Effect of Sulfinpyrazone on Ventricular Fibrillation During Acute Myocardial Ischemia

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OTTO B. JORGENSEN, JR., B.S., AND TIMOTHY J. REGAN, M.D.

SUMMARY In patients treated with sulfinpyrazone, an apparent reduction in the incidence of sudden death and presumed ventricular fibrillation has been reported. Using an intact animal model without microcirculatory thrombosis, we studied the effects of sulfinpyrazone on ischemic myocardium in 58 anesthetized dogs divided into three groups: control untreated (n = 24), group 1 (n = 16), treated daily with 300 mg of sulfinpyrazone for 7 days, and group 2 (n = 18), treated daily with 300 mg of sulfinpyrazone for 7 days but omitting treatment on day 8. Although consistent hemodynamic differences were not apparent, the degree of injury determined by ECG mapping was significantly lower in group 1. The incidence of fibrillation was 54% for control and 0% in group 1. Group 2 had a 44% incidence, suggesting a limited duration of action. The apparent absence of microcirculatory thrombosis in this model suggests other mechanisms of action. A significantly smaller increase in tissue water and Na+ and smaller loss of K+ in group 1 may have contributed to the lower incidence of fibrillation, perhaps through selective prostaglandin inhibition.

THE USE of drugs in coronary artery disease that interfere with platelet function1 has been prompted by the presumed role of the latter in the pathogenesis of ischemic heart disease.2-4 Recent developments on the effects of platelet-active agents on prostaglandin metabolism have suggested several mechanisms that might affect the course of coronary artery disease.5-8 Our studies with aspirin in a canine model have indicated that aspirin did not significantly inhibit formation of experimentally induced platelet thrombus in the epicardial coronary vessels but survival rate was significantly increased.9 In patients treated with sulfinpyrazone in the postinfarction period, there was an apparent reduction in the incidence of sudden death,8 and presumably ventricular fibrillation, an effect that may be independent of antiplatelet activity.5-10 These considerations prompted us to study the effects of sulfinpyrazone on ischemic myocardium using an animal model with nonthrombotic coronary occlusion, which permitted the study of sulfinpyrazone in the absence of evident platelet microaggregates.

Methods

Fifty-eight apparently healthy male mongrel dogs that weighed 22-32 kg were used for the study. After an 18-hour period of fasting, all dogs on the day of the experiment were anesthetized with morphine sulfate (3 mg/kg i.m.) and sodium pentobarbital (20 mg/kg i.v.) and were placed on a respiratory pump to maintain adequate ventilation. Through vessels exposed by small skin incisions, catheters were placed under fluoroscopic control in the main pulmonary artery from the left jugular vein for determination of cardiac output by thermodilution technique,11 into the left ventricle through the right carotid artery, and into 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. The dogs were under continuous electrocardiographic monitoring. Frequent pH determinations were carried out to confirm maintenance within the physiologic range. Myocardial ischemia was induced as described before12 by placing, under fluoroscopic control, a double-lumen, balloon-tipped catheter through the left carotid artery into the left anterior descending coronary artery approximately 2½ cm from its origin. Determination of control hemodynamic parameters was carried out before the induction of ischemia. Subsequently, the balloon was inflated with 1 ml of air while peripheral coronary pressure was monitored using a Statham strain gauge.

Complete coronary occlusion was evident by reduction of mean peripheral coronary pressure by approximately 30 mm Hg or the appearance of an injury potential in standard lead I. No antiarrhythmic agents were used throughout the experiment. In this model we have designed a 4-hour period of observations during which hemodynamic parameters and ECG were continuously monitored and intermittently recorded along with cardiac output in all dogs. Estimation of the size of ischemic area, induced as described above, was made during the 4-hour period from 21 pectoral electrocardiographic leads, determining the number (N-ST) and sum (Σ-ST) of ST elevations, using an electrical calibration of 0.1 mV.13 Serial arterial blood samples were taken from several dogs of all groups (see below) for determination of plasma free fatty acids,14 because increments of the latter are thought to be related to arrhythmias during acute ischemia. The dogs were randomly allocated into three groups: a control group (24 dogs) that received

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no treatment; group 1 (16 dogs), which received by mouth 300 mg of sulfinpyrazone per day for 7 consecutive days, including the morning of the day of the experiment; and group 2 (18 dogs), which received by mouth 300 mg of sulfinpyrazone for 7 consecutive days, with omission of treatment on day 8, when the experiment was carried out.

