Effects of a Digitalis Glycoside on Coronary and Systemic Dynamics in Conscious Dogs

By Stephen F. Votmer, Charles B. Higgins, Dean Franklin, and Eugene Braunwald

ABSTRACT

The effects of ouabain (C-strophantin), 20 μg/kg, were compared in 12 conscious dogs with Doppler flow transducers on the ascending aorta and left circumflex coronary artery and pressure gauges in the aorta, and in 9 of these dogs after general anesthesia with Na pentobarbital. In conscious dogs ouabain caused an initial bradycardia, but heart rate returned almost to control at 15 to 30 minutes, while arterial pressure rose and remained elevated. Cardiac output and coronary blood flow decreased initially, returned to control by 5 minutes and then remained constant. Systemic, mean, and late diastolic coronary resistances were elevated within 1 minute and remained elevated for 30 minutes. After anesthesia, ouabain caused similar increases in arterial pressure and slightly greater increases in systemic resistance, but the bradycardia and reduction of cardiac output were more profound and sustained. In the anesthetized state, coronary resistance rose when heart rate was allowed to slow after ouabain but was not elevated when heart rate was returned to control. Thus, in the conscious state, ouabain caused a distinct elevation in coronary and systemic resistances with no change in cardiac output, while in the anesthetized state ouabain reduced cardiac output and when heart rate was controlled, did not alter coronary resistance.

KEY WORDS ouabain coronary blood flow cardiac output blood pressure general anesthesia heart rate

Previous investigations on the effects of digitalis glycosides on the nonfailing heart in man and experimental animals have shown that these drugs produce an increase in arterial blood pressure and peripheral vascular resistance (1-6), an augmentation of the myocardial contractile state (3, 7-12) and of myocardial oxygen consumption (13-15), a reduction of heart rate and cardiac output (1, 2, 4, 16-19). Since digitalis glycosides are so frequently administered to patients with myocardial ischemia, an understanding of their action on the coronary vascular bed is of considerable importance. However, there is considerable dispute concerning this effect of the drugs. It has been demonstrated in various studies that digitalis glycosides elevate coronary resistance (20-22), decrease it (23), first raise, then lower it (24-26), have little effect (27-29) or variable effects (30) on the coronary vascular bed. These differing results could possibly be explained by the effects of the drug on the many factors that regulate the coronary vascular bed. Thus, digitalis may act directly to constrict the coronary vessels, while on the other hand, the stimulation of myocardial oxygen consumption produced by digitalis would tend to reduce coronary vascular resistance, and the alterations in arterial pressure and heart rate produced by these drugs would modify extracoronary vascular compression (31, 38). The results of earlier studies were also complicated by the use of...
general anesthesia with its direct and indirect effects on the myocardium (33) and on coronary circulation (34). Accordingly, in the present investigation the effects of ouabain were studied in intact unanesthetized dogs instrumented for the measurement of phasic arterial pressure and aortic and coronary blood flow. In addition, to interpret the results in the light of previous investigations in anesthetized preparations, the effects of ouabain were compared in the same dogs after general anesthesia had been induced.

Methods

Twelve mongrel dogs weighing between 20 and 27 kg were anesthetized with Na pentobarbi-
tal, 30 mg/kg. Through a thoracotomy in the fourth left intercostal space, Doppler ultrasonic flow transducers were implanted around the ascending aorta (9 dogs) and the left circumflex coronary artery (12 dogs); miniature solid state blood pressure gauges were implanted in the thoracic aorta (4 dogs), and catheters were inserted into the ascending aorta via the internal mammary or femoral arteries (8 dogs); pacemaker electrodes were sutured to the left atrium (6 dogs).

