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The Role of Arterial Baroreceptors in Mediating the Cardiovascular Response to a Cardiac Glycoside in Conscious Dogs

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SUMMARY To determine the role of the arterial baroreceptor reflex in mediating the cardiovascular response to a cardiac glycoside, we examined the effects of ouabain (G-strophanthin), 17.5 $\mu\text{g/kg}$, iv, on direct and continuous measurements of left ventricular diameters, pressures, velocity of shortening, $(dP/dt)/P$, arterial pressure, cardiac output, and total peripheral resistance. These studies were conducted on healthy conscious dogs before and after total arterial baroreceptor denervation (TABD). Maximal pressor effects were observed in the first 3-5 minutes; mean arterial pressure increased by 11 ± 1 mm Hg in normal dogs compared to 33 ± 4 mm Hg in denervated dogs. In intact dogs at this time heart rate de-

creased by 18 ± 2 beats/min and cardiac output fell by $18 \pm 3\%$; these values gradually returned toward control over 15-30 minutes. When heart rate was kept constant, cardiac output did not fall after injection of ouabain. In contrast, heart rate and cardiac output did not change significantly after ouabain in dogs with TABD. The maximal effects on the contractile state of the heart occurred between 15-30 minutes and were similar in both groups. Arterial baroreceptor reflexes appear to be responsible for the reduction in heart rate and cardiac output caused by administration of ouabain to the intact dog. They exert an important buffering action on the vasopressor effect but a less important action on the inotropic response.

CARDIAC glycosides increase cardiac output through a strong inotropic action on the failing heart. In contrast, cardiac glycosides, when administered to man or animals without heart failure, either reduce or do not change cardiac output.^{1, 2} One of the most prevalent hypotheses offered to explain why digitalis exerts little effect on output of the nonfailing heart is that the arterial baroreceptors, stimulated either directly by the cardiac glycoside³ or by the rise in arterial pressure that occurs, attenuate the normally powerful inotropic action of the drug and thereby prevent cardiac output from rising.²⁻⁶ A corollary of this hypothesis, i.e., that the cardiac glycoside would cause a striking inotropic response sufficient to elevate stroke volume and cardiac output in the absence of arterial baroreceptors, was the subject of this investigation.

In order to accomplish this goal the effects of a subtoxic dose of ouabain were studied before and after recovery from denervation of arterial baroreceptors in conscious dogs which had been instrumented for direct measurements of stroke volume, cardiac output, left ventricular dimensions and pressures, dP/dt , and velocity of myocardial fiber shortening. It was considered important to conduct this study in conscious animals because general anesthesia, per se, depresses cardiac function,^{7, 8} and cardiac glycosides exert a more potent action on the depressed myocardium.⁹

Methods

Ten mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg, iv). Through a thoracotomy in the 4th left intercostal space an electromagnetic flow transducer (Zepeda Instruments, Seattle) was implanted around the ascending aorta and pacemaker electrodes were sutured to the left atrium. A catheter was implanted in the ascending aorta via the femoral artery. In another group of seven dogs under pentobarbital anesthesia and through a thoractomy in the 5th left intercostal space, miniature pressure gauges (model P22, Konigsberg Instruments, Pasadena, Calif.) were implanted within the left ventricle through a stab wound in the apex. A Tygon catheter was implanted through

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the left atrial appendage to measure left atrial pressure. Opposing ultrasonic diameter transducers* were implanted on the endocardial surfaces of the anterior and posterior walls of the left ventricle, and pacemaker electrodes were sutured to the left atrium. Total arterial baroreceptor denervation (TABD) was performed during a subsequent operation through an anterior cervical incision by first dividing the carotid sinus nerves and then the aortic nerves according to the technique described by Edis and Shepherd.⁹ Adequacy of the denervation was confirmed postoperatively by observing the responses to intravenous bolus doses of nitroglycerin, 48 $\mu\text{g}/\text{kg}$, and methoxamine, 48 $\mu\text{g}/\text{kg}$. Any dog exhibiting a reciprocal change of heart rate of more than 6 beats/min was considered to be not denervated and was excluded from the study. Normally these drugs elicited changes of 97 ± 11 and 47 ± 2 beats/min, respectively, in heart rate.

Experiments were conducted 2–4 weeks postoperatively when the dogs had recovered fully from the surgery. While the trained, conscious, unsedated dogs of the first group were resting quietly in a darkened laboratory, control records of arterial pressure, aortic flow, cardiac output, and heart rate were obtained. In the other group of dogs control records of left ventricular pressure and diameter, the time rate of change of diameter (dD/dt), the time rate of change of pressure (dP/dt), and heart rate were obtained. Ouabain, 17.5 $\mu\text{g}/\text{kg}$, which is the largest dose that can be administered consistently to the conscious dog without producing toxic side effects, was given as an intravenous bolus and recordings were obtained continuously during the subsequent 30 minutes. In some experiments recordings were taken for periods of up to 60 minutes. Records during the control period and during peak pressor and inotropic responses also were obtained with heart rate controlled at a frequency slightly higher than the control spontaneous rate.

The electromagnetic flow probes were precalibrated in vitro. During the experiments zero flow was assumed to occur in mid-diastole and late diastole. The left ventricular pressure gauges were calibrated in vivo against a calibrated Statham P23Db strain gauge manometer. Diastolic pressure for the implanted gauge was calibrated in relation to the corresponding left atrial pressure. At autopsy the position of the miniature pressure transducer within the ventricular lumen was confirmed. Arterial pressure was measured with a Statham P23Db strain gauge manometer. An ultrasonic transit time dimension gauge was used to measure left ventricular diameter;¹⁰ the principle of its operation is similar to that of other ultrasonic gauges which have been described previously. In brief, the instrument measured the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 ± 10^6 mm/sec between the 3-MHz piezoelectric crystals implanted on the left ventricular endocardium at opposing sites. The transit time was calibrated by substituting signals of known duration from a pulse generator which was referenced to the