Effects of a Cardiac Glycoside on Regional Function, Blood Flow, and Electrograms in Conscious Dogs with Myocardial Ischemia

STEPHEN F. VATNER, HANK BAIG, W. THOMAS MANDERS, AND PAUL A. MURRAY

SUMMARY We studied the effects of coronary occlusion and of subsequent ouabain administration on regional myocardial function, flow, and electrograms in 14 conscious dogs. Coronary occlusion resulted in a graded loss of regional function as reflected by measurements of segment length (SL), velocity of SL shortening and myocardial "work" from the normal to severely ischemic zones, along with graded flow (radioactive microsphere technique) reductions and graded elevation of the regional S-T segment. Ouabain, 20 μg/kg, improved function in the normal zone, in which stroke shortening rose by 0.23 ± 0.07 mm (mean ± SE) and "work" rose by 30.2 ± 9.5 mm Hg-mm. In moderately ischemic segments, stroke shortening rose by 0.60 ± 0.05 mm and "work" rose by 58.1 ± 6.1 mm Hg-mm. In the majority of severely ischemic segments, stroke shortening and "work" also increased; the average effect in all severely ischemic segments was an increase in stroke shortening of 0.35 ± 0.10 mm and in "work" of 31.5 ± 9.8 mm Hg-mm. In addition, ouabain reduced S-T elevation by 0.90 ± 0.20 mV in moderately ischemic zones and by 3.14 ± 0.35 mV in severely ischemic zones, and increased flow by 28 ± 6% and 46 ± 9% in moderately and severely ischemic zones, respectively. All these changes were significant, P < 0.01. Thus, ouabain caused an improvement in perfusion of ischemic tissue, which was associated with significant enhancement of stroke shortening and "work." Most strikingly, ouabain returned normal systolic shortening to 10 severely ischemic segments which previously were akinetic.

THE POSITIVE inotropic effects of cardiac glycosides in normal and failing nonischemic hearts are well established,1-5 whereas their action on the acutely ischemic myocardium remains controversial.6-19 It could be hypothesized that in the ischemic setting the increase in myocardial oxygen demands induced by cardiac glycosides would be deleterious. This point of view gains support from several studies in which overall cardiac function, assessed primarily by measurements of cardiac output, was found not to improve,6,9,10,11,13 or in which electrographic15 or enzymatic19 indicators of ischemia were found to increase. Moreover, it has been shown that cardiac glycosides normally constrict coronary vessels in conscious animals.20,21 If this action also occurred in vessels subserving ischemic zones, it could be deleterious.

Accordingly, the goal of this investigation was to examine the effects of ouabain on simultaneous measurements of regional myocardial function, blood flow, and electrograms in normal and moderately and severely ischemic zones in conscious dogs with acute myocardial ischemia. The specific goals were to ascertain (1) whether function of ischemic tissue improved or deteriorated with ouabain, (2) whether the change in function was associated with a change in blood flow, and (3) whether...
cardiac glycosides constrict coronary vessels in the ischemic heart as has been shown in the normal heart. Since inotropic interventions and, in particular, cardiac glycosides can induce differing results in conscious and anesthetized animals, the present experiments were conducted in conscious dogs in which baseline contractility was not depressed by administration of a general anesthetic or by recent surgery.

Methods

Twenty-six dogs, weighing between 25 and 35 kg, were anesthetized with iv sodium pentobarbital, 30 mg/kg. Through a thoracotomy in the 5th left intercostal space, miniature pressure gauges (Konigsberg P22; Konigsberg Instruments) were implanted within the left ventricle through a stab wound in the apex, and Doppler ultrasonic flow transducers were placed around either the left anterior descending (24 dogs) or circumflex coronary arteries (two dogs). Doppler transducers were used to determine the instantaneous myocardial fiber length. The instrument gives a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 X 10^6 mm/sec between the 3 MHz piezoelectric crystals, thus giving a record of the instantaneous myocardial fiber length. The instrument used in the present study was modified to provide simultaneous measurements of 12 segment lengths and the regional electrograms from each crystal site located in normal, border, and ischemic zones. Thus, in addition to providing dimension measurements, the ultrasonic transducers also served as intramyocardial ECG electrodes which were connected to Clevite-Brush ECG preamplifiers for recording. The standard limb lead configuration was used for ground reference. The position of the miniature ultrasonic transducers was confirmed at autopsy and minimal fibrosis, less than 1 mm, was observed at the site of implantation.