Experiments were conducted 1 to 4 weeks after thoracotomy, when the dogs had recovered from the operation. While the dogs were reclining quietly or sleeping, control records of arterial pressure, coronary and aortic blood flow, and heart rate were obtained. Ouabain, 0.02 mg/kg, a dose which does not produce toxic effects, was administered intravenously in half the experiments and into the aorta through the pressure catheter in the others. Recordings of blood flow and arterial pressure were made continuously for the subsequent 30 minutes. In six dogs, heart rate was controlled during the experiment with atrial stimulation. Nine dogs were studied on a separate occasion; heart rate was returned to control levels by means of timed collections of blood, volume flow calibrations in three dogs verified the linear relationship between velocity, as measured by the Doppler flowmeter, and volume blood flow (36). At autopsy, the flow transducers were found to be firmly adherent to the blood vessels through a fibrous scar which minimized changes in the cross-sectional area of the vessel within the flow transducers. Reverse flow was not sensed by the demodulation scheme used in this flowmeter, but since reverse flow in the ascending aorta is readily detected and reverse flow in the left coronary circulation is considered to be negligible in the conscious dog when systemic pressure is maintained (32, 34), this should not have been a significant source of error in these experiments. Aortic blood pressure was measured either with miniature implanted solid state pressure gauges1 (37), which were calibrated in vivo against a Statham P23 Db strain gauge manometer, or sampled through a previously implanted catheter and measured with a Statham P23 Db strain gauge manometer. A pacemaker2 was used for electrical stimulation of the atrium.

Data were recorded on a multichannel tape recorder and played back on a direct writing oscillograph. Mean arterial pressure and mean coronary blood flow were derived with electronic RC filters having a 2-second time constant, while a filter with an 8-second time constant was used to derive mean aortic blood flow. A cardiotachom-
eter triggered by the signal from the aortic pressure pulse provided instantaneous and continuous records of heart rate. Systemic vascular resistance and mean coronary vascular resistance were calculated as the quotients of mean arterial blood pressure and mean coronary blood flow and mean aortic blood pressure and mean coronary blood flow. Late diastolic coronary vascular resistance was calculated as the quotient of late diastolic pressure and late diastolic coronary flow.Values at 1, 3, 5, 10, 15 and 30 minutes following injection of ouabain were averaged and standard errors of the mean were calculated.

Results

Results were not affected by the route of administration of the drug (intravenous or intraarterial) nor by the sequence of the experiments (conscious or anesthetized state first); therefore pooled results are presented. The average results for the nine dogs studied...
Comparison of the effects of ouabain in the same dogs studied in the conscious and anesthetized states. The broken line joining the solid dots represents measurements made after returning heart rate to control with electrical stimulation in six dogs.

in both the conscious and anesthetized states are compared in Figure 1; the individual results from these experiments during control and 15 minutes after ouabain are presented in Table 1.

**Arterial Pressure.**—Ouabain increased mean arterial pressure in all 12 conscious dogs studied; pressure was already elevated at 1 minute following injection and reached a maximum of 24 ± 2% (SE) above a control of 93 mm Hg at 5 to 10 minutes, and gradually declined but remained above control at 30 minutes. In nine anesthetized dogs, control heart rate was significantly (P < 0.01) higher than in the conscious animals and ouabain produced a significantly greater reduction of heart rate, which decreased at 5 minutes to a minimum level of 23 ± 2% below a control of 117 beats/min and was still depressed at 30 minutes.

**Systemic Hemodynamics.**—In nine conscious dogs, ouabain decreased cardiac output slightly, at 1 minute following injection to a minimum of 4 ± 2% below a control of 2683 ml/min. Cardiac output returned to within 2% of control by 5 minutes and remained there throughout the 30-minute observation period (Fig. 2). In contrast, when these dogs were anesthetized, ouabain produced a significantly greater decline in cardiac output, which fell within 1 minute and at 3 minutes reached a minimum of 16 ± 2% below a control of 2462 ml/min, and then gradually rose but was still depressed at 30 minutes (Fig. 3). In the conscious dogs, systemic vascular resistance rose within 1 minute and at 3 to 5 minutes reached a maximum of 27 ± 3% above a control of 0.033 mm Hg/ml/min, and gradually declined but remained elevated at 30 minutes. In the anesthetized state, the average level of systemic vascular resistance was significantly higher than in the conscious state (0.042 as compared to 0.033 mm Hg/ml/min; P < 0.05). The elevation of systemic vascular resistance produced by ouabain was significantly greater (P < 0.01) in anesthetized dogs, in which it increased in 1 minute, reached a maximum of 38 ± 5% above control at 3 minutes, and remained elevated at 15 to 30 minutes.

