Antiarrhythmic Effects of Aspirin during Nonthrombotic Coronary Occlusion

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SUMMARY To study the action of aspirin upon the myocardium per se, independent of thrombosis, coronary occlusion with a balloon catheter was induced in 53 anesthetized dogs divided into two groups. One group (N = 20) was treated daily with aspirin (600 mg/dog) for seven days and another (N = 33) was untreated. Left ventricular hemodynamics and precordial ECG mapping were used to assess the influence of myocardial ischemia over a four hour period. There were no significant differences in left ventricular function or extent of injury as judged by ECG mapping between the two groups. However, there was a significant decrease in the incidence of ventricular fibrillation in the treated dogs (5% vs 39%). Serial plasma samples for free fatty acid determination showed a significant rise in the untreated group. Aspirin blocked the FFA increment in the treated animals. Tissue samples from the ischemic area of left ventricle exhibited a significant reduction of the sodium and water increments, as well as a lesser potassium loss in the treated animals compared to the controls and may have been the basis for the lower incidence of arrhythmias. Since infusion of 51Cr labelled platelets showed no myocardial accumulation of platelets in either group, microthrombi did not appear to contribute to the observed differences.

ANTI-INFLAMMATORY AGENTS interfere with platelet aggregation.1,2 A number of investigations have examined these effects of anti-inflammatory agents upon platelet function but there has been limited evaluation of the responses of other cells and tissues. In a recent experimental study, we evaluated the effects of aspirin pretreatment upon survival following coronary thrombosis induced by means of a catheter electrode.3 Despite the inability of aspirin to inhibit the formation of a platelet thrombus in the epicardial coronary vessels of this model, survival of the animals was significantly increased.

In subsequent studies, we postulated that the reduced incidence of ventricular fibrillation in the aspirin treated animals was probably due to a decrease in microcirculatory thrombosis which was observed in untreated animals with epicardial thrombotic obstruction.4 Alternatively, an action of aspirin upon the myocardium itself independent of thrombosis may influence the ischemic process and the incidence of arrhythmias. To test this potential mechanism we produced a nonthrombotic coronary occlusion with a balloon catheter in intact anesthetized dogs.

Methods

A total of 57 apparently healthy male mongrel dogs weighing from 21–26 kg were used. Twenty-one of the animals were placed on aspirin by mouth in the amount of 600 mg/day for seven consecutive days prior to the day of the experiment. The remaining dogs were used as controls. After an 18 hour fast, all animals on the day of the experiment were anesthetized with morphine sulfate (3 mg/kg of body weight given intramuscularly) and sodium phenobarbital (20 mg/kg of body weight given intravenously) and subsequently were placed on a respiratory pump to maintain adequate ventilation. Frequent pH determinations were performed to confirm maintenance within the physiologic range. While blood gases were not assessed, arterial samples for substrate taken during the course of the study appeared to be well oxygenated. We have previously observed that pO2 is generally well maintained during experiments of this type.5 The left jugular vein and left and right carotid arteries were exposed through small skin incisions. Number 8F catheters were passed into the left ventricle via the right carotid artery and at the root of the aorta via the femoral artery. Left ventricular and aortic pressures were recorded by means of Statham strain gauge transducers using an Electronics for Medicine DR-8 amplifier recorder. Cardiac output was determined by the thermodilution technique6 with the thermodilution catheter placed in the main pulmonary artery via a jugular vein. All animals were under continuous electrocardiographic monitoring.

Myocardial ischemia was induced by means of a double lumen balloon tipped catheter inserted through the left carotid artery and positioned under fluoroscopic control in the left anterior descending coronary artery (LAD) approximately 2.5 cm from its origin. After determining control hemodynamic parameters prior to the induction of ischemia, the balloon was inflated with approximately 1 ml of air and peripheral coronary pressure was monitored using a Statham strain gauge. Complete coronary occlusion was evidenced by a reduction of mean peripheral coronary pressure to approximately 30 mm Hg and the appearance of an injury potential on standard lead I. No antiarrhythmic drugs were used and animals that fibrillated within the initial 15 minute high risk period were excluded from the study, including three animals from the untreated group and one from the treated group. The experiment was designed for a four hour period during which the hemodynamic parameters and electrocardiograms were continuously monitored and intermittently recorded along with cardiac output. Estimation of size of the ischemic area was made during the four hour period from 20 precordial ECG leads7 determining the number with ST elevation (N-ST) and the sum of the ST elevation (ΣST), using an electrical calibration of 0.1 mV. Serial arterial blood samples were taken from both groups for plasma free fatty acid determination.8 At the conclusion of the studies, the thorax was incised and the heart was rapidly arrested with iced Ringer's solu-

