Ouabain Induced Primary Coronary Vasoconstriction[1] (36685)

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Cardiac glycosides act both centrally and peripherally (1), although most investigations have focused on their prominent cardiac inotropic action. Ross *et al.* (2) reported a generalized arteriolar constriction in a cardiopulmonary bypass preparation after the injection of ouabain. If this occurred in the coronary vascular bed, it would be of considerable importance, since digitalis glycosides are often administered to patients with myocardial ischemia, and further constriction of the coronary bed would compound their injury. Vatner *et al.* (3) showed that injected intravenously ouabain increased mean coronary resistance in the unanesthetized dog. This increase in calculated resistance may reflect either a direct vasoconstrictive action of ouabain or the sustained elevation of aortic blood pressure without any persistent change in coronary blood flow.

To determine if ouabain constricts the coronary vasculature primarily by direct action, we measured aortic blood pressure and aortic and coronary blood flow directly in the unanesthetized dog during intracoronary administration of ouabain.

Materials and methods. We anesthetized ten mongrel dogs (23–38 kg body wt) with sodium pentobarbital (30 mg/kg iv), performed thoractomy and implanted electromagnetic flow transducers on the ascending aorta and left circumflex coronary artery (4). An occlusive latex cuff (5) was placed on the left circumflex branch, distal to the flow transducer, to obtain mechanical zero flow. We implanted a silastic catheter in the aorta to obtain aortic blood pressure and heart rate. In two dogs we implanted a modified Herd–Barger tube (6, 7) in the left circumflex coronary artery distal to the occlusive cuff to administer ouabain directly into the coronary circulation.

Before and after surgery, we trained the dogs to lie quietly on a padded table. After the dogs recovered from surgery (usually 7–10 days), we recorded control systemic and coronary hemodynamics from resting dogs. We measured aortic and coronary blood flows with Biotronex BL-310 electromagnetic flowmeters and aortic blood pressure with an Elema–Schonander transducer. All data were recorded with a 12-channel high-frequency response Elema-Schonander Mingograf 81 inkjet recorder. Calculations of systemic and coronary hemodynamics were conducted according to Gregg *et al.* (4). Areas under the phasic flow and pressure curves were measured by planimeter or by a hybrid computing system.

After control observations, we gave ouabain either intravenously (20 μg/kg) or intracoronary (2 μg/kg), and monitored systemic and coronary hemodynamics continuously until they had returned to control levels. After intravenous administration of ouabain, we averaged values at the time of maximum change in late diastolic coronary resistance (usually 1–4 min after injection) and at 15 min after injection. After intracoronary administration of ouabain, we averaged values at the time of maximum change in late diastolic coronary resistance before any significant changes in systemic hemodynamics. Statistical analysis of our data was performed according to Snedecor (8).

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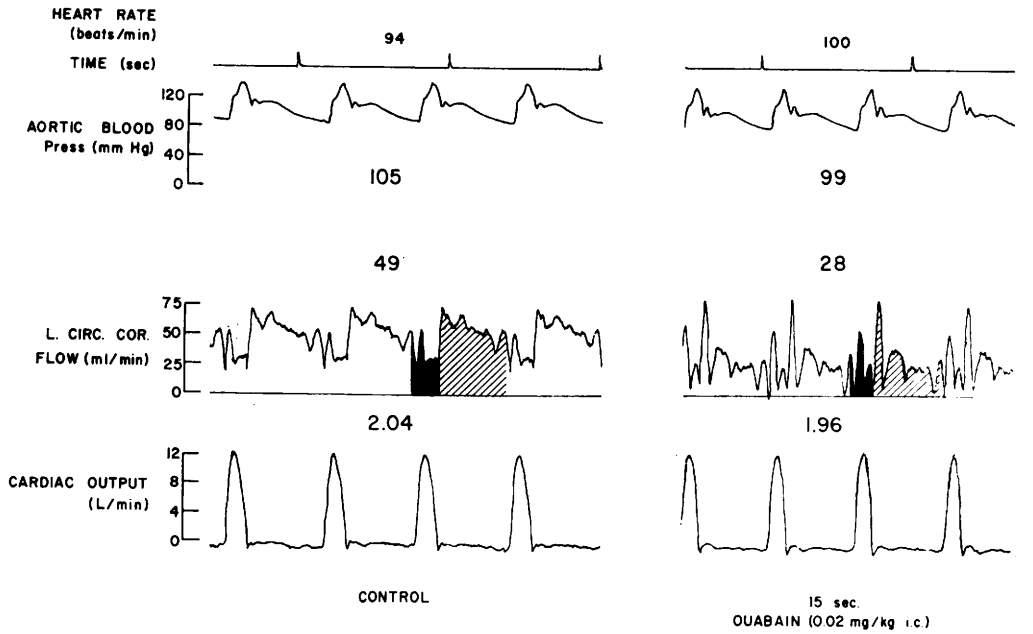