Regional myocardial blood flow was measured by the radioactive microsphere technique. The microspheres (3M Co.) were suspended in 0.01% polysorbate 80 (Twee 80) solution (10% dextran) and placed in an ultrasonic bath for 60 minutes. They subsequently were agitated by direct application of an ultrasonic probe to ensure dispersion of the spheres just prior to injection. Absence of microsphere aggregation was verified by microscopic examination. Prior to injection of microspheres, 0.7 ml of the Tween 80-dextran solution (without microspheres) was injected to determine whether the diluent for the microsphere suspension had an adverse effect on cardiac dynamics. Four to six million microspheres (9 ± 2 μm) labeled with 51Cr, 85Sr, 141Ce, and 48Sc were injected through the catheter implanted in the left atrium for four determinations of blood flow. A reference sample of arterial blood was withdrawn beginning 10 seconds before microsphere injection and continuing for 40 seconds after the injection was completed. After the dog was killed, myocardial tissue samples were obtained from the sites at which function and electrograms were measured. These were dissected into epicardial and endocardial layers, weighed, placed in a multi-channel gamma well counter (Searle Analytic), and counted with appropriately selected energy windows for 10 minutes. The raw counts then were corrected for background and crossover and compared with the reference blood samples to obtain flow expressed in ml/min/g of tissue. Cardiac output was calculated from the ratio of total injected radioactivity to radioactivity in the reference blood sample multiplied by the reference flow rate.

Experiments were conducted 2-4 weeks after operation. While the conscious, unsedated dogs rested quietly, control records of left ventricular (LV) pressure (P), mean arterial pressure, the rate of change of pressure (dP/db), coronary blood flow, heart rate, multiple segment lengths (SL) and velocity (V) of SL shortening were recorded, along with intramyocardial electrograms. After control measurements were recorded and the first injection of microspheres was completed, the coronary vessel was occluded. Occlusion was confirmed by absence of coronary flow until termination of the experiment. Measurements were recorded continuously and the second microsphere injection was made 10-15 minutes after coronary occlusion, at a time when regional myocardial function and electrograms were stable. Ouabain, 20 μg/kg, was administered iv 5 minutes later over a 30-second period to 14 dogs, whereas saline was injected iv at a similar time to 12 control dogs. Data were averaged during preoc-

* Construction details available from authors.
clusion control, at 10–15 minutes after occlusion, and then 3–5 and 10–20 minutes after ouabain. Data collected 10–15 minutes after occlusion were compared for these two groups. In addition, in these two groups, the responses observed 10–20 minutes after ouabain administration were compared with the responses observed 10–20 minutes after saline administration. These protocols are depicted in Figure 1. After 30 minutes of further recordings, the dogs were anesthetized with sodium pentobarbital, 30 mg/kg, and killed to confirm placement of intramyocardial transducers and to obtain myocardial samples at the transducer sites for regional blood flow determination.

Ouabain, 20 μg/kg, was administered iv to the five additional dogs that did not have coronary artery occluders. Microspheres were injected prior to, then 3–5 and 10–20 minutes after ouabain in these dogs. This protocol is also depicted in Figure 1.

Data were recorded on a multichannel tape recorder and played back on three multichannel direct-writing oscillographs at a paper speed of 100 mm/sec. A cardiotachometer, triggered by the pressure pulse signal, provided an instantaneous and continuous record of heart rate. Continuous records of dP/dt and dSL/dt were derived from the signals of LVP and SL with Philbrick operational amplifiers (Teledyne Philbrick Co.) connected as differentiators having frequency responses of 700 and 140 Hz, respectively. A triangular wave signal with known slope (rate-of-change) was substituted for LVP and SL signals to calibrate the differentiators directly. Coronary resistance was calculated for the normal zone as the quotient of mean arterial pressure and coronary flow in the normal zone.

