Effects of Digitalis on Subendocardial and Subepicardial Dysfunction During Acute Ischemia

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SUMMARY The effects of digitalis (ouabain infusion, priming dose of 10 μg/kg/min followed by 2.0 μg/kg/min) on subepicardial and subendocardial ischemic dysfunction during partial occlusion (59.4% reduction in coronary flow) and total coronary occlusion were evaluated in 14 dogs using pairs of ultrasonic crystals implanted in the epicardial and endocardial layers. After 30 minutes of partial coronary occlusion, systolic shortening in the ischemic zone decreased from 12.4 ± 2.9% to −0.4 ± 0.9% (p < 0.001) in the epicardium and from 18.9 ± 3.1% to −1.0 ± 1.1% (p < 0.001) in the endocardium. Ouabain infusion increased the systolic shortening from −0.4 ± 0.9% to 10.6 ± 3.1% (p < 0.001) in the epicardium and from −1.0 ± 1.1% to 17.2 ± 3.4% (p < 0.001) in the endocardium. The end-diastolic length did not change. In contrast, after 30 minutes of total coronary occlusion, systolic shortening in both epicardial and endocardial layers was replaced by systolic lengthening and remained unaffected by ouabain infusion in both layers. Systolic shortening in the nonischemic epicardial and endocardial layers increased consistently. We conclude that ouabain improves the contractile function of both ischemic epicardial and endocardial layers layers after partial coronary occlusion and does not worsen subendocardial ischemic dysfunction. After total coronary occlusion, however, the contraction of the ischemic zone is unaffected by ouabain.

THE ROLE of digitalis in acute myocardial infarction remains controversial.1-4 Digitalis improves regional left ventricular contraction.5 8-10 However, it may increase ischemic injury.1-5 The subendocardium is reported to be more vulnerable to ischemia than the subepicardium.11-12 The present investigation was designed to examine the differential effects of digitalis on the regional contraction pattern of the subendocardium and subepicardium in the presence of partial and total coronary occlusion.

Materials and Methods

Experiments were performed on 14 open-chested dogs that weighed 26–33 kg. The dogs were anesthetized with i.v. sodium pentobarbital, 30 mg/kg, and ventilated with a Harvard respirator. A polyethylene tube was introduced through an external jugular vein for i.v. infusion. Standard ECG lead II was monitored. Left ventricular pressure (LVP) was measured with a Millar catheter-tip transducer. High-sensitivity left ventricular end-diastolic pressure and the first derivative of LVP were measured with an electronic amplifier and differentiator.

After performing a midline thoracotomy, the heart was suspended in a pericardial cradle. The heart rate was controlled at 120 beats/min by right atrial pacing after injecting the sinus node with 0.1 ml of formaldehyde. The left anterior descending coronary artery was isolated and an electromagnetic flow probe (Micron 1001-B) placed in its middle segment. Zero flow reference was established by transiently occluding the vessel.

Two pairs of ultrasonic crystals were implanted in the potentially ischemic area subtended by the left anterior descending coronary artery, one pair in the subendocardium and the other in the subepicardium, as described previously.13 Two pairs of ultrasonic crystals were also implanted in the nonischemic zone both in the epicardial and endocardial layers. In seven dogs, the left anterior descending coronary artery was ligated just beyond its origin. In seven other dogs, partial coronary occlusion was produced with the help of a microscrew snare14 and the coronary flow in the left anterior descending coronary artery was reduced by 59.4 ± 3.3% of control. The following measurements were recorded using Electronics for Medicine VR-16 and DR-8 recorders: (1) segment lengths from the epicardial and endocardial layers of the nonischemic zone; (2) segment lengths from the epicardial and endocardial layers of the ischemic zone; (3) high-sensitivity left ventricular end-diastolic pressure; (4) first derivative of LVP (LV dP/dT); and (5) the pressure-length loop. On the segment length recordings, the end-diastolic and end-systolic length were identified and the percent shortening was calculated using the method of Theroux et al.15

Protocol

Thirty minutes after coronary occlusion (total or partial), ouabain was administered initially as a priming dose of 10 μg/kg and then as a constant infusion of 2.0–2.5 μg/kg using a Harvard apparatus infusion pump.16 Recordings were taken every 3 minutes until digitalis toxicity appeared. Digitalis toxicity was defined as the induction of ventricular or junctional tachycardia and the development of atrioventricular block. Results were expressed as mean ± SEM and statistical significance was determined by the t test for paired values.
Results