FIG. 1. Hemodynamic effects of ouabain administered by intracoronary injection (2 μg/kg) in the unanesthetized dog. The left-hand panel shows control observations. The right-hand panel is a record made 15 sec after ouabain injection. The number above each parameter is the mean value for that complex, expressed in the units on the ordinate. L. CIRC. COR. FLOW = left circumflex coronary blood flow (ml/min). Zero coronary blood flow line redrawn from mechanical occlusion. Systolic (black) and diastolic (cross-hatch) portions of coronary blood flow are outlined. Paper speed = 50 mm/sec. Time mark = 1.0 sec.

Results. Control values for systemic and coronary hemodynamics (Fig. 1 and Table I) resembled those reported in the unanesthetized dog (4). Table I shows the responses observed after the intravenous and intracoronary administrations of ouabain.

Intravenous administration (Table I). After intravenous administration of ouabain (20 μg/kg) the maximum change in late diastolic coronary resistance occurred within 1–4 min of the injection in all dogs. At that time heart rate and cardiac output decreased significantly ($p < .001$) from control, 15 beats/min (15%) and 165 ml/min (7%), respectively. Significant increases ($p < .05$) occurred in mean aortic pressure of 22 mm Hg (24%), in stroke volume of 2 ml (8%), in total systemic resistance of 16.9 mm Hg/ml/min (38%), in stroke coronary blood flow of 0.07 ml/beat (14%), and in mean and late diastolic coronary resistances (30% and 44%, respectively). These changes persisted through 15 min, and control levels were not attained until 30 min after the administration of ouabain. These changes after intravenous administration resembled those reported by others (3), and since coronary blood flow was unchanged, it was still possible that ouabain acted secondarily to the persistently elevated aortic blood pressure.

Intracoronary administration (Table I and Fig. 1.). After intracoronary administration of ouabain (2 μg/kg), the maximum increase in late diastolic coronary resistance occurred within 1 min of injection. The primary action of ouabain on the coronary vascular bed was confirmed by significant decreases ($p < .01$) in coronary blood flow of 25 ml/min (36%) and in stroke coronary blood flow of 0.32 ml/beat (39%) from controls, significant increases ($p < .01$) in mean and late diastolic coronary resistances (44% and 33%, respectively), and no significant changes in systemic hemodynamics, namely, heart rate,

TABLE I. Systemic and Coronary Hemodynamic Responses to Ouabain.[a]

Time (min)	HR	MABP	CBF	SCBF	MCR	LDCR	CO	SV
				Intravenous administration (20 μg/kg) $N = 10$				
0	101	91	58	0.57	2.0	1.6	2525	24
1–4	86***	113***	56	0.65*	2.6***	2.3***	2360*	26*
	-18 ± 3^c	22 ± 3	-3 ± 4	0.07 ± 0.03	0.6 ± 0.1	0.7 ± 0.1	-165 ± 69	2 ± 1
15	86***	102***	57	0.68*	2.2	2.1**	2453	29**
	-16 ± 4^c	11 ± 3	-1 ± 2	0.11 ± 0.04	0.2 ± 0.1	0.5 ± 0.2	-72 ± 63	6 ± 2
				Intracoronary administration (2 μg/kg) $N = 5$				
0	82	97	68	0.82	1.6	1.2	2238	27
0–1	87	92	44**	0.50**	2.3**	1.6**	2245	26
	5 ± 3^c	-4 ± 3	-25 ± 6	-0.32 ± 0.06	0.7 ± 0.2	0.4 ± 0.1	7 ± 85	1 ± 1