The effects of interventions on regional myocardial function were assessed by measurement of stroke shortening, velocity of segment shortening, and end-diastolic segment lengths. In addition, an X-Y plot of the instantaneous LV pressure and regional SL signals were recorded on a storage oscilloscope and photographed. The area described by this loop was taken as an index of regional myocardial "work" in units of mm Hg • mm. End-diastolic length was the point just before isovolumetric contraction. End-systole coincided with isovolumetric relaxation. These points were identifiable readily in most instances. However, the precise timing of the end-systolic point may have varied by as much as 0.01 second, which could introduce a slight error in measurements reported for some ischemic segments.

Data Presentation and Analysis

The data for the effects of ouabain in the presence of coronary occlusion were compared to the pre-ouabain, occlusion baseline. The figures present the early (3–5 minute) and late (10–20 minute) effects of ouabain in the 14 dogs which received ouabain after occlusion. The tables present only the late (10–20 minute) effects of ouabain in the same 14 dogs described above and compare these effects to those of saline injections in the 12 dogs that underwent coronary occlusion for a similar time period, but were not given ouabain. All data were compared to baseline values by paired t-test, and an unpaired t-test was used to compare changes over identical time periods among different groups. Results are expressed as mean ± SE. The data in the Results section and the figures are presented as percent change from baseline, with the exception of data for regional electrograms and myocardial function after occlusion. These were expressed as absolute changes, because control values were in some in-
LV Systolic Pressure (%Δ)

Mean Arterial Pressure (%Δ)

Heart Rate (%Δ)

Flow (%Δ)

FIGURE 2 The effects of coronary occlusion and subsequent ouabain administration 3-5 minutes (early) and 10-20 minutes (late) are shown on measurements of left ventricular (LV) systolic pressure, dP/dt, mean arterial pressure, and heart rate for 14 dogs. Baseline values (mean ± SEM) are shown at the base of the bars. Significant changes from baseline (P < 0.01) are denoted by asterisks.

stances near or equal to zero. All data in the tables are presented in absolute values.

Results

Effects of Coronary Occlusion Compared to the Preischemic Control State

As stated in Methods, the effects of coronary occlusion before ouabain administration were assessed 10-15 minutes after the onset of ischemia (Figs. 2 and 3).

Overall LV Function (Fig. 2)

After coronary occlusion, LV systolic pressure rose insignificantly, mean arterial pressure rose by 9.1 ± 3.1% from 98 mm Hg, peak dP/dt fell by 82 ± 2.6% from 3340 mm Hg/sec, and heart rate rose by 29 ± 5.0% from 80 beats/min. Although not shown in Figure 2, cardiac output fell by 24 ± 6.3% from 2.82 ± 0.29 liters/minute. These changes were all significant, P < 0.01.

Regional LV Function

The normal zone was the portion of the heart remote from the area of distribution of the occluded vessel. The severely ischemic zone was in the central area of distribution of the occluded vessel, showing reductions in flow of 77 ± 3.5% and in velocity and SL shortening of 94 ± 2.5% and 107 ± 4.6%, respectively. The moderately ischemic zone comprised the intermediate area. The effects of coronary artery occlusion on SL shortening and velocity for the three zones are shown in Figure 3. Additionally, the effects of occlusion on end-diastolic length and segment “work” (not shown in Fig. 3) are reported in detail below.

We studied 16 segments in the normal zone of the 14 dogs that received ouabain. Coronary occlusion exerted only minor effects on regional function in the normal zone. End-diastolic SL rose by 2.5 ± 0.5% from 15.57 ± 1.00 mm, P < 0.01, whereas SL shortening, velocity, and “work” did not change significantly.

We studied 37 segments in the moderately ischemic zone of the 14 dogs that received ouabain. Coronary occlusion reduced function substantially in the moderately ischemic zone. End-diastolic SL rose by 4.8 ± 0.5% from 18.10 ± 1.15 mm, SL shortening fell by 53 ± 3.6% from 3.52 mm, velocity fell by 47 ± 2.9% from 36.7 mm/sec, and segment “work” fell by 47 ± 2.9% from 336 ± 25 mm Hg mm. These changes were significant, P < 0.01.

