Effects of Ouabain on Myocardial Potassium and Sodium Balance in Man

By F. James Brennan, M.D., John L. McCans, M.D., Miguel A. Chiong, M.D., Ph.D., and John O. Parker, M.D.

SUMMARY
Myocardial electrolyte balance and hemodynamics were studied in 14 patients before and after the administration of ouabain. The drug caused a significant loss of potassium from the myocardium. This was accompanied by a significant positive inotropic response, indicated by an increase in the rate of rise of left ventricular pressure and systolic ejection-rate index. Heart rate, cardiac output, left ventricular end-diastolic pressure, brachial artery pressure, and left ventricular stroke-work index remained unchanged. These observations in man are compatible with those theories of digitalis action which associate inotropic effect with the inhibition of membrane sodium- and potassium-activated adenosine triphosphatase.

Additional Indexing Words:
Cardiac glycosides  Hemodynamics

In 1931 Calhoun and Harrison demonstrated a lowered potassium content of the canine heart following the administration of digitalis.1 This observation led to much research into the effects of cardiac glycosides on ion balance in the myocardium. Although the original observation of myocardial loss of potassium has been repeated many times, most such studies have been done in animal preparations1-24 and have used toxic doses of digitalis.1-14 When nontoxic doses have been used, myocardial potassium loss has not been demonstrated regularly.5-24 Few studies have been on the effects of digitalis on myocardial potassium balance in man, and these have yielded conflicting results.25-27 The present study, therefore, was designed to examine the effects of the acute administration of a therapeutic dose of the cardiac glycoside ouabain on myocardial potassium and sodium balance in man and to correlate these alterations with hemodynamic events.

Methods
Metabolic and hemodynamic investigations were carried out during diagnostic cardiac catheterization in 14 patients with known or suspected heart disease. Informed consent was obtained from each patient. Three subjects were subsequently shown to be free of heart disease, and the diagnoses given to the others included coronary artery disease (five patients), atrial septal defect (two patients), and primary myocardial disease, atrioventricular communis, patent ductus arteriosus, and tetralogy of Fallot (one patient each). No patient showed clinical signs of heart failure at the time of the study, and none was receiving digitalis, diuretics, or antihypertensive medication. Studies were carried out in the fasting state, without premedication. Under local anesthesia, the brachial artery and two veins were isolated in the right antecubital fossa. A no. 7 Goodale-Lubin catheter was positioned in the main pulmonary artery and a no. 8 Goodale-Lubin catheter was passed to the midportion of the coronary sinus. A no. 8 Sones catheter was introduced into the left ventricle from the right...
brachial artery, and the left brachial artery was cannulated with a Teflon catheter by the Seldinger technic. Blood was withdrawn continuously at a rate of 1.6 ml/min from the coronary sinus and left brachial artery simultaneously by using an automated sampling technic throughout a period of 40 min. The blood was delivered into tubes placed in a fraction collector set to change position at 2-min intervals; thus each tube contained an integrated sample collected over a 2-min period. At minute 14 of the sampling period, ouabain 0.01 mg/kg (with the total dose not exceeding 0.75 mg) was administered intravenously in 1 min; this gave a control sampling period of 14 min and a post-ouabain period of 26 min. The collected blood was centrifuged at 5°C; the plasma was removed within 30 min and stored at −35°C. Plasma sodium and potassium were measured by automated flame photometry.* On sequential analysis of pooled plasma the standard deviation for potassium was 0.18 mEq/liter at a mean concentration of 4.40 mEq/liter, and that for sodium was 2.78 mEq/liter at a mean concentration of 136.9 mEq/liter.

In nine patients hemodynamic data were obtained during the control period and after the administration of ouabain. In these patients heart rate, pulmonary artery pressure, and left ventricular pressure were recorded throughout the sampling period. The brachial artery pressure was recorded, and the cardiac output was determined over at least 2 respiratory cycles, the mean being by the dye-dilution technic using indocyanine green dye, immediately before and after the period of sampling. Incomplete hemodynamic data were obtained in the remaining five patients.

Pressures were measured with P23 Db Statham strain gauges from a zero reference level 5 cm below the angle of Louis and were recorded photographically.† Phasic pressures were recorded obtained electronically. Recording speed was normally 25 mm/sec, but for left ventricular end-diastolic pressure a speed of 100 mm/sec was employed at a high sensitivity. The first derivative of the left ventricular pressure curve (dp/dt) was measured by a resistance-capacitance differentiating circuit. There are theoretical objections to measurements of dp/dt using a fluid-filled catheter and an external transducer, but direct in vivo comparison with measurements with a catheter-tip transducer at rates of 75 to 150/min has shown that the two methods of measurement correspond closely up to a value of 2,000 mm Hg/sec. Left ventricular stroke-work index in gram-meters per square meter (g·m/m²) was calculated using the formula:

$$LVSWI = \frac{(BAm - LVEDP) \times SI \times 13.6}{1.00}$$

where BAm = brachial artery mean pressure in mm Hg, LVEDP = left ventricular end-diastolic pressure in mm Hg, and SI = stroke index in ml/m².

