Effects of a Cardiac Glycoside in Combination with Propranolol on the Ischemic Heart of Conscious Dogs

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SUMMARY The effects of coronary occlusion and of subsequent propranolol and ouabain administration were examined in 12 conscious dogs. Overall left ventricular (LV) function was assessed by measurement of LV pressure and dP/dt, and regional myocardial function was assessed by measurements of segment length (SL), velocity of SL shortening and regional myocardial “work,” i.e., pressure-length loops in normal and moderately and severely ischemic zones. Regional intramyocardial electrograms were measured at the same sites as function along with regional myocardial blood flow as determined by the radioactive microsphere technique. Coronary occlusion resulted in graded loss of function from the normal to severely ischemic zones, along with graded flow reductions and graded elevation of the ST segment. Propranolol, 1 mg/kg, depressed overall LV function and function in the normal zone more than in ischemic zones. Propranolol reduced flow to the normal zone and increased flow to ischemic zones, while not affecting ST-segment elevation significantly. In the presence of occlusion and propranolol, ouabain, 20 μg/kg, improved overall LV function as well as regional function in the normal, moderately ischemic and severely ischemic zones. In addition, ouabain reduced ST elevation and increased blood flow further in moderately and severely ischemic zones. Most strikingly, ouabain returned normal systolic shortening to eight severely ischemic segments which were previously akinetic.

PROPRANOLOL HAS BEEN ADVOCATED for therapy in acute ischemic heart disease, since the drug normally reduces cardiac rate and contractility and on this basis should lower myocardial oxygen demands and thereby protect ischemic myocardium.1 However, the myocardial depressant action of propranolol, which is even evident in ischemic myocardium,2 could be deleterious when cardiac function is already compromised. In this situation it would be important to enhance contractility. Therefore, the clinical question remains regarding the effects of a non-beta adrenergic positive inotropic agent, e.g., digitalis, in the presence of myocardial depression induced by ischemia and propranolol.

The goal of this investigation was to examine the effects of ouabain in combination with propranolol on simultaneous measurements of regional myocardial function, blood flow, and electrograms in normal, moderately and severely ischemic zones of the heart of the conscious dog with acute myocardial ischemia. The specific goals of this study were to ascertain 1) whether ouabain could reverse the negative inotropic effects of propranolol on the ischemic heart, 2) whether the changes in function were associated with changes in blood flow, and 3) whether digitalis would enhance or ameliorate the ischemic condition, as indicated by ST-segment elevation.3 Since inotropic interventions can produce differing results in conscious and anesthetized animals4 and in particular cardiac glycosides can induce different results in these two states,5 the present experiments were conducted in conscious animals, where baseline contractility was not depressed by administration of a general anesthetic or by recent surgery.

Methods

Twenty-one dogs, weighing between 25 and 35 kg, were anesthetized with i.v. sodium pentobarbital, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, Konigsberg P22 miniature pressure gauges 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 (13 dogs) or circumflex coronary (8 dogs) arteries, 2–3 cm from the bifurcation of these vessels. Hydraulic occluders were implanted just distal to the flow transducers and heparin-filled Tygon catheters were implanted in the left atrium and aorta. Up to six pairs of miniature ultrasonic transducers* were implanted intramyocardially, parallel to the muscle fibers, 1–2 cm apart and varying in depth from 4 to 15 mm, in potentially normal, and moderately and severely ischemic zones. These zones were confirmed by regional flow determination after sacrifice of the animal.

The miniature pressure gauges were calibrated in vitro and in vivo against a calibrated Statham P23 Db strain gauge manometer connected to the left atrial and aortic catheters. At autopsy the position of the gauge within the ventricular cavity was confirmed. Instantaneous coronary blood flow was measured with an ultrasonic CW Doppler flowmeter. An improved ultrasonic transit-time dimension gauge was used to measure regional myocardial segment length (SL).2, 5, 6 The instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 × 10^8 mm/μsec between the 3 MHz piezoelectric crystals, thus giving a record of instantaneous myocardial fiber length. At a constant room temperature the thermal drift of the instrument is minimal, i.e., less than 0.01 mm in six hours. The

*Construction details available from the authors.
frequency response is flat to 60 Hz. Any drift in the measuring system, i.e., in the instrument electronics, the data tape recorder and the oscillograph that displayed data, was eliminated during the experiment by periodic calibrations.