= heart (beats/min); MABP = mean aortic blood pressure (mm Hg); CBF = coronary blood flow (ml/min); SCBF = stroke cor
/beat); MCR = mean coronary resistance (mm Hg/ml/min); LDCR = late diastolic coronary resistance (mm Hg/ml/min); CO
ml/min); SV = stroke volume (ml/beat); TSR = total systemic resistance (mm Hg/ml/min).

response values were obtained at the time of maximum increase in late diastolic coronary resistance.

difference ± standard error of mean difference. Significance of the differences between mean values of the experimental and con
ed using a two-tailed Student's t test for paired observations (8).

$< .05$.

$< .01$.

$< .001$.

mean aortic blood pressure and cardiac output.

In a representative experiment (Fig. 1), an intracoronary bolus of ouabain (2 μg/kg) did not change heart rate, mean blood pressure, or cardiac output significantly during the first 2 min after injection, compared with control values. But ouabain did decrease coronary blood flow by 43% to 28 ml/min, reducing both systolic and diastolic coronary flow, and increased mean and late diastolic coronary resistance.

Discussion. Digitalis preparations are known to cause direct vasoconstriction in the systemic arterial vasculature, increasing total systemic vascular resistance (2, 9–11). Direct arterial administration of ouabain into the superior mesenteric and common carotid arteries have shown increased vascular resistance and decreased blood flow, while heart rate and aortic blood pressure were unaltered (12). If digitalis glycosides exerted similar action on the coronary vascular bed, as has been proposed (3, 13–15), then this action would oppose the coronary vasodilation expected from the stimulation of myocardial metabolism and oxygen consumption (16–18). The balance between these two opposing actions on the coronary vascular bed would be particularly critical in patients with myocardial ischemia receiving digitalis glycosides, since it could compound their injury.

Our study indicates that intravenously administered ouabain in the normotensive awake dog induces bradycardia and increases aortic blood pressure, stroke volume, peripheral vascular resistance, and mean coronary resistance. These changes are similar to those reported by Vatner *et al.* (3). However, since coronary blood flow did not change signficantly from control, the calculated changes in mean coronary resistance may only reflect the sustained elevation of aortic blood pressure rather than a direct vasoconstriction of the coronary arteries. The administration of ouabain directly into the coronary artery of the intact awake animal is a valuable technique for studying the direct action of the drug on the coronary artery. When this route of administration was used, there was a significant decrease in coronary blood flow and a significant increase in coronary vascular resistance, while systemic arterial pressure, heart rate and cardiac output were not altered. This indicates a direct effect of ouabain on the coronary artery rather than an indirect effect via the heart or adrenergic nervous system.

One implication of our study is that the direct action of the digitalis glycosides on the coronary vascular bed may intensify myocardial injury resulting from preexisting ischemic heart disease. The occurrence of such vasoconstrictor effects in man may explain the complications due to digitalis administration reported in patients with known or presumed coronary vascular disease (19–22). Thus, the use of digitalis glycosides, particularly rapidly acting ones, in patients with possible myocardial ischemia should be considered cautiously.

Summary. Given intravenously, ouabain decreased heart rate and cardiac output and increased mean aortic pressure, stroke volume, total systemic resistance, and mean and late diastolic coronary resistance. Given directly into the coronary circulation, it decreased coronary blood flow and stroke coronary blood flow, increased mean and late diastolic coronary resistance, and produced no systemic effects. This indicated a direct effect on the coronary vasculature. This direct action on the coronary vessels implies possible intensified myocardial damage if administered to an already ischemic heart.

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