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tion. The ischemic area of left ventricle was excised parallel to and 1 cm lateral to the anterior descending artery, beginning 1 cm below the obstruction site, down to the apex and then perpendicular to the anterior descending artery across to the termination of the most inferior diagonal branch or an imaginary extension when this branch terminates short of the apical level. The outer margin was formed at the termination of the main epicardial segment of the other diagonal branches. This formed an approximately triangular shaped sample with the base at the cardiac apex and the peak just below the obstruction site. In previous studies we have observed that injection of Evans Blue dye distal to the obstruction site at diastolic pressure levels stains this area, except where there is aberrant vessel distribution. Such animals were excluded from this study. A similar sized segment approximating 12 g was taken from the nonischemic posterior wall. In view of the potential heterogeneity of the myocardial metabolic response, the ventricle was divided into inner and outer layers; the tip of the papillary muscle was excluded and the epicardial adipose tissue removed. To analyze for sodium and potassium concentrations, samples were homogenized and extracted for 48-72 hours in distilled water, a sufficient time for complete extraction. Potassium and sodium were determined in duplicate on an Auto Analyzer system with flame attachment. Water content was determined by drying samples in an oven at 100°C to constant weight.

Assessment of microcirculatory thrombosis in this model was made by means of 14C-radiolabeled autologous platelets in seven controls and four aspirin treated animals. Platelets were separated from the animal prior to the experiment and reinfused as previously described. One hour was allowed for equilibration before the coronary balloon catheter was inserted. Multiple myocardial tissue samples (36 to 42) of comparable weight were taken from the region of the obstructed coronary artery and the contralateral nonischemic area. Radioactivity in these tissue samples and in 1 ml of blood taken at the time of sacrifice was determined in a well-type scintillation counter. Tissue isotopic activity was expressed as the percentage of that in blood and tabulated by comparing the ratio of ischemic to nonischemic tissue counts. In the evaluation of the results the study was blind with regard to precordial ECG mapping, tissue analysis for electrolytes and water, free fatty acid levels and radioactive counting of tissue samples. For statistical analysis Student's t-test for paired and nonpaired observations was used as appropriate. Mortality rates were assessed by χ² formula.

**Results**

Table 1 summarizes the groups studied as well as the number of animals and the procedures employed to assess the effects of aspirin pretreatment upon a four hour nonthrombotic coronary occlusion. As shown in table 2 the only significant hemodynamic change occurred in the untreated group with a decrease in stroke volume significant at the P < 0.01 level. Precordial ECG mapping indicated that in the untreated animals, the ΣST rose slightly from 4.41 ± 0.74 mV at 15 minutes to 4.50 ± 0.73 mV over a four hour period. In the aspirin treated animals ΣST fell from 6.25 ± 1.60 mV to 4.23 ± 0.89 but this was not significantly different from the untreated group. The extent of ischemia as judged by the N-ST remained unchanged in the untreated animals, from 14 ± 1.11 to 14.53 ± 1.25 sites. The tendency in the treated group for the N-ST to decrease, from 12.4 ± 1.52 at 15 minutes of ischemia to 9.38 ± 1.34 sites at four hours, was also not significant when compared with the untreated animals.

Analysis of electrolyte composition in the ischemic tissue of untreated animals showed a significant increase of sodium and water associated with a decrease of K⁺ concentration in all myocardial layers compared to the nonischemic area (table 3). In the aspirin treated group the degree of intracellular sodium increase and potassium decrease in the ischemic area was less than for the nontreated group. Thus comparing the ischemic areas of the treated and nontreated groups, this difference was significant for sodium in the outer layers and potassium in the inner layers and the gain of water was significantly less in all layers. It should be noted that even the nonischemic tissue in the aspirin treated animals contained significantly less water than the nonischemic tissue of the untreated animals (P < 0.01). Since the only variable between the two groups was aspirin pretreatment, such differences may be associated with the effects of aspirin, the nature of which are not clear.