This involved substitution of pulses of precisely known duration from a crystal-controlled pulse generator having a basic stability of 0.001%. The instrument used in the present study was modified further to provide simultaneous measurement of 12 segment lengths and the regional electrograms from all crystal sites, located in normal, border, and ischemic zones. The ultrasonic transducers also served as intramyocardial ECG electrodes and were connected to Cleve-Brush ECG preamplifiers for recording. 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 were suspended in 0.01% Tween 80 solution (10% dextran) and placed in an ultrasonic bath for 60 minutes. They were subsequently agitated by direct application of an ultrasonic probe to insure 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 if the diluent for the microsphere suspension was to have an adverse effect on cardiac dynamics. Four to six million microspheres (9 ± 2μ), labeled with 51Cr, 85Sr, 41Ce and 45Sc suspended in 0.7 ml of 10% dextran, 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 sec before microsphere injection and continuing for 40 sec after the injection was completed. After sacrifice of the animal, myocardial samples were obtained from the sites where function and electrograms were measured, dissected into epi and endocardial layers, weighed, placed in a Searle multi-channel gamma well-counter, and counted with appropriately selected energy windows for 10 min. The raw counts were then corrected for background and cross-over and compared with the reference blood sample 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, unseeded dogs rested quietly, control records of LV pressure (P), the rate of change of pressure (dP/dt), mean arterial pressure, 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, including the first injection of microspheres, the coronary vessel was occluded and the occlusion was confirmed by absence of coronary flow until sacrifice of the animal. Measurements were recorded continuously and the second microsphere injection was made 10–15 min after coronary occlusion, at a time when regional myocardial function and electrograms were stable. Then propranolol was injected, 1.0 mg/kg. Twelve of the dogs studied received ouabain, 20 μg/kg i.v. 10–15 minutes later, while the rest were used as controls. Data were averaged during preocclusion control, at 10–15 min after occlusion, at 10 min after propranolol, and at 10–20 min after ouabain. After 30 min of further recordings the animals were anesthetized with 30 mg/kg of pentobarbital sodium, and sacrificed to confirm placement of intramyocardial transducers and to obtain myocardial samples at the same sites for regional blood flow determination. Data were compared to appropriate baseline values using the paired t-test, while data between the treated and control groups were compared using the unpaired t-test.

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 cardio- tachometer, triggered by the pressure pulse signal, provided instantaneous and continuous records of heart rate. Continuous records of dP/dt and dSL/dt were derived from the signals of LVP and SL with Philbrick operational amplifiers 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 P and SL signals to calibrate the differentiators directly.

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

**Results**

The data for the effects of propranolol in the presence of coronary occlusion were compared to the pre-propranolol, occlusion baseline. The data for the effects of ouabain in the presence of propranolol and occlusion were compared to the pre-ouabain, occlusion plus propranolol baseline. Although the positive inotropic effects of ouabain were evident within one minute, data were summarized at 10–20 min since that was the time of regional flow determination. Only statistically significant changes will be discussed. All changes were significant, P < 0.01, unless noted otherwise.

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 and showed reductions in flow and function greater than 60% and 90%, respectively. The moderately ischemic zone comprised the intermediate area.

**Overall LV Function (N = 21) (table 1)**

Coronary occlusion increased heart rate by 35 ± 5.6% (SEM) from 79 ± 3.7 beats/min, and mean arterial pressure by 14.0 ± 3.0% from 95 ± 2.2 mm Hg and reduced peak dP/dt by 4.1 ± 1.7% (P < 0.05) from 3160 ± 130 mm Hg/sec and cardiac output by 0.39 ± 0.11 L/min from 2.41 ± 0.15 L/min, while LV peak systolic pressure did not change significantly. Propranolol did not affect cardiac output, LV systolic or mean arterial pressures significantly, but
reduced heart rate by 5.6 ± 1.8% and dP/dt by 14 ± 1.2%. Ouabain increased LV systolic pressure by 6.4 ± 2.2% \((P < 0.05)\) and dP/dt by 24 ± 1.2% and decreased heart rate by 9.6 ± 2.8%, while cardiac output and mean arterial pressure did not change significantly.