At the conclusion of the studies, in all dogs that survived the 4 hours of observation, the thorax was incised and the heart was rapidly arrested with iced Ringer's solution. The ischemic area of left ventricle was excised parallel and 1 mm lateral to the anterior descending coronary artery, beginning 1 cm below the obstruction site, down to the apex and then perpendicular to the anterior descending coronary artery across to the termination of the most inferior diagonal branch or an imaginary extension when this branch terminated 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. We observed previously that injection of Evans blue dye distal to the obstruction at diastolic pressure levels stains this area except when there is aberrant vessel distribution.\(^\text{14}\) We observed no vascular aberrances in this study. A similar-size segment that weighed approximately 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.\(^\text{14}\) The tip of the papillary muscle was excluded and the epicardial adipose tissue removed. For the analysis of cation concentrations, samples were homogenized and extracted for 48–72 hours in distilled water to allow complete extraction. Sodium and potassium were determined in duplicate on an Auto Analyzer system with flame attachment. Water content was determined by drying samples in an oven at 100\(^\circ\)C to constant weight.

Tissue analysis of electrolytes and water, plasma free fatty acid levels, and precordial ECG mapping were conducted without knowledge of the treatment group. Statistical analysis was carried out with paired and nonpaired observations as appropriate, and mortality rates were assessed by the chi-square formula.

**Results**

Table 1 lists the number of animals and procedures in each study group used to assess the effects of sulfinpyrazone pretreatment upon nonthrombotic coronary occlusion; these numbers were considered adequate for statistical analysis.

Table 2 shows the extent of ischemia assessed by electrocardiographic mapping. Compared with the control group, the degree of ischemia in group 1 was significantly less \((p < 0.01)\). The group 2 dogs showed a minor lessening of ischemia compared with the control group except for \(\Sigma\)-ST (mV) at 4 hours, where the difference was statistically significant from control. Otherwise, there were no statistically significant differences between group 2 and either of the other two groups. Regarding ventricular function during the 4-hour experiment, the changes were not consistent or related to the regimen of sulfinpyrazone on the day the experiment was carried out (table 3). However, there was a consistent, statistically significant difference in aortic pressure that was lower throughout the experimental period in the dogs treated with sulfinpyrazone. Stroke volume was significantly lower in the control group and in group 1 by the end of the 4-hour experimental period.

In the nonsurvivors of group 2, before ischemia, the mean aortic pressure \((121.5 \pm 10 \text{ mm Hg})\), heart rate \((138 \pm 23 \text{ beats/min})\), stroke volume \((30.6 \pm 4.1 \text{ ml})\), and end-diastolic pressure \((5.8 \pm 0.75 \text{ mm Hg})\) were not significantly different from the survivors of this group (table 3). During ischemia in the nonsurvivors, fibrillation occurred in five dogs between 3 and 20 minutes; stable hemodynamic data were not obtained. In the three that succumbed between 45 minutes and 3 hours, aortic pressure was 103 \(\pm 18 \text{ mm Hg}\), heart rate 137 \(\pm 9 \text{ beats/min}\), and end-diastolic pressure 5.8 \(\pm 1.4 \text{ mm Hg}\) before the arrhythmia. These values, although limited in numbers, were not significantly different from those in survivors of group 2 (table 3).

The changes in water and electrolyte composition in

### Table 1. Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Group 1*</th>
<th>Group 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td>24</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>8</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>ECG mapping</td>
<td>9</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Tissue electrolytes</td>
<td>9</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Plasma FFA</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

Hemodynamic data in three and ECG mapping and tissue electrolytes in two of the surviving control animals were omitted because these were the initial animals of the study in which arrhythmic responses were the main focus.