Effects of Ouabain Infusion on the Ischemic Zone

After Partial Coronary Occlusion

After partial coronary occlusion, coronary blood flow decreased from 37.4 ± 2.9 to 15.2 ± 1.6 ml/min (59.4% reduction from control). After ouabain administration and before the onset of toxicity, the coronary blood flow was 16.2 ± 1.8 ml/min, not significantly different from the blood flow after partial coronary occlusion. Figure 1 shows the effects of ouabain on the systolic shortening of the subepicardial and subendocardial layers after partial coronary occlusion. Before partial coronary occlusion, the segment-length curve shows marked systolic shortening in both the epicardial and endocardial layers. After partial coronary occlusion, both the epicardial and endocardial layers show a small increase in end-diastolic length, loss of systolic shortening and appearance of systolic lengthening. After digitalis infusion, the systolic lengthening is replaced by systolic shortening in both layers.

Quantitatively, the systolic shortening in the epicardial layer decreased from 12.4 ± 2.9% to −0.4 ± 0.9% after partial coronary occlusion (p < 0.001). Ouabain restored the systolic shortening to 10.6 ± 3.1% (p < 0.001) (fig. 2). Similarly, in the endocardial layer, the systolic shortening decreased from 18.9 ± 3.1% to −1.0 ± 1.1% (p < 0.001) after partial coronary occlusion and increased to 17.2 ± 3.4% (p < 0.001) after ouabain (fig. 2).

Figure 3 shows the effect of partial coronary occlusion and ouabain infusion on the pressure-length loop recorded from the epicardial and endocardial layers. Before coronary occlusion, the loop was inscribed counterclockwise, indicating segmental shortening during systolic increase of intraventricular pressure. After partial coronary occlusion, the epicardial pressure-length loop shows maintenance of counterclockwise inscription but a marked decrease in the area, indicating a decrease in segmental shortening during systole. With ouabain infusion, the counterclockwise inscription was maintained, with a marked increase in the area of the loop, indicating an increase in segmental shortening. In the endocardial layer, the pressure-length loop, which showed normal counterclockwise rotation in the control recording, demonstrated a clockwise inscription after partial coronary occlusion, indicating passive segment lengthening during rise in intraventricular pressure. After ouabain infusion, the counterclockwise inscription was reinstalled and the area of the loop increased, indicating replacement of systolic lengthening by systolic shortening.

Effects of Ouabain on the Ischemic Zone

After Total Coronary Occlusion

The effects of ouabain on the epicardial and endocardial segment shortening after total coronary occlusion are shown in figure 4. Thirty minutes after total coronary occlusion, the end-diastolic length increased remarkably and holosystolic lengthening appeared. Ouabain resulted in no significant change in either end-diastolic length or systolic lengthening (fig. 4).

Quantitatively, the systolic shortening in the subepicardial ischemic zone decreased from 11.6 ± 2.4 to 10.6 ± 2.1% after ouabain infusion (fig. 4). Figure 2. Effect of ouabain on the systolic shortening of ischemic epicardial and endocardial layers after partial coronary occlusion.
-6.6 ± 2.1% after total coronary occlusion, and was not affected by digitalis (fig. 5). Similarly, in the endocardial layer, the systolic shortening decreased from 20.4 ± 2.6 to -6.3 ± 1.4% after total coronary occlusion and did not change after digitalis (-6.4 ± 1.6%).

Figure 6 shows the effect of total coronary occlusion and digitalis infusion on the pressure-length loop in the epicardial and endocardial layer. Before coronary occlusion, the pressure-length loop in both layers was inscribed counterclockwise, indicating segmental shortening. After total coronary occlusion, the loop showed clockwise inscription indicating systolic lengthening in both epicardial and endocardial layers. After ouabain infusion, the clockwise inscription persisted showing persistence of systolic lengthening in both layers.

The Effect of Digitalis on the End-Diastolic Length After Total and Partial Coronary Occlusion

Both partial and total coronary occlusion increased the end-diastolic length of the epicardial and endocardial layers (table 1). With ouabain infusion, the end-diastolic length did not change in both zones. The end-diastolic length of the epicardial and endocardial layers in the nonischemic zone remained unaffected by partial or total coronary occlusion and was not affected by digitalis.