### Regional LV Function (table 2, fig. 1)

**Normal Zone** (29 segments). Coronary occlusion increased end-diastolic SL by 1.4 ± 0.4% while SL shortening, velocity and "work" did not change significantly. Propranolol increased end-diastolic SL by 1.2 ± 0.2% and reduced SL stroke shortening by 9.2 ± 1.5%, velocity by 13 ± 1.6% and work by 14 ± 2.1%. Ouabain \((N = 20)\) did not change end-diastolic SL and increased SL shortening by 14 ± 3.4%, velocity by 18 ± 3.1% and work by 23 ± 4.6%.

**Moderately Ischemic Zone** (39 segments). Coronary occlusion increased end-diastolic SL by 4.7 ± 0.6% from 18.27 ± 0.91 mm and reduced SL shortening by 57 ± 3.6% from 2.98 ± 0.25 mm, velocity by 45 ± 2.6% from 29.5 ± 2.1 mm/sec and segment work by 45 ± 3.6% from 284 ± 24 mm Hg-mm. Propranolol increased end-diastolic SL by 1.1 ± 0.2% and reduced SL shortening by 11 ± 3.4% and velocity by 13 ± 2.4%, while work did not change significantly. Ouabain \((N = 21)\) did not change end-diastolic SL and increased SL shortening by 84 ± 23%, velocity by 45 ± 6.5% and work by 49 ± 8.1%.

**Severely Ischemic Zone** (45 segments). Coronary occlusion increased end-diastolic SL by 6.7 ± 0.8% from 17.19 ± 0.68 mm, and reduced SL shortening by 115 ± 3.5% from 2.37 ± 0.17 mm, velocity by 94 ± 1.7% from 25.1 ± 1.7 mm/sec and segment work by 97 ± 24% from 240 ± 19 mm Hg-mm. All these changes were significantly greater than observed in the moderately ischemic zone. Propranolol increased end-diastolic SL by 1.1 ± 0.2% and reduced the extent of paradoxical bulging, while work did not change significantly. Ouabain \((N = 29)\) reduced end-diastolic SL by 0.14 ± 0.03 mm and increased SL shortening by 0.23 ± 0.07 mm, velocity by 3.1 ± 0.77 mm/sec, and work by 27 ± 7 mm Hg-mm. It should be pointed out that these data reflect the responses of 17 segments that improved, five segments that did not change and seven segments in which function deteriorated slightly (fig. 2). There were eight akinetic segments that reverted to

### Table 1. Effects of Propranolol and Ouabain on Overall Left Ventricular Function Following Coronary Occlusion

<table>
<thead>
<tr>
<th>Effect</th>
<th>Change induced by propranolol</th>
<th>Change induced by subsequent ouabain (D) or no further intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular pressure (mm Hg)</strong></td>
<td>116 ± 2.8</td>
<td>2.0 ± 1.1</td>
</tr>
<tr>
<td><strong>Left ventricular dP/dt (mm Hg/sec)</strong></td>
<td>2970 ± 113</td>
<td>-415 ± 43*</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td>102 ± 2.9</td>
<td>1.4 ± 1.6</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>102 ± 3.7</td>
<td>-6.2 ± 1.9*</td>
</tr>
</tbody>
</table>

*P <0.01 compared to previous baseline.  
1P <0.05 compared to previous baseline.  
2P <0.01 compared to NI group.  
3P <0.05 compared to NI group.