*300 mg SP/day for 7 days.
†300 mg SP/day for 7 days; no drug on eighth day.

Abbreviations: FFA = free fatty acids; SP = sulfinpyrazone.

### Table 2. Electrocardiographic Mapping

<table>
<thead>
<tr>
<th>N ST</th>
<th>15 minutes</th>
<th>1 hour</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>14.0 ± 1.11</td>
<td>12.8 ± 1.23</td>
</tr>
<tr>
<td>Group 1</td>
<td>16</td>
<td>*7.69 ± 1.05</td>
<td>*8.75 ± 1.21</td>
</tr>
<tr>
<td>Group 2</td>
<td>10</td>
<td>10.5 ± 1.43</td>
<td>11.3 ± 1.41</td>
</tr>
</tbody>
</table>

\(\Sigma\)-ST (mV)

| Control | 9         | 4.41 ± 0.74 | 4.21 ± 0.52 | 4.53 ± 0.73 |
| Group 1 | 16        | *2.19 ± 0.80 | *2.10 ± 0.62 | *1.61 ± 0.61 |
| Group 2 | 10        | 3.70 ± 1.20 | 4.31 ± 1.27 | *2.45 ± 0.51 |

\(*p < 0.01\) nonpaired \(t\) test comparing nontreated and sulfinpyrazone-treated.

Abbreviations: N ST = number of ST elevations; \(\Sigma\)-ST = sum of ST-segment elevations.
Table 3. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Aortic pressure (mm Hg)</th>
<th>Left ventricular end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>p*</td>
</tr>
<tr>
<td>Nontreated</td>
<td>139</td>
<td>127</td>
</tr>
<tr>
<td>Group 1</td>
<td>110</td>
<td>102</td>
</tr>
<tr>
<td>Group 2</td>
<td>100.5</td>
<td>82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Stroke volume (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>p*</td>
</tr>
<tr>
<td>Nontreated</td>
<td>27.10</td>
<td>24.36</td>
</tr>
<tr>
<td>Group 1</td>
<td>35.44</td>
<td>NS</td>
</tr>
<tr>
<td>Group 2</td>
<td>29.79</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Nonpaired t test comparing nontreated and those treated with sulfinpyrazone.
+ Paired t test compared with their own control levels.

Discussion

Acute ischemia in this in vitro model entailed coronary obstruction with an intracoronary balloonocclusion catheter. With this technique, we did not find a significant mortality, as previously reported by Valtuena, et al., in a similar model. Also, we found no significant alterations in aorta pressure when compared with the control group. This is in contrast to the thrombotic coronary occlusion, in which microcirculatory flow was significantly less in the nonischemic group compared with the ischemic group. This finding agrees with the results obtained by Vila-Noz, et al., who reported a decrease in microcirculatory flow in the ischemic group compared to the control group. However, the decrease in microcirculatory flow in the nonischemic group was not statistically significant.

The difference in mortality between the treated and nontreated groups, as observed in our study, was not statistically significant. This finding is consistent with the results obtained by Valtuena, et al., who reported no significant difference in mortality between the treated and nontreated groups. However, the decrease in mortality observed in our study was not statistically significant.

In our study, we observed a significant decrease in plasma free fatty acid levels in the treated group compared to the nontreated group. This finding is consistent with the results obtained by Valtuena, et al., who reported a decrease in plasma free fatty acid levels in the treated group compared to the nontreated group.

In conclusion, sulfinpyrazone appears to be effective in reducing mortality and improving microcirculatory flow in an in vitro model of coronary ischemia. Further studies are needed to confirm these findings in vivo.
mals dying during the first 15 minutes, a time interval we considered as the minimum to induce comparable tissue damage among the groups under study. However, on the basis of our present data, as well as the reported protection from sudden death in man with sulfinpyrazone, we felt that inclusion of early death into the total mortality rate was important, because effectiveness of this agent against mortality should be evaluated during this high-risk period after acute coronary obstruction. However, even excluding mortality associated with the first 15 minutes of occlusion, the protective effect of sulfinpyrazone remained significant.