Effect of Digitalis on Systolic Shortening of the Nonischemic Zone

Figure 7 shows the effect of ouabain on the epicardial and endocardial systolic shortening of the nonischemic zone. The systolic shortening of the nonischemic zone was not affected by total and partial coronary occlusion. Ouabain infusion consistently increased the systolic shortening in both the epicardial and endocardial layers.

Discussion

The effects of cardiac glycosides on acutely ischemic myocardium are controversial.1-3 Cardiac glycosides may have a deleterious effect in acute myocardial infarction, presumably because they cause an increase in bulging of the ischemic zone or in the spil-
lage of myocardial enzymes. An increase in the extent of the myocardial infarct zone may occur, as demonstrated by an increase in ST-segment elevation in epicardial electrograms. Experimental studies indicate that the effects of cardiac glycosides on the contractile function of the central ischemic zone were minimal. However, the contraction measurements of the border zone were remarkably improved. Similarly, ventriculographic studies in patients with chronic ischemic heart disease have shown an improvement of the asynergic zones after administration of cardiac glycosides. Thus, the effect of cardiac glycosides on the border zone or on a chronic ischemic zone, which might be composed of normal and ischemic cells, may be different from that on the central ischemic area, presumably due to preservation of coronary flow, though at a lower level.

In contrast to uniform transmural distribution of myocardial blood flow in normal conditions, both total and partial reduction in coronary blood flow tend to reduce the flow in the endocardium, while flow in the epicardial layer is preserved. This conclusion is supported by the clinical and experimental observations that indicate that progressive ischemic involvement occurs from endocardium to epicardium. Thus when coronary flow is limited, cardiac glycosides, by increasing myocardial oxygen consumption and causing direct vasoconstrictive action, may have deleterious effects in the ischemic zone, particularly in the subendocardium, where ischemic injury is more pronounced. Gross et al. suggested that cardiac glycosides decrease the effective capillary blood flow by producing a shunting of the blood supply away from the endocardium to the epicardium. However, functionally, our observations show that cardiac glycosides dramatically increase segmental shortening in both the subendocardium and the subepicardium after partial coronary occlusion. The increase in the segmental shortening of the subepicardial layer did not have any deleterious effects on the segmental shortening of the subendocardial layer. After total coronary occlusion, however, the segment lengthening in both the endocardial and epicardial layers was unchanged quantitatively or qualitatively by the cardiac glycosides. Thus, the effect of cardiac glycosides on the border zone or on a chronic ischemic zone, which might be composed of normal and ischemic cells, may be different from that on the central ischemic area, presumably due to preservation of coronary flow, though at a lower level.
TABLE 1. Effect of Digitalis on the End-diastolic Length After Total and Partial Coronary Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Coronary occlusion</th>
<th>Digitalis</th>
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</thead>
<tbody>
<tr>
<td>Total occlusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(ischemic zone)</td>
<td></td>
<td></td>
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<tr>
<td>Epicardial</td>
<td>1.00</td>
<td>1.17 ± 0.02*</td>
<td>1.18 ± 0.02</td>
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<tr>
<td>Endocardial</td>
<td>1.00</td>
<td>1.16 ± 0.01</td>
<td>1.16 ± 0.01</td>
</tr>
<tr>
<td>Partial occlusion</td>
<td></td>
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<td></td>
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<tr>
<td>(ischemic zone)</td>
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<td></td>
</tr>
<tr>
<td>Epicardial</td>
<td>1.00</td>
<td>1.06 ± 0.01*</td>
<td>1.05 ± 0.01</td>
</tr>
<tr>
<td>Endocardial</td>
<td>1.00</td>
<td>1.07 ± 0.01</td>
<td>1.06 ± 0.01</td>
</tr>
<tr>
<td>Nonischemic zone</td>
<td></td>
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<tr>
<td>Epicardial</td>
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<td>1.01 ± 0.01</td>
<td>1.01 ± 0.01</td>
</tr>
<tr>
<td>Endocardial</td>
<td>1.00</td>
<td>1.01 ± 0.01</td>
<td>1.00 ± 0.01</td>
</tr>
</tbody>
</table>

*p < 0.05 vs control.

glycosides, despite an increase in contraction measurements of the nonischemic zone.