### Table 2. Effects of Ouabain (D) or No Intervention (NI) after Propranolol (P) Pretreatment

<table>
<thead>
<tr>
<th>Effect</th>
<th>Normal zone</th>
<th>Moderately ischemic zone</th>
<th>Severely ischemic zone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-diastolic length (mm)</strong></td>
<td>ΔD = 0.20*</td>
<td>ΔD or ΔNI</td>
<td>ΔD = 0.20*</td>
</tr>
<tr>
<td></td>
<td>±0.01 (D)</td>
<td>±0.03 (NI)</td>
<td>±0.03 (NI)</td>
</tr>
<tr>
<td><strong>Segment shortening (mm)</strong></td>
<td>ΔD = 0.28*</td>
<td>ΔD or ΔNI</td>
<td>ΔD = 0.28*</td>
</tr>
<tr>
<td></td>
<td>±0.03 (D)</td>
<td>±0.03 (NI)</td>
<td>±0.03 (NI)</td>
</tr>
<tr>
<td><strong>Velocity (mm/sec)</strong></td>
<td>ΔD = 3.9*</td>
<td>ΔD or ΔNI</td>
<td>ΔD = 3.9*</td>
</tr>
<tr>
<td></td>
<td>±0.67 (D)</td>
<td>±0.67 (NI)</td>
<td>±0.67 (NI)</td>
</tr>
<tr>
<td><strong>Segment work (mm Hg-mm)</strong></td>
<td>ΔD = 55.7*</td>
<td>ΔD or ΔNI</td>
<td>ΔD = 55.7*</td>
</tr>
<tr>
<td></td>
<td>±6.5 (D)</td>
<td>±6.5 (NI)</td>
<td>±6.5 (NI)</td>
</tr>
</tbody>
</table>

*P <0.01 compared from previous baseline.  
1P <0.01 compared to NI group.  
2P <0.01 compared to NI group.  

Abbreviations: Ocel. = occlusion baseline; ΔP = change induced by propranolol; ΔD or ΔNI = change induced by ouabain or no intervention.
normal motion with ouabain. One of these responses is shown in figure 3. The beneficial effects on function were maintained until the end of the recording period, i.e., one hour after ouabain administration.

Intramycocardial Electrogram (table 3, fig. 4)

Coronary occlusion failed to elicit ST elevation in the normal zone, but increased ST elevation by 3.1 ± 0.2 mV from 0.5 ± 0.1 mV in the moderately ischemic zone and by 11.8 ± 0.7 mV from 0.5 ± 0.1 mV in the severely ischemic zone. Propranolol failed to lower ST elevation significantly in the normal, moderately or severely ischemic zones from the occlusion levels. Ouabain reduced ST elevation by 0.6 ± 0.2 and 4.0 ± 0.5 mV in the moderately and severely ischemic zones, respectively.

Regional Myocardial Blood Flow (table 4, fig. 5)

With coronary occlusion flow did not change significantly in the normal zone, but fell by 43 ± 2.7% from 0.98 ± 0.03 ml/min/g in the moderately ischemic zone and by 80 ± 2.2% from 0.83 ± 0.03 ml/min/g in the severely ischemic zone. The endocardial/epicardial (endo/epi) flow ratio did not change significantly in the normal zone, but fell in the moderately and severely ischemic zones, from 1.12 ± 0.06 to 0.89 ± 0.07 and from 1.09 ± 0.04 to 0.52 ± 0.06, respectively. Propranolol reduced flow in the normal zone by 7.8 ± 1.4% but increased flow in the moderately ischemic zones (16 ± 3.7%) and severely ischemic zones (50 ± 10%). Ouabain did not change flow significantly in the normal zone, but increased flow in the moderately ischemic zone (14 ± 3.7%) and in the severely ischemic zone (44 ± 5.7%). The endo/epi ratio was not affected significantly.

Control Experiments

Nine control dogs underwent coronary occlusion and were treated with propranolol but were subsequently given normal saline instead of ouabain. The effects of occlusion and subsequent propranolol were not significantly different in these animals from the changes observed in dogs subsequently treated with ouabain. However, there were important differences following ouabain from the propranolol-occlusion baseline which are covered in detail above in the Results, and in tables 1 to 4.