**Coronary Hemodynamics.**—In 12 conscious dogs, left circumflex coronary blood flow decreased immediately after ouabain and at 1 minute reached a minimum level of 12 ± 2% below a control of 44 ml/min. Coronary blood flow returned to control by 5 minutes and then remained within 3% of control during the remainder of the observation period (Fig. 4). Calculated mean coronary vascular resistance...
Table 1

Results before and Fifteen Minutes after Ouabain for the Dogs Studied Both Conscious and Anesthetized

<table>
<thead>
<tr>
<th>Animal</th>
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<td>Arterial pressure (mm Hg)</td>
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<td>Coronary flow (ml/min)</td>
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<td>Coronary resistance (mm Hg/ml/min)</td>
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<td>Cardiac output (l/min)</td>
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<td>Systemic resistance (mm Hg/ml/min)</td>
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*Heart rate returned to control.
An example of the phasic waveforms of aortic blood flow and arterial blood pressure and of mean pressure, cardiac output and calculated systemic vascular resistance in a conscious dog before and at 1, 15, and 30 minutes after ouabain. The marked sinus arrhythmia is characteristic of the conscious dog.

Records from the same dog as in Figure 3 while it was anesthetized.

Increased at 1 minute to a maximum of 31 ± 5% above a control of 2.11 mm Hg/ml/min. Mean coronary vascular resistance remained elevated at 23 ± 3% above control at 15 minutes and 17 ± 2% above control at 30 minutes, even though heart rate had returned to within 2% of control levels at these times. The increases in late diastolic coronary vascular resistance paralleled the increases in mean coronary resistance. Returning heart rate by atrial stimulation precisely to control levels at 5, 10, 15, and 30 minutes following...
ouabain did not significantly alter these changes in coronary blood flow or coronary vascular resistance induced by the drug.

In eight dogs studied in the anesthetized state, when the slowing of heart rate was allowed to occur, coronary blood flow decreased initially to a minimum level of 8 ± 3% below a control of 51 ml/min and returned to within 4% of control levels by 5 minutes. Mean coronary vascular resistance increased to a somewhat lesser extent than in conscious dogs, reaching a maximum at 3 minutes of 27 ± 4% above a control of 2.02 mm Hg/ml/min and remaining above control at 15 and 30 minutes. Similar increases occurred in calculated late diastolic resistance.
In the anesthetized state, when heart rate was returned to control levels by electrical stimulation 5, 10, 15, and 30 minutes following ouabain, the changes in coronary blood flow and in mean and late diastolic coronary vascular resistances were significantly altered; under these conditions, ouabain resulted in increases in coronary blood flow which averaged $19 \pm 3\%$ and $17 \pm 4\%$ of control at 15 and 30 minutes respectively; changes which paralleled those in arterial pressure. Hence, no change from control in calculated mean and late diastolic coronary vascular resistance occurred (Fig. 5). In this regard, the effects of ouabain in the anesthetized state differed markedly from those in the conscious state, in which, as noted above, coronary blood flow did not rise and coronary vascular resistance became elevated even when heart rate was not allowed to vary.

Discussion

Previous work has suggested that digitalis glycosides may have dual and opposite effects on the coronary circulation in the nonfailing heart. Digitalis is known to exert a direct constrictor effect on the arterial vasculature which is responsible for the elevation of total systemic vascular resistance (1, 2, 5, 6). If the drug exerted a similar action on the coronary vascular bed, as has been proposed (20-22), then this action would oppose the coronary vasodilatation expected from the stimulation of myocardial metabolism. In the present study, a nontoxic dose of ouabain produced a considerable increase in both mean and late diastolic coronary vascular resistances. The initial increase in coronary vascular resistance observed in this study may have been caused, in part, by the associated modest bradycardia that was observed immediately following injection, since it has been shown that by reducing myocardial oxygen consumption, bradycardia tends to lower coronary blood flow and thereby increase coronary vascular resistance (38). However, since heart rate spontaneously returned to within 2% of control levels and since it was brought precisely to control levels by electrical stimulation without alteration in the evident coronary vasocstriction, the elevation of coronary vascular resistance produced by the drug cannot be attributed to the minor changes in heart rate. The augmentation of coronary vascular resistance in the face of increases in arterial pressure and myocardial contractility, factors which would tend to elevate myocardial oxygen consumption and therefore to dilate the coronary vascular bed, indicates that the changes in calculated resistance observed in the conscious dog actually underestimated the direct coronary vasocostractive effects of the drug.