During progressive reduction in coronary blood flow, the subendocardial contraction was related to subendocardial perfusion in a sigmoidal fashion, while the subepicardial contraction was unrelated to subepicardial flow under these conditions. Subepicardial contraction, on the other hand, is directly related to subendocardial contraction. These observations suggest a "tethering" effect between the two layers. In the present study, the segmental shortening decreased to a similar level after partial coronary occlusion and showed similar increases in shortening following digitalis infusion. Whether a similar degree of improvement in subendocardial and subepicardial contraction is the result of a direct effect of digitalis on the two layers or a tethering of the subendocardial layer to better-preserved subepicardium is conjectural. Our observations are consistent with those of Vatner et al., who demonstrated that after total coronary occlusion, many segments that showed akinesis or dyskinesis after total coronary occlusion began to shorten after the administration of ouabain.

Studies using radioisotope-labeled digoxin have shown a marked diminution of digoxin concentration in the ischemic myocardium and significant transmural concentration gradients between the epicardium and endocardium after total coronary occlusion. The digoxin concentration gradients between the epicardium and endocardium are presumably related to coronary blood flow patterns in the two layers after partial or total coronary occlusion. Variability in the severity of ischemia and variability in tissue glycoside concentration may account for the differential effects of cardiac glycosides on regional contraction of the epicardium and endocardium after total and partial coronary occlusion and may explain the consistent improvement of the severely dyskinetic endocardial layer after partial coronary occlusion not observed during total coronary occlusion.

The present study is limited by the lack of information on the regional subendocardial and subepicardial flow measurements. The distribution of digitalis administered as a single dose may be expected to remain blood flow-dependent, and subendocardial and subepicardial contraction may be related to flow. However, with continuous infusion of the glycoside in the setting of partial coronary occlusion, the myocardial concentration of digitalis in the epicardial and endocardial layers may equilibrate, and thus, may not remain flow-dependent. In the presence of total coronary occlusion, because of complete limitation of blood flow to the ischemic zone, the myocardial concentration of digitalis may be negligible, and thus, little effect on epicardial and endocardial contraction pattern is visualized. Although the epicardial flow is higher than the endocardial flow in this setting, differential effects on the epicardial and endocardial contraction were not observed, probably because of negligible differences in absolute flows.

In the dog model, free collateralization may be an important determinant of blood flow to the ischemic myocardium. This may result in the viability of ischemic myocardium after coronary occlusion and may help to provide adequate regional myocardial concentrations of the glycoside. Whether similar results will be found in the pig model or in the human, where free collateralization does not occur, is conjectural, but one can imagine that the findings will be similar. Free collateralization in the dog should be helpful in maintaining blood flow in the setting of total coronary occlusion, and thus ouabain should have improved systolic shortening of the ischemic subepicardial and subendocardial zones if the collateral flow was adequate. However, during total coronary occlu-
sion, there was no significant change in systolic shortening with ouabain. This indicates that the collateral flow in the dog was not sufficient to maintain viability of the myocardium or to deliver adequate amounts of the glycoside to the ischemic myocardium. In this regard, the findings in the pig or in the human might be similar. With partial coronary occlusion, the significance of collateral flow depends upon the severity of occlusion. In less severe occlusions, it may not change the blood flow to the jeopardized myocardium significantly. However, in very severe partial coronary occlusion, collaterals may be an important source of blood supply to maintain myocardial viability and provide delivery of the drug to the subserved zone. The relative quantitative ratio between the blood flow from a partially occluded artery and that from collateral flow is difficult to assess. The effects of ouabain on systolic shortening in the presence of partial coronary occlusion may be qualitatively similar in the pig model or in the human, but may be quantitatively different.

The subendocardial ischemic zone consistently shows improvement in segmental shortening during digitalis infusion despite its blood flow characteristics under conditions of partial coronary occlusion. These acute studies do not demonstrate the deleterious effects of cardiac glycosides in acute ischemic states on myocardial function. It is conjectural whether, by chronic use of digitalis, the persistent increase in inotropy of the subepicardial ischemic zone in chronic ischemic states produces deleterious effects on subendocardial myocardial contraction.

Although such an experimental study cannot be extrapolated to humans, one may speculate that beneficial contractile effects on the subepicardial and subendocardial layers may be achieved with digitalis in patients with coronary disease when such inotropic effects are desired. Although the dose of digitalis in humans is much smaller than that used in this experimental study, a previous study indicates that the magnitude of contractile effects is directly related to the dose administered. Thus, with smaller doses of digitalis, only minimal inotropic effects may occur. With equilibration of myocardial concentration and plasma levels after 5–7 days of administration of a maintenance digitalis dose, the desired inotropic effects may appear.

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