Discussion

A recent study from our laboratory indicated that propranolol increases blood flow to ischemic myocardium in
conscious dogs, but at the same time depresses function slightly. These effects of propranolol were observed in the present study as well. In brief, propranolol depressed function slightly, more so in normal than in ischemic zones, while it improved flow to ischemic myocardium and had little effect on the ST-segment elevation. Because of propranolol’s myocardial depressant effects its salutary action on blood flow could be lost if severe cardiac depression ensued. Under these circumstances, a positive inotropic agent would be indicated. However, the inotropic agent should not act through stimulation of beta adrenergic receptors, since it would be ineffective due to the prior administration of propranolol. The most commonly employed non-beta adrenergic positive inotropic agent is digitalis. It is of interest that a combination of propranolol and digitalis therapy has recently been shown to be beneficial in patients with ischemic heart disease in that it reduced heart size and improved exercise tolerance. For these reasons the effects of digitalis in combination with propranolol pretreatment were examined on regional flow, mechanical function and electrograms in the presence of acute myocardial ischemia.

The effects of cardiac glycosides on ischemic myocardium have been controversial. Some studies have shown that function may deteriorate with digitalis. Theoretically this could occur, since the drug increases myocardial oxygen demands, which in the presence of fixed coronary blood supply should impair myocardial performance. However, one of the major findings of the present study was that ouabain improved perfusion to ischemic tissue, i.e., flow rose to moderately and severely ischemic zones by 14% and 41%, respectively, even after propranolol had induced a prior increment in flow to these ischemic zones. It was felt

**Figure 2. Examples of pressure-length loops for a normal zone (NZ), a moderately ischemic zone (MIZ), and two severely ischemic zones (SIZ) from one dog are shown prior to occlusion (first panel), after occlusion (Occl) (second panel), after propranolol (Prop) (third panel) and finally after subsequent addition of ouabain (Dig) (fourth panel). With occlusion, there was an intermediate loss of function in the moderately ischemic zone, and complete loss of function with paradoxical bulging and reversal of normal counter-clockwise rotation of the pressure-length loop in the two severely ischemic zones. Propranolol reduced function slightly in the NZ and MIZ and decreased the extent of bulging and postsystolic shortening in severely ischemic zones. With the addition of ouabain, function improved in the NZ and MIZ, but most impressively in one of the SIZ in which normal counter-clockwise rotation returned. However in the other SIZ there was no improvement of function, and in fact a slight increase in the amount of negative “work,” i.e., clockwise rotation of the loop, occurred.**
However, significantly. 

Control dogs did not act to have time for diastolic flow. First, bain was associated with a significant reduction in LV PRESSURE (mmHg) over this time period of coronary occlusion. With propranolol slightly less paradoxical bulging and post-systolic stretching of the segment were observed. However, with the addition of ouabain complete reversal to a normal pattern of active systolic shortening ensued with a substantial fall in ST-segment elevation.

**Table 3. Effects of Ouabain and Propranolol on Regional ECG (mV) Following Coronary Occlusion.**

<table>
<thead>
<tr>
<th>Occlusion zone</th>
<th>Control baseline</th>
<th>Change induced by propranolol</th>
<th>Change induced by subsequent ouabain (Dig) or no further intervention (NI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal zone</td>
<td>0.3 ± 0.13</td>
<td>0.2 ± 0.09</td>
<td>0.1 ± 0.11 (D)</td>
</tr>
<tr>
<td>Moderately ischemic zone</td>
<td>3.7 ± 0.16</td>
<td>-0.1 ± 0.19</td>
<td>-0.6 ± 0.13*§ (D)</td>
</tr>
<tr>
<td>Severely ischemic zone</td>
<td>12.2 ± 0.66</td>
<td>-0.4 ± 0.32</td>
<td>-4.0 ± 0.50*§ (D)</td>
</tr>
</tbody>
</table>

*P <0.01 compared to previous baseline.

**Figure 3.** An example of the phasic waveforms for left ventricular (LV) pressure, segment length and the electrograms from that segment are shown along with the pressure-length loop plot from that segment prior to occlusion (Occl) (first panel). After coronary occlusion (second panel), after addition of propranolol (Prop) (third panel), and after the further addition of ouabain (Dig) (fourth panel). With coronary occlusion (second panel), paradoxical bulging was evident along with substantial ST elevation. With propranolol slightly less paradoxical bulging and post-systolic stretching of the segment were observed. However, with the addition of ouabain complete reversal to a normal pattern of active systolic shortening ensued with a substantial fall in ST-segment elevation.