We studied 25 segments in the severely ischemic zone of the 14 dogs that received ouabain. Coronary occlusion reduced function substantially in the severely ischemic zone. End-diastolic SL rose by 8.2 ± 3.5% from 19.07 ± 1.00 mm, SL shortening fell by 63 ± 3.6% from 3.52 mm, velocity fell by 56 ± 2.9% from 36.7 mm/sec, and segment “work” fell by 63 ± 3.6% from 336 ± 25 mm Hg mm. These changes were significant, P < 0.01.

FIGURE 3 The effects of coronary occlusion on regional myocardial function, flow and electrograms are shown for the normal zone (NZ), moderately ischemic zone (MIZ), and severely ischemic zone (SIZ). Baseline values (mean ± SEM) prior to occlusion are shown at the base of the bars. Significant changes from baseline (P < 0.01) are denoted by the asterisks.
TABLE 1 Effects of Ouabain following Coronary Occlusion on Systemic Dynamics (n = 14) Compared with a Saline-Treated Control Group (n = 12)

<table>
<thead>
<tr>
<th>Group</th>
<th>Change from occlusion baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>109 ± 5.9</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>106 ± 3.1</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>3200 ± 220</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>3060 ± 120</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>116 ± 3.3</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>103 ± 5.3</td>
</tr>
</tbody>
</table>

The data for changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes after ouabain in the treated group of 14 dogs were compared with the changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes later in the saline-treated control group.

zone of the 14 dogs that received ouabain. Coronary occlusion resulted in virtually complete loss of function in the severely ischemic zone. End-diastolic SL rose by 8.2 ± 1.0% from 15.10 ± 1.16 mm, while SL shortening fell by 107 ± 4.6% from 2.69 mm, velocity fell by 94 ± 2.5% from 29.6 mm/sec, and segment “work” fell by 81 ± 5.2% from 266 ± 34 mm Hg • mm. These changes were significant, P < 0.01, and were significantly greater, P < 0.01, than those observed in the moderately ischemic zone.

Intramycocardial Electrogram (Fig. 3)

Coronary occlusion failed to elicit S-T elevation in the normal zone, but increased (P < 0.01) S-T elevation by 3.2 ± 0.2 mV in the moderately ischemic zone and by 9.1 ± 0.7 mV in the severely ischemic zone.

Regional Myocardial Blood Flow (Fig. 3)

With coronary occlusion, flow did not change significantly in the normal zone but fell significantly, P < 0.01, by 44 ± 3.9% from 0.94 ml/min per g and by 77 ± 3.5% from 0.98 ml/min per g in the moderately and severely ischemic zones, respectively. Although not shown in Figure 3, the endocardial-epicardial (ENDO/EPI) flow ratio did not change in the normal zone, but fell significantly, P < 0.01, in the moderately and severely ischemic zones from 1.20 ± 0.03 to 0.83 ± 0.06 and from 1.16 ± 0.05 to 0.60 ± 0.09, respectively.

Effects of Ouabain in the Presence of Coronary Occlusion

The changes that occurred 3-5 and 10-20 minutes after ouabain are compared to the values obtained

TABLE 2 Effects of Ouabain following Coronary Occlusion on Regional Function Compared with a Saline-Treated Control Group

<table>
<thead>
<tr>
<th>Normal zone (n = 10)</th>
<th>Moderately ischemic zone (n = 37)</th>
<th>Severely ischemic zone (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic length (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>17.19 ± 1.86</td>
<td>14.24 ± 1.18</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>15.94 ± 1.02</td>
<td>18.95 ± 1.19</td>
</tr>
<tr>
<td>Segment shortening (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>2.04 ± 0.27</td>
<td>0.88 ± 0.17</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>2.68 ± 0.28</td>
<td>1.64 ± 0.17</td>
</tr>
<tr>
<td>Segment velocity (mm/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>23.8 ± 2.26</td>
<td>10.2 ± 1.28</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>27.6 ± 3.24</td>
<td>19.6 ± 1.65</td>
</tr>
<tr>
<td>Segment work (mm Hg • mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated</td>
<td>186.4 ± 38.08</td>
<td>-0.07 ± 4.93</td>
</tr>
<tr>
<td>Ouabain-treated</td>
<td>274.0 ± 41.84</td>
<td>30.2 ± 9.48§</td>
</tr>
</tbody>
</table>

The data for changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes after ouabain in the treated group were compared with the changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes later in the saline-treated control group.