*Technicon auto-analyzer.

†DR12 recorder, Electronics for Medicine, White Plains, New York.

Table 1

<table>
<thead>
<tr>
<th>Sequential Changes in Myocardial Potassium Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial K (mEq/liter)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Control 3.64 ± 0.28</td>
</tr>
<tr>
<td>After ouabain 0-2 min</td>
</tr>
<tr>
<td>2-4 min</td>
</tr>
<tr>
<td>4-6 min</td>
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<tr>
<td>6-8 min</td>
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<td>8-10 min</td>
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<td>18-20 min</td>
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<tr>
<td>20-22 min</td>
</tr>
<tr>
<td>22-26 min</td>
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</tbody>
</table>

*Null hypothesis: Arterial-coronary sinus difference = 0.
EFFECTS OF OUABAIN

Potassium and Sodium (Table 1, Fig. 1)

Plasma potassium concentration averaged 3.64 ± 0.28 mEq/liter (mean ± sp) in the brachial artery and 3.61 ± 0.27 mEq/liter in the coronary sinus during the control period. Following ouabain administration the concentration of potassium in coronary sinus blood rose promptly and steeply. Arterial potassium concentration also rose but did so more gradually. This resulted in a significant negative arterial-coronary sinus difference, indicating myocardial potassium loss, beginning 2 min after the drug was given. The peak difference (−0.21 mEq/liter P < 0.001) occurred 4 to 6 min after ouabain administration (table 1, fig. 1). The period of potassium loss lasted 18 min, following which there was again no significant difference between the arterial (3.88 ± 0.20 mEq/liter) and coronary sinus (3.91 ± 0.19 mEq/liter) potassium concentrations. At this new plateau these values were significantly higher than during the control period (P < 0.001).

The pattern of myocardial potassium loss was similar in all patients, irrespective of the cardiac diagnosis. This is illustrated in figure 2, which shows the results obtained from three patients, one free of heart disease, one with an

Figure 1

Sequential changes in arterial and coronary sinus concentrations of potassium and hemodynamics during the control and post-ouabain periods. The administration of ouabain resulted in rapid loss of myocardial potassium, accompanied by an increase in LV dp/dt but no significant change in LVEDP, BA pressure, or cardiac index.

Abbreviations: LV dp/dt = first derivative of left ventricular pressure pulse; LVEDP = left ventricular end-diastolic pressure; BA = brachial artery mean pressure; CI = cardiac index.

Figure 2

Arterial and coronary sinus potassium concentrations in three patients: See text for discussion. CAD = coronary artery disease.
endocardial cushion defect, and one with coronary artery disease.

Plasma sodium concentration during the control period was similar in both the brachial artery (135.20 ± 0.76 mEq/liter) and coronary sinus (3.91 ± 0.19 mEq/liter) potassium there was no significant change following administration of ouabain.

Hemodynamics (Table 2, Fig. 1)

After ouabain administration there was no significant change in heart rate, cardiac index, stroke index, left ventricular end-diastolic pressure, or brachial artery pressure, but a significant rise in systolic ejection-rate index occurred (P < 0.05). Left ventricular dp/dt increased significantly within 8 to 12 min and continued to rise throughout the study (P < 0.001).

Electrocardiogram

There was no change in rate, rhythm, S-T segments, or the P-R and Q-T intervals during the period of observation.

Table 2

<table>
<thead>
<tr>
<th>Summary of Hemodynamic Results*</th>
<th>Control</th>
<th>Post-ouabain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.5 ± 9.4</td>
<td>69.0 ± 12.2</td>
</tr>
<tr>
<td>Cardiac index (liters/min m²)</td>
<td>2.72 ± 0.39</td>
<td>2.64 ± 0.43</td>
</tr>
<tr>
<td>Stroke index (ml/m²)</td>
<td>36.9 ± 4.5</td>
<td>37.9 ± 7.7</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12.9 ± 6.1</td>
<td>11.7 ± 6.5</td>
</tr>
<tr>
<td>BAm (mm Hg)</td>
<td>100.3 ± 13.8</td>
<td>100.8 ± 16.3</td>
</tr>
<tr>
<td>LVSWI (g/m²)</td>
<td>44.2 ± 12.5</td>
<td>46.3 ± 12.0</td>
</tr>
<tr>
<td>SERI (ml/sec/m²)</td>
<td>122.8 ± 21.1</td>
<td>131.1 ± 20.4†</td>
</tr>
<tr>
<td>LV dp/dt (mm Hg/sec)</td>
<td>1346 ± 238</td>
<td>1574 ± 254†</td>
</tr>
</tbody>
</table>

*All values are mean ± sd.
†Indicates a significant change from the corresponding control value (P ≤ 0.05).