![Image of Figure 3](image-url)

that the increase in flow was not a spontaneous occurrence over this time period of coronary occlusion, since nontreated control dogs did not demonstrate a further increase in flow after propranolol (table 2). There are several mechanisms which could be responsible for the improvement in blood flow. First of all, heart rate fell, which would allow greater time for diastolic coronary filling. In addition, mean arterial pressure rose slightly, although nonsignificantly, which would tend to improve perfusion. Secondly, the drug may have acted to dilate either collateral channels or primary vessels from the nonoccluded artery. This effect of ouabain, i.e., to dilate coronary vessels, would be particularly surprising in view of digitalis' well recognized action to constrict coronary vessels in the normal, nonischemic heart. 

A final point to consider is the possibility that ouabain improved myocardial efficiency in the ischemic heart.

The increase in blood flow to ischemic tissue induced by propranolol did not reduce ST-segment elevation significantly. However, the additional blood flow provided by ouabain was associated with a significant reduction in ST-

**Figure 4.** The effects of propranolol (Prop) in the presence of coronary occlusion (Occl) (left panel) and the subsequent addition of ouabain (Dig) (right panel) are shown on regional electrograms for the normal (NZ), moderately ischemic (MIZ) and severely ischemic zones (SIZ). Baseline values prior to propranolol are shown at the base of the bars on the left, while significant changes are denoted by the asterisks. Propranolol had little effect on the ST-segment elevation but the subsequent administration of ouabain decreased ST-segment elevation significantly in the moderately and severely ischemic zones.

![Image of Figure 4](image-url)
segment elevation in moderately and severely ischemic zones. It should be pointed out that ST elevation tends to diminish with time. However, the nontreated control dogs exhibited significantly less diminution of ST-segment elevation than did the ouabain treated dogs. While the extent to which changes in ST-segment elevation reflect changes in the ischemic state remains controversial,1, 18, 17 the supportive data on flow and function in the present study suggest that ouabain acted to ameliorate the ischemic condition.

While it is important to improve perfusion of ischemic myocardium, an essential question is whether this effect has been sufficient to induce an improvement in function. Another major finding of the present investigation was that ouabain after pretreatment with propranolol improved function not only in normal and moderately ischemic zones but also in the most severely ischemic zones. A clear improvement in function occurred within a few minutes of ouabain administration and was more pronounced at 10–20 minutes following ouabain, a time course consistent with previous measurements of maximal inotropic responses to the drug in normal conscious dogs.4 It is important to point out that the improvement in function was not transient, but was sustained for the entire observation period, i.e., up to one hour after ouabain administration. In some examples ouabain returned active systolic shortening to segments that were not shortening and actually expanding paradoxically during systole (fig. 3). In our experience this reversal phenomenon occurs only rarely after 10 min of coronary occlusion, as reflected in the data for control dogs not treated with ouabain (table 2), and previous studies from this laboratory.2, 8 While a statistically significant improvement in function occurred in the severely ischemic zone, all segments studied did improve with ouabain, some did not change or deteriorated slightly (fig. 2).

The beneficial effects of cardiac glycosides on ischemic tissue observed in this study were not seen with another positive inotropic agent, e.g., isoproterenol, studied previously. We observed that isoproterenol uniformly intensified paradoxical bulging in severely ischemic segments, and increased ST elevation, while having no significant effect on blood flow.5 In contrast, ouabain improved blood flow, decreased ST-segment elevation and generally improved function. These differences in action suggest that in the presence of regional myocardial ischemia cardiac glycosides would be a preferable mode of inotropic stimulation to beta adrenergic stimulation.