When ouabain was administered to anesthetized dogs, coronary vascular resistance again rose, but the associated bradycardia was more intense than in the conscious dogs. Also, the slowing was sustained throughout the entire observation period. It is likely that in the anesthetized state, the observed increase in coronary vascular resistance may be attributed to a great extent to this slowing of heart rate, since when heart rate was returned to the pre-digitalis control levels with atrial stimulation, coronary blood flow rose and coronary vascular resistance returned to control levels. It is probable that even in the face of an unchanged coronary vascular resistance, ouabain acted to constrict the coronary vascular bed, since the stimulation of myocardial oxygen consumption (13-15) produced by the augmentation of the contractile state of the heart and of arterial pressure (7-12) should have resulted in a decline in coronary vascular resistance, as occurs when catecholamines are administered (31, 32). The markedly differing effects of ouabain on the calculated coronary vascular resistance in the anesthetized dogs, depending on whether or not heart rate was controlled, may be responsible in part for the differing conclusions from previous studies in anesthetized dogs (20-26, 30) with varying degrees of bradycardia and often with an open chest. In addition, experiments conducted in our laboratory in which measurements of left ventricular pressure, dimensions, $dp/dt$, and velocity of contraction were made in conscious and anesthetized dogs.
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without heart failure, have indicated that ouabain exerts a significant isotropic effect in anesthetized dogs but only little effect in conscious dogs (30). It would then follow that the direct vasoconstrictor action of the drug would be masked to a greater extent in the anesthetized dogs, since the greater increases in myocardial contractility produced by digitals in this condition should result in greater decreases in coronary vascular resistance.

Digitalis decreased cardiac output only slightly and transiently in the conscious state but produced a more significant and sustained reduction in cardiac output in the anesthetized state which resulted in a greater elevation of systemic resistance, despite a lesser rise of arterial pressure. Previous work has shown that digitalis causes an increase in systemic vascular resistance in anesthetized humans and dogs (3, 5, 11) and in conscious dogs (4). In the dog without heart failure, digitalis has been shown to decrease cardiac output (1, 2, 4, 16-19), presumably on the basis of hepatic venous constriction and consequent decreased venous return (1, 2, 40). However, studies in conscious human subjects have indicated that cardiac output may not always decrease with digitalis (41, 42). This difference may be due to differences in technique, to the presence of a hepatovenousconstrictor mechanism in the dog but not in man, or to the fact that the studies were carried out in conscious man (41, 42) but in anesthetized dogs. Since, as in earlier studies, we too found that ouabain uniformly decreased cardiac output in anesthetized dogs, but not in the conscious dog, our findings support the last possibility.

The finding that ouabain constricts the coronary vascular bed may be of some clinical import. Digitalis is often administered acutely to patients with myocardial infarction as well as to elderly patients without heart failure but with coronary artery disease who undergo thoracic or cardiac operations. To the extent that these findings in dogs with normal coronary vascular beds can be extended to the human with diseased coronary vessels, they would introduce a note of caution concerning prophylactic intravenous administration of loading doses of rapidly acting cardiac glycosides. Digitalis exerts a direct constrictor effect on the systemic vascular bed in man (4, 43, 44), and when a rapidly acting glycoside is given intravenously, the vasoconstrictor effect commences before the isotropic action of the drug (11). Complications due to digitalis administration have been noted in patients with known or presumed coronary vascular disease (43, 45-47), which may have been related to the vasoconstrictor effect of the drug. Thus these observations suggest that when rapidly acting glycosides are indicated, they should not be administered intravenously as a single bolus, particularly in patients with possible myocardial ischemia.

Acknowledgment

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References

8. Cattell, M., and Gold, H.: Influenza of...


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