* Change significantly different from control group (P < 0.05).
† Change significantly different from baseline (P < 0.05).
‡ Change significantly different from control group (P < 0.01).
§ Change significantly different from control group (P < 0.05).
Effects of Ouabain following Coronary Occlusion on Regional S-T Elevation (mV) Compared with a Saline-Treated Control Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Occlusion</th>
<th>Change from occlusion baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated (n = 17)</td>
<td>4.3 ± 0.9</td>
<td>-0.3 ± 0.1*</td>
</tr>
<tr>
<td>Ouabain-treated (n = 31)</td>
<td>4.1 ± 0.2</td>
<td>-0.9 ± 0.2†</td>
</tr>
<tr>
<td>Severe ischemic zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline-treated (n = 20)</td>
<td>11.1 ± 0.9</td>
<td>-0.4 ± 0.5</td>
</tr>
<tr>
<td>Ouabain-treated (n = 44)</td>
<td>9.9 ± 0.7</td>
<td>-3.1 ± 0.4‡§</td>
</tr>
</tbody>
</table>

The data for changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes after ouabain in the treated group were compared with the changes observed between occlusion baseline (10-15 minutes after occlusion) and 10-20 minutes later in the saline-treated control group.

* Change significantly different from baseline (P < 0.05).
† Change significantly different from baseline (P < 0.01).
‡ Change significantly different from control group (P < 0.05).
§ Change significantly different from control group (P < 0.01).

Overall LV Function

Ouabain caused transient changes in pressures and heart rate and more sustained effects on cardiac output and myocardial contractility. At 3-5 minutes after ouabain, LV systolic and mean arterial pressures rose by 9.1 ± 1.1% and 11 ± 1.7%, respectively, peak dP/dt increased by 13 ± 1.9%, and heart rate fell by 11 ± 2.9%. These changes all were significant, P < 0.01. Cardiac output (not shown in Fig. 2) increased by 26 ± 7.3% from 1.98 ± 0.11 liters/min, P < 0.02.

At 10-20 minutes after ouabain, mean arterial and LV systolic pressures were no longer elevated significantly and heart rate was no longer significantly depressed, although dP/dt rose, P < 0.01, to a value 20 ± 2.8% above occlusion baseline, and cardiac output was still 28 ± 7.9%, P < 0.01, above occlusion baseline. Table 1 compares the responses 10-20 minutes after ouabain with those at this time in saline-treated dogs.

Regional LV Function

Ouabain improved regional myocardial function in all zones. The early (3-5 minute) and later (10-20 minutes after occlusion) changes in pressures, velocities, and "work" are shown for the early (3-5 minute) effects of ouabain after coronary occlusion (left panel), and the later (10-20 minute) effects of ouabain (right panel). Significant changes from baseline are denoted by the symbols, whereas baseline values (mean ± SEM) are noted at the base of the bars. Ouabain improved function significantly not only in normal but also in moderately and severely ischemic zones.
The simultaneous phasic waveforms for left ventricular pressure (LVP), dP/dt, and segment shortening in a moderately ischemic zone (MIZ), and three severely ischemic zones (SIZ), and the electrogram from one of the severely ischemic zones are shown during control (left panel), during coronary occlusion (middle panel), and after administration of ouabain (right panel). This example from one of the dogs demonstrates that ouabain improved function, as reflected by increased segment shortening, in the moderately ischemic zone and in two of the three severely ischemic zones, while reducing the S-T electrogram.

Intramyocardial Electrogram (Fig. 6)

At 10-20 minutes after ouabain (Table 3), S-T elevation did not change in the normal zone, while it fell significantly in the moderately and severely ischemic zones.