In conclusion, a cardiac glycoside in combination with propranolol exerts several salutary actions on ischemic myocardium of conscious dogs. Propranolol improved perfusion of ischemic tissue, while depressing overall and regional function slightly. Ouabain was able to improve function substantially in moderately and severely ischemic zones to the point of reversing paradoxical motion to active systolic shortening in many 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 ST elevation. The question remains whether ouabain in the absence of propranolol would exert these beneficial effects on ischemic myocardium. Recent data from our laboratory suggest that it does.18

References
2. Vatner SF, Baig H, Manders WT, Ochs H, Pagani M: Effects of propranolol on regional myocardial function, electrograms and blood

<table>
<thead>
<tr>
<th>TABLE 4. Effects of Ouabain and Propranolol on Regional Myocardial Blood Flow (ml/min/g) Following Coronary Occlusion</th>
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<tr>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Severely ischemic zone</td>
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*<P <0.01 compared to previous baseline.  §P <0.05 compared to previous baseline.  ¶P <0.01 compared to NI group.

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**Figure 5.** The effects of propranolol (Prop) after coronary occlusion (Occl) (left panel) and the subsequent administration of ouabain (Dig) (right panel) are shown on regional blood flow in the normal (NZ), moderately ischemic (MIZ) and severely ischemic zones (SIZ). Significant changes from the baseline are denoted by the symbols, while baseline values prior to propranolol are denoted beneath the bars on the left. Propranolol reduced flow in normal tissue and increased flow to ischemic tissue. The subsequent addition of ouabain increased flow further to the severely ischemic and moderately ischemic zones.

Beneficial Effect of Physical Training on Blood Flow to Myocardium Perfused by Chronic Collaterals in the Exercising Dog

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SUMMARY To determine the effect of physical training on collateral blood flow, we measured regional myocardial blood flow (MBF) by injecting 15 μ radioactive microspheres at rest and during exercise in 14 dogs with chronic coronary occlusive lesions. Seven dogs subsequently trained for 6 weeks while the other seven remained in kennels. Training effect was documented by decrease in heart rate during exercise that averaged 27 beats/min. MBF studies were repeated after 6 weeks. Myocardial samples were obtained from normally perfused zones (NZ) and from regions supplied via collaterals (collateral dependent zones or CZ). Initially, endocardial blood flow in CZ averaged 1.10 ml/min/g (83% of NZ, P < 0.05) at rest and 1.36 ml/min/g (69% of NZ, P < 0.05) during exercise, indicating relative underperfusion. Epicardial blood flow was equal in NZ and CZ. After 6 weeks MBF was not significantly changed in control animals. After training, however, MBF to underperfused endocardium of CZ during exercise was 39% greater than it had been prior to training. The epicardial portion of CZ (not exhibiting underperfusion) showed no change in MBF during exercise after training. Our data suggest that beneficial effects of training in coronary disease may include improvement in MBF to underperfused collateral-dependent portions of myocardium.

THE INFLUENCE OF PHYSICAL TRAINING on chronic coronary artery disease has not been fully defined.1,2 Patients with limitation by angina pectoris due to coronary artery disease frequently have substantial increases in exercise capacity following a program of physical training.3,4 This beneficial effect of training is, in part, related to a decrease in heart rate for any given submaximal work load. Such a decrease causes reduction in myocardial metabolic activity, and consequently a favorable influence on the balance of myocardial oxygen demand and myocardial oxygen delivery via the coronary arteries. It is possible, however, that physical training may also exert a beneficial effect by improving coronary blood flow to potentially underperfused regions of the myocardium. Eckstein5 demonstrated a higher index of coronary collateral function in previously trained open chest dogs with chronic single vessel coronary occlusive lesions than in similarly prepared dogs without prior physical training. However coronary collateral blood flow has not been measured directly during exercise before and after physical training in animals with chronically occlusive coronary lesions. Recently, use of radioactive microspheres has permitted accurate measurement of coronary blood flow in conscious unmedicated dogs at rest and during exercise before and after acute partial constriction of a coronary artery.6 Microsphere flow data are particularly valuable in that they

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Received August 16, 1977; revision accepted October 20, 1977.
Effects of a cardiac glycoside in combination with propranolol on the ischemic heart of conscious dogs.
S F Vatner, H Baig, W T Manders and P A Murray

_Circulation_. 1978;57:568-575
doi: 10.1161/01.CIR.57.3.568

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/57/3/568

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