Abbreviations: LVEDP = left ventricular end-diastolic pressure; BAm = brachial artery mean pressure; LVSWI = left ventricular stroke-work index; SERI = systolic ejection-rate index; LV dp/dt = first derivative of the left ventricular pressure pulse.

Discussion

The mechanism of action of digitalis has been the object of much study during the past 40 years. It is now well established that this family of drugs inhibits membrane sodium-and potassium-activated adenosine triphosphatase (Na-K ATPase), the enzyme involved in the active transport of sodium out of the cardiac cell against an electrochemical gradient.20, 31 Such an action results in the accumulation of sodium within the cell and loss of potassium into the extracellular fluid.32 Several investigators postulate that sodium and calcium compete for binding sites on the cardiac cell membrane, with the result that when sodium is displaced intracellularly it vacates sites on the extracellular side of the membrane to which calcium then binds.20, 33 This results in an increased amount of calcium being available on the membrane to enter the cell and to participate in contraction. It is well known that calcium plays a vital role in the contractile process, the strength of contraction being proportional to the amount of calcium available to the contractile proteins.32, 33 Thus the inhibition of Na-K ATPase by digitalis may be directly related to its inotropic effect.

Such theories predict a direct relation of the increased contractility that follows administration of digitalis with myocardial sodium uptake, calcium uptake, and potassium loss. Many studies have been conducted to investigate these phenomena, the potassium ion having received the most attention because of its relative ease of measurement. The results have been conflicting. While most investigators agree that toxic doses of digitalis result in loss of myocardial potassium,2, 14 the administration of nontoxic doses has been reported to cause loss,5-7, 15-20 uptake,8, 10, 21 or no change in myocardial potassium.1, 11-14, 22-24 The majority of studies have been carried out in experimental preparations, including isolated myocardial strips,5, 6, 10-14, 17, 18, 20 or perfused heart or heart-lung preparations,5, 8, 16, 19, 21 or intact animals.1, 3, 4, 7, 9, 15, 22-24

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EFFECTS OF OUABAIN

These inconsistencies, coupled with the fact that a species difference has been demonstrated in the sensitivity of membrane Na-K ATPase to digitalis, make it surprising that little investigation has been done in man. Clarke and Mosher studied the hearts obtained at autopsy from patients who had died in congestive heart failure. They found the potassium content of the myocardium to be decreased in those patients who had not received the drug. Regan and co-workers, however, found a marked myocardial potassium loss occurring within 4 min of giving ouabain to patients with congestive heart failure. In a study of a group of patients including some with and some without congestive heart failure, Gonlubol and associates could demonstrate no change in myocardial potassium balance following the administration of lanatoside C.

The present study was undertaken in an effort to clarify the effects of digitalis on potassium and sodium balance in the nonfailing human heart and to correlate such ionic movements with hemodynamic events. Because data obtained from animal studies can be extrapolated to the intact human heart only by inference, the information obtained in this study may be useful in understanding the mechanism of action of digitalis in man. In addition, despite the fact that the major clinical use of digitalis is in patients with congestive heart failure, it is difficult to interpret biochemical data obtained from such patients because this condition is characterized by grossly abnormal metabolism of the cardiac cell.

The results reported herein indicate that ouabain, in a therapeutic dose, results in significant potassium loss from the myocardium within 4 min of its administration. Although no measurements of coronary flow were made, other studies have shown no change in coronary blood flow following administration of digitalis. Assuming a constant coronary blood flow of 100 ml/min/100 g of left ventricle, it can be calculated that a net myocardial potassium loss of approximately 0.15 mEq/100 g of left ventricle occurred in this study during the period of observation.

The progressive, gradual rise in arterial potassium cannot be explained solely on the basis of myocardial potassium loss into the circulating plasma, and presumably reflects release of this ion by other tissues, such as red blood cells, skeletal muscle, and liver.

Arterial and coronary sinus sodium concentrations showed no significant change following ouabain administration. Since plasma sodium concentration is large compared to that of potassium, it is possible that the analytical method was not sufficiently accurate to detect the relatively small myocardial sodium uptake expected on theoretical grounds to accompany the observed potassium loss.

The hemodynamic observations agree with those obtained in other studies of the effects of digitalis on the nonfailing human heart. The significant rise in dp/dt and systolic ejection rate indicates that myocardial contractility was enhanced despite the absence of other hemodynamic changes, and emphasizes that the dose of ouabain administered was sufficient to cause a measurable inotropic response. It should be noted that dp/dt was maximal at 26 to 30 min after ouabain, when the potassium arterial-coronary sinus differences were no longer significant. Thus, the increase in contractility was temporally related to the total accumulated potassium loss, not to the instantaneous rate of loss. Statistical analysis did not demonstrate close correlation between these two parameters (r = 0.58), but this could be due to modification of the hemodynamic effects of digitalis by autonomic reflexes, and does not necessarily imply that the increase in contractility and the potassium loss are unrelated.

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EFFECTS OF OUABAIN

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