Free fatty acid levels in arterial plasma of untreated animals rose during ischemia from a control of 210 ± 38 µEq/L to 696 ± 246 µEq/L by four hours (P < 0.05). In the

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**TABLE 1. Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Aspirin-treated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>ECG mapping</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Platelet-14Cr studies</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Tissue electrolytes</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Plasma FFA</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*600 mg/day for seven days.

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**TABLE 2. Hemodynamic Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>147 ± 9</td>
<td>131 ± 7.90</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>139 ± 8.2</td>
<td>119 ± 7.2</td>
</tr>
<tr>
<td>LVEDP pressure (mm Hg)</td>
<td>12 ± 2.0</td>
<td>10 ± 1.2</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>27.1 ± 2.5</td>
<td>17.8 ± 2.52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>60'</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Treated</td>
<td>Untreated</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>142 ± 8.1</td>
<td>126 ± 6.70</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>127 ± 10.1</td>
<td>120 ± 8.4</td>
</tr>
<tr>
<td>LVEDP pressure (mm Hg)</td>
<td>12 ± 1.2</td>
<td>11 ± 1.2</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>24.36 ± 1.23</td>
<td>16.22 ± 1.74</td>
</tr>
</tbody>
</table>

*P <0.01 compared to their own control levels.

Abbreviations: SV = stroke volume; LVEDP = left ventricular end-diastolic pressure.
Aspirin treated group this response was aborted. Control
levels at 232 ± 46 μEq/L did not differ significantly from
the four hour levels of 287 ± 42 μEq/L.

Table 4 indicates the average radioactivity distribution
of labelled platelets in the myocardium after four hours of coro-

Table 4. Radioactivity Distribution (Platelet-51Cr) after Four Hour Coronary Occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Ratio (ischemic/nonischemic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreated</td>
<td>7</td>
<td>1.30</td>
</tr>
<tr>
<td>Aspirin treated</td>
<td>4</td>
<td>1.44*</td>
</tr>
</tbody>
</table>

*P = NS.
stable preischemic heart rates of 80 to 100 per minute were compared to those with significantly higher levels. This is not the case when heart rate is acutely increased during ischemia.

Despite the failure to find a significant difference in the hemodynamic response or the area of ischemia as judged by the multiple precordial ECG leads, there was a significant difference in the electrolyte and water composition of the ischemic area. The aspirin treated group exhibited less loss of potassium and gain of sodium and water compared to untreated animals. This may have been the basis for the reduced incidence of fibrillation, as has been suggested during the use of classical antiarrhythmic agents.

Whether aspirin has a direct or indirect effect on the myocardium to alter electrolyte and arrhythmia incidence is not known. Salicylates have been shown to inhibit catecholamine-induced lipolysis in vitro. Since the rise of plasma free fatty acids, postulated by others to increase arrhythmia incidence during untreated myocardial ischemia, was prevented in the aspirin treated group, the action of this agent may be related to this alteration of lipid transport. Further, since aspirin has been observed to reduce catecholamine-induced vasoconstriction, an inhibitory action on catecholamines in the myocardium may be a basis for an antiarrhythmic response during acute ischemia. In therapeutic dose aspirin has been found to decrease cAMP in lymphocytes as well as inhibit the rise of the nucleotide in these cells in response to isoproterenol and prostaglandin. Such an action of aspirin in the myocardium may be a basis for antiarrhythmic activity since enhanced cAMP formation in the ischemic myocardium has been postulated to be a major factor in the genesis of arrhythmias.

Acetyl salicylic acid may also act through inhibition of prostaglandin or its endoperoxide precursors. However, it should be noted that the acute administration of indomethacin to inhibit prostaglandin synthesis during myocardial ischemia was associated with evidence of enhanced injury, suggesting that prostaglandin, instead of promoting injury during ischemia, may be protective.

We have previously reported that the blood levels of aspirin achieved by this dose regimen was in therapeutic range for man. Whether a dosage and duration of therapy are critical to the observed response require further delineation.

Acknowledgments

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References

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