Regional Blood Flow

Ouabain induced only a transient reduction in flow to the normal zone but caused a sustained
The effects of ouabain 3-5 minutes after coronary occlusion are shown on regional S-T elevation in the normal zone (NZ), moderately ischemic zone (MIZ), and severely ischemic zone (SIZ). Significant changes ($P < 0.01$) are noted by asterisks, while baseline values (mean ± SEM) are noted at the base of the bars. Ouabain significantly reduced S-T segment elevation in ischemic tissue.

elevation in flow to ischemic zones. The early (3-5 minute) and later (10-20 minute) effects of ouabain are shown on regional flow in Figure 7. Table 4 compares the responses 10-20 minutes after ouabain with those at this time in saline-treated animals.

At 3-5 minutes after ouabain, flow fell in the normal zone by $7.3 \pm 2.8\%$, $P < 0.05$, and increased by $16 \pm 4.5\%$, $P < 0.01$, in the moderately ischemic zone and by $54 \pm 23\%$, $P < 0.05$, in the severely ischemic zone.

At 10-20 minutes after ouabain, flow in the normal zone was not significantly different from baseline occlusion values. However, in the saline-treated group, flow rose during this time period, which was a significantly different response from the normal zone of the ouabain-treated group (Table 4). In contrast to saline-treated controls, in the dogs receiving ouabain, flow rose significantly, $P < 0.01$, in the moderately ischemic zone by $28 \pm 6.2\%$, and in the severely ischemic zone by $46 \pm 9.2\%$. However, the ENDO/EPI flow ratio did not change significantly in the normal, moderately or severely ischemic zones.

Coronary resistance (Fig. 8)

Coronary vascular resistance could be calculated only for the normal zone, since coronary perfusion pressure for the ischemic zones was not measured. The effects of ouabain were compared on normal zone coronary resistance in 14 dogs with myocardial ischemia and five other dogs without coronary occlusion (see Fig. 1 for protocol). Ouabain induced only transient coronary vasoconstriction in the normal zone of dogs with myocardial ischemia but caused sustained vasoconstriction in dogs without myocardial ischemia. Coronary resistance increased by $22 \pm 3.8\%$ from 114 mm Hg/ml per min per g at 3-5 minutes after ouabain, but was no longer significantly elevated at 10-20 minutes after ouabain. This response at 10-20 minutes was significantly different, $P < 0.01$, from that observed when ouabain was administered to nonischemic dogs; i.e., in these animals coronary resistance increased by $25 \pm 5.8\%$ at this time (Fig. 8). Moreover, the response was significantly different, $P < 0.01$, from that observed in dogs with myocardial ischemia that were treated with saline rather than ouabain. In these dogs, at 10-20 minutes following saline administration, resistance in the normal zone fell by $14 \pm 3.1\%$. Therefore, in the presence of ischemia, ouabain induced less constriction in the normal zone than observed in nonischemic dogs. However, this should not be interpreted to mean that ouabain exerted no vasoconstrictor action on the vessels in the normal zone of ischemic dogs, since later dilation in that zone, which occurred in saline-treated dogs, was not observed.

Control Ischemia Experiments (Protocol Shown in Figure 1)

As discussed above, in the 12 dogs that underwent coronary occlusion but were given normal saline instead of ouabain, changes in overall function, regional function, flow and electrograms from preoclusion baseline to occlusion were not significantly different from the changes observed in dogs subsequently treated with ouabain. However, ouabain caused significant changes in function, flow, and S-T elevation in ischemic tissue that were not
EFFECTS OF DIGITALIS ON ISCHEMIC MYOCARDIUM/Vatner et al.

The coronary vasoconstrictor effects of ouabain are compared for a group of dogs in which no coronary occlusion (No Occl) was carried out and in another group which had coronary occlusion (Cor Occl). The early (3–5 minute) (left panel) and later (10–20 minute) (right panel) effects of ouabain are compared on mean arterial pressure (AP), normal zone (NZ) flow, and calculated resistance. Significant changes from baseline are denoted by the symbols, while baseline values (mean ± SEM) are shown at the base of the bars. Ouabain initially increased arterial pressure and decreased flow and caused coronary vasoconstriction in both groups of dogs. However, at 10–20 minutes after ouabain, a significant increase in resistance was still observed in the nonischemic dogs but was no longer evident in the normal zones of dogs with myocardial ischemia. Ouabain initially increased arterial pressure and decreased flow and caused coronary vasoconstriction in both groups of dogs. However, at 10–20 minutes after ouabain, a significant increase in resistance was still observed in the nonischemic dogs but was no longer evident in the normal zones of dogs with myocardial ischemia. Observed in these saline-treated dogs, and these differences are covered in detail in Tables 1 to 4.