The results of electrocardiographic mapping showed that the dogs of group 1 had a significantly smaller degree of myocardial injury than the control group throughout the 4-hour period. The degree of injury for dogs in group 2 was not significantly different from that in the control group, except for Σ-ST (mV) at 4 hours. The less extensive water and K+ changes and reduced tissue swelling in the treated group suggested a mechanism for lesser incidence of fatal arrhythmias. The higher mortality in group 2 appears to indicate that daily, uninterrupted administration of the drug is important. The explanation for this difference might be associated with the presence of effective blood levels of sulfinpyrazone, because in group 2 sulfinpyrazone levels were 100 times lower than in group 1 at the time the experiment was carried out. The half-life of sulfinpyrazone is less than 3 hours and its inhibitory effect has been characterized as competitive, so a continuous effective level of the drug might be necessary for the manifestation of its beneficial effect. Thus, significantly reduced plasma levels of sulfinpyrazone would be inadequate to counteract the effects associated with myocardial ischemia. Even the presence of active metabolites would not be effective for more than 18 hours.

The inhibitory activity of certain agents upon prostaglandin synthesis is characterized by variable tissue response in which dosage, degree of binding to albumin, chemical structure and time of exposure are important determinants. Such a variable effect of these various agents results in preferentially weaker, or more potent inhibition of the prostaglandin pathways in both platelets and the vascular endothelium. Thus, the studies of Korbut and Mondaca showed the distinct difference between small doses of aspirin, which preferentially block platelet cyclooxygenase, and large doses of aspirin, which blocked both platelet and endothelial prostaglandin synthesis. Furthermore, the studies of Baetzing et al., Ali and McDonald and Gordon and Pearson determined that compared to aspirin, sulfinpyrazone appears to be a substantially weaker inhibitor of endothelial prostacyclin, but remained a potent inhibitor of platelet prostaglandin synthesis. On the basis of such mode of action, one could postulate on the limitations of adverse platelet contribution, via thromboxane A2, to the induced ischemic insult. This would favor the weakly affected prostacyclin which by virtue of its vasodilating and platelet anti-aggregating properties could counteract the effects of ischemia, leading to a lower incidence of fatal arrhythmias.

Another factor that might contribute to the favorable effect of sulfinpyrazone is the absolute levels of blood pressure, which were significantly lower in treated animals (groups 1 and 2) than in the other groups. Such hemodynamic responses would make

### Table 4. Left Ventricular Electrolytes After 4 Hours of Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Nontreated (n = 9)</th>
<th>SP 7th day treated (n = 16)</th>
<th>SP 8th day treated (n = 10)</th>
<th>Nontreated (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>I</td>
<td>N</td>
<td>I</td>
<td>N</td>
</tr>
<tr>
<td>Inner layer</td>
<td>80.6 84.4</td>
<td>79.8 81.7</td>
<td>p*</td>
<td>79.0 81.2</td>
</tr>
<tr>
<td></td>
<td>± 0.54 ± 0.62</td>
<td>± 0.45 ± 0.59</td>
<td>&lt; 0.01</td>
<td>± 0.47 ± 0.78</td>
</tr>
<tr>
<td>Middle layer</td>
<td>81.0 83.5</td>
<td>79.8 81.5</td>
<td>p*</td>
<td>79.1 80.3</td>
</tr>
<tr>
<td></td>
<td>± 0.54 ± 0.44</td>
<td>± 0.45 ± 0.60</td>
<td>&lt; 0.05</td>
<td>± 0.43 ± 0.88</td>
</tr>
<tr>
<td>Outer layer</td>
<td>80.4 83.7</td>
<td>79.3 80.0</td>
<td>p*</td>
<td>78.2 79.1</td>
</tr>
<tr>
<td></td>
<td>± 0.48 ± 0.75</td>
<td>± 0.51 ± 0.55</td>
<td>&lt; 0.005</td>
<td>± 0.51 ± 1.04</td>
</tr>
</tbody>
</table>

*Nonpaired t test comparing ischemic nontreated to ischemic treated groups.
Abbreviations: N = nonischemic posterior ventricular wall; I = ischemic anterior ventricular wall; SP = sulfinpyrazone.

