial Images

HENRY GEWIRTZ, M.D., GAIR J. GRÖTTE, M.D., H. WILLIAM STRAUSS, M.D., DENNIS D. O’KEEFE, M.D., CARY W. AKINS, M.D., WILLIARD M. DAGGETT, M.D., AND GERALD M. POHOST, M.D.

SUMMARY We studied 10 dogs to determine if changes in myocardial images could result from alterations in left ventricular (LV) geometry independent of any change in tracer distribution. All dogs received 20 mCi of 99mTc-labeled albumin microspheres (10–45 μ) via the left atrium, after which control multigated, gated and ungated myocardial perfusion images were obtained. Next, five dogs were sequentially imaged 1) during partial aortic occlusion to increase LV volume; 2) after release of the aortic occlusion; 3) after ligature of the coronary vasculature of the apex of the LV to produce regional dyskinesia; and 4) after nitroprusside induced hypotension to decrease ventricular volume. Only ligation and nitroprusside studies were done in the remaining five dogs. We gave 1.5 mCi of thallium-201 intravenously to two other dogs and obtained sequential ungated control, ligation, and nitroprusside images.

At postmortem exam, tracer activity was equivalent at the apex and base for both microspheres and thallium. Nevertheless, partial aortic occlusion caused defects in the apex and anterior wall in four of five dogs. Coronary ligation caused new defects in eight of 10 dogs given microspheres and in both dogs given thallium. With nitroprusside, microsphere and thallium defects generally decreased in size. Gated images showed that defects caused by ligation tended to be larger in end-systole than in end-diastole, while all partial aortic occlusion-induced defects were equal or greater in size in end-diastole compared with end-systole.

These results indicate that changes in LV geometry or contraction pattern may cause defects on myocardial images without any change in tracer distribution.

SERIAL IMAGING after administration of 201TI has been used by several investigators to differentiate between myocardial ischemia and infarction.1-4 Defects related to ischemia eventually fill in, while those related to infarction persist. Sometimes regions which initially demonstrate normal or reduced activity appear to lose 201TI activity over time. Such changes, when they occur, have usually been ascribed to concomitant changes in tracer concentration related to alterations in regional blood flow.4 However, alterations in hemodynamics during ischemia may produce important changes in left ventricular volume or regional wall motion or both.5-9 The influence that ventricular volume and regional wall motion might have on 201TI images, independent of changes in actual tracer distribution, has not been systematically investigated. Therefore, we undertook the present study to assess the effect of these geometric factors on the appearance of myocardial images.

Materials and Methods

Ten mongrel dogs (mean weight 23 kg, range 21–28 kg) were anesthetized with sodium pentobarbital (45 mg/kg i.v.), intubated, and ventilated with a Harvard respirator. We adjusted tidal volume, respiratory frequency, and FIO2 as needed to maintain arterial PO2 above 100 mm Hg and arterial pH and PCO2 within the physiologic range (pH 7.38–7.42; PCO2 35–45 mm Hg). We exposed the heart through a left thoracotomy and suspended it in a pericardial cradle. Through a

From the Departments of Medicine (Cardiac Unit), Surgery and Radiology, Massachusetts General Hospital, Boston, Massachusetts.

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Address for reprints: Gerald M. Pohost, M.D., Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114.

Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease.

P Côté, M G Bourassa, J Delaye, A Janin, R Froment and P David

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