Discussion

Cardiac glycosides remain one of the primary approaches to treatment of patients with heart failure. However, their therapeutic utility in patients with acute myocardial infarction, especially when heart failure is not present, remains controversial. Several studies in man6, 10, 13 and experimental animals6, 11, 15 have failed to show a beneficial action of cardiac glycosides on the acutely ischemic heart. In contrast, one of the major findings of the present investigation was the ability of ouabain to improve function, not only in normal and moderately ischemic zones, but also in the most severely ischemic zones. The extent and rate of systolic shortening as well as regional “work” rose in all normal and moderately ischemic segments, and in most severely ischemic segments at 3–5 minutes following ouabain administration, and was more pronounced at 10–20 minutes following ouabain, a time course consistent with previous measurements of the peak inotropic responses to the drug in conscious dogs without myocardial ischemia.1 It must be pointed out that, whereas not all severely ischemic segments responded favorably to ouabain, the average effect was a significant, $P < 0.01$, improvement in shortening, velocity, and “work.” Moreover, in some examples, ouabain returned active systolic shortening to segments that were not shortening and actually expanding paradoxically during systole. This effect was not observed in control dogs not treated with ouabain (Table 2).

The enhancement of function of severely ischemic myocardial tissue observed with ouabain in the present investigation has not been noted previously. This is probably due to several factors. Studies in patients have generally focused on measurements of overall ventricular function, or cardiac output,9, 10, 13, which might not be sufficiently sensitive to detect changes in separate zones of the ischemic heart, where a portion is functioning normally and another portion is not contracting at all during systole. Moreover, as pointed out by Rahimotoo et al.12 in a study showing a beneficial effect of digitalis in patients with acute myocardial infarction, cardiac output is a particularly insensitive indicator of myocardial performance, since it is affected by changes in heart rate as well as changes in preload and afterload. The differences observed between the present and prior studies may be due to either sensitivity of technique or to differences in the responses of conscious and anesthetized animals. The latter explanation derives support from the fact that ouabain reduced S-T segment elevation significantly in this study, whereas it has been shown to induce the opposite, i.e., increase S-T elevation, in anesthetized dogs with acute myocardial ischemia.13 Thus, it appears that measurements of mechanical function as well as electrographic parameters respond qualitatively differently to cardiac glycosides in conscious and anesthetized animals with acute myocardial ischemia. The differences may be due to the manner in which collateral flow responds to the drug in the two states or the differing effects on cardiac size and contractility caused by the drug in the conscious and anesthetized animal. Other differences between the present investigation and that of Maroko et al.15 include the extent of myocardial ischemia induced and the methods used to collect data. In the present study, the occlusions were more proximal and the electrograms were recorded from intramyocardial as opposed to epicardial electrodes. However, the determination of the precise difference between the results of the study by Maroko et al.15 and the present investigation awaits paired acute and chronic studies in the same animals.

The positive inotropic effects of digitalis could
actually be harmful to ischemic myocardium if blood flow did not increase to provide sufficient oxygen to meet the increased demand induced by the cardiac glycoside. Another major finding of the present study was that ouabain improved perfusion to ischemic tissue, i.e., flow rose by 28 ± 6% and 46 ± 9% in moderately and severely ischemic zones at 10-20 minutes following ouabain. This improvement in perfusion was probably the critical factor that enabled function to improve concomitantly. Since flow to ischemic tissue can increase spontaneously with time due to opening of collateral or primary channels from the nonoccluded arteries, it was considered important to conduct a series of control experiments, where saline instead of ouabain was administered. In these experiments, flow to ischemic regions did not change significantly over the 30- to 40-minute period of occlusion studied (Table 4). This is consistent with measurements of regional myocardial function in the present investigation, which also did not change significantly over this period in the dogs in which ischemia was induced, but saline instead of ouabain, was administered (Table 2).