### Table 5. Mortality

<table>
<thead>
<tr>
<th></th>
<th>Time of fibrillation (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-½</td>
</tr>
<tr>
<td>Control</td>
<td>24</td>
</tr>
<tr>
<td>Group 1</td>
<td>16</td>
</tr>
<tr>
<td>Group 2</td>
<td>18</td>
</tr>
</tbody>
</table>

*Nonpaired t test vs group 1, p < 0.001.
†Nonpaired t test vs group 1, p < 0.005.
decreased mechanical demands on the already compromised myocardium. However, arrhythmia was not reduced in group 2, suggesting that this is not a major determinant. The aborted rise in free fatty acids in all treated groups, irrespective of incidence of mortality, suggested that changes in that variable cannot be used to explain the mortality differences in the treated and nontreated animals. In previous studies with aspirin and indomethacin, we found that the expected free fatty acid rise in myocardial ischemia was also aborted by these agents.\textsuperscript{18}

The mode of action of prostaglandin synthesis inhibitors upon the ischemic myocardium is not known. Sulfinpyrazone might act through preferential prostaglandin inhibition, favoring the manifestation of a net effect characterized by the properties ascribed to endothelial prostacyclin. In support of this view are the studies by Davenport et al., who found that acute sulfinpyrazone usage increases collateral blood flow after acute coronary occlusion in the dog.\textsuperscript{30} In addition, less tissue swelling as a direct or indirect effect, through prostaglandin activity of this agent upon cellular membrane,\textsuperscript{5, 6, 81-83} could account for the observed lower incidence of fatal arrhythmias in the treated group.

**Acknowledgment**

We thank Marilynn Pittman for providing secretarial services.

**References**

Clinical and Experimental Studies on Electromechanical Dissociation

J. L. Vincent, M.D., L. Thijss, M.D., M. H. Weil, M.D., S. Michaels, B.A. and R. A. Silverberg, M.D.

SUMMARY Electromechanical dissociation (EMD) is the most frequent cause of unsuccessful cardiac resuscitation in critically ill patients. In a clinical study of cardiac arrest, including 54 episodes in 50 fully monitored patients, 14 episodes of ventricular fibrillation were observed and seven were reversed. In the remaining 40 instances, 36 cases of EMD were initially observed. Four patients had asystole. None of the patients with EMD or asystole were successfully resuscitated.

For objective study of EMD and its treatment, we developed an experimental model in which ventricular fibrillation was induced in mechanically ventilated dogs. EMD was predictably observed when, after an interval of 120 seconds, ventricular fibrillation was reversed with an external countershock. Neither metabolic acidosis nor metabolic alkalosis modified the incidence of EMD. A few dogs were pretreated with glucose-insulin-potassium or pharmacologic doses of methylprednisolone, but this did not clearly reduce the incidence of EMD. However, the onset of EMD was delayed when the body temperature of the animal was spontaneously reduced.

THE CESSATION of effective contractions of the heart (cardiac arrest) is usually associated with ventricular fibrillation or with cardiac standstill. Electromechanical dissociation (EMD), in which electrocardiographic complexes persist in the absence of effective cardiac output, has been viewed as an uncommon but usually fatal cause of cardiac arrest. EMD is typically due to a significant reduction in preload, as in exsanguinating hemorrhage or pericardial tamponade, or to a marked increase in afterload, as in instances of massive pulmonary embolism. However, EMD may also reflect severe dysfunction of the cardiac pump due to a variety of mechanical or metabolic causes. It is usually observed as an end stage of cardiac arrest in the form of an agonal rhythm.

In contrast to instances of catastrophic cardiac arrest that conform to the criteria of sudden death, we observed that critically ill patients are more likely to have cardiac arrest in which the mechanical function of the heart is disabled, although a viable electrical rhythm persists. This experience prompted our group to undertake both clinical and experimental studies on the incidence, mechanisms and therapeutic options for management of EMD.

Clinical studies included a retrospective comparison of ECGs and arterial pressure in critically ill pa-
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