There are several possible mechanisms responsible for the ouabain induced improvement in blood flow. Although arterial pressure rose, this factor does not appear to be the essential mechanism, since, during the greatest increase in flow at 10-20 minutes, arterial pressure was elevated only slightly. Heart rate fell slightly, which allowed greater diastolic coronary filling. Although the changes in arterial pressure and heart rate at 20 minutes were not significantly different from the occlusion baseline, they were significantly different from responses observed over a similar time period in the untreated control dogs. Also, the drug may have acted to dilate either collateral channels or primary vessels from the nonoccluded artery.

The latter effect of ouabain, i.e., to dilate coronary vessels, would be particularly surprising in view of digitalis' well-recognized ability to constrict coronary vessels of the normal heart.20-21 The peak coronary vasoconstrictor effect of ouabain occurs within 3-5 minutes of administration. At this time in the present study, flow did not fall in the ischemic zones but did fall in the normal zone. Coronary resistance was calculated only for the normal zone, since the measurement of arterial pressure does not reflect the pressure in coronary vessels in ischemic zones. Coronary resistance in the normal zone rose initially following ouabain, as it did in control animals without myocardial ischemia (Fig. 8). In contrast to the response in control animals without ischemia, ouabain did not reduce blood flow in the normal zone at the 10- to 20-minute measurement period. However, it must be pointed out that untreated dogs with ischemia demonstrated an increase in coronary flow 10-20 minutes after the occlusion response. Therefore, ouabain not only induced early constriction but then acted to restrain the expected increase in flow in the normal zone that should have occurred later, resulting in a redistribution of coronary flow from the normal to the ischemic zones. The effects of ouabain on the normal zone in dogs with myocardial ischemia, but without heart failure, resemble the action of ouabain on peripheral vascular beds in dogs with chronic heart failure.20 In that study, ouabain elicited only transient constriction in peripheral beds, whereas it induced sustained constriction in dogs with normal hearts. Thus, digitalis can exert differing effects in the presence or absence of cardiac disease.

The ouabain-induced increase in blood flow and improvement in function in the ischemic zone was associated with a significant fall in S-T segment elevation. Although the extent to which S-T segment elevation reflects changes in the ischemic state remains controversial,15-29-31 the supportive data on flow and function in the present study as well as the significantly different responses of the nontreated control dogs, suggest that ouabain alleviated the ischemic condition. It is important to keep in mind, however, that ouabain may alter myocardial [Na⁺], [K⁺], and [Ca²⁺] concentration gradients, which could affect the electrographic potentials.

In conclusion, ouabain, a cardiac glycoside, exerts several salutary actions on the ischemic myocardium of conscious dogs which have not been appreciated previously. Ouabain improved function substantially in moderately and severely ischemic zones, even to the point of reversing paradoxical motion to active systolic shortening in some of the severely ischemic segments studied. This effect occurred with a concomitant increase in blood flow to moderately and severely ischemic segments and reduction in S-T elevation. In contrast to results obtained from dogs without ischemia, the coronary vasoconstrictor action of cardiac glycosides was attenuated in normal zones and was apparently absent in the ischemic zones. Thus, cardiac glycosides can exert differing effects not only in conscious and anesthetized animals, but also in the presence and absence of myocardial ischemia.

**Acknowledgments**

The technical assistance of P. Quinn and A. Sherman, and the help in preparation of the manuscript by E. Tennenholz and C. Conran are appreciated.

**References**

3. Braunwald E, Bloodwell RD, Goldberg Ll, Morrow AG: Studies on digitalis. IV. Observations in man on the effects...
Effects of a cardiac glycoside on regional function, blood flow, and electrograms in conscious dogs with myocardial ischemia.
S F Vatner, H Baig, W T Manders and P A Murray

Circ Res. 1978;43:413-423
doi: 10.1161/01.RES.43.3.413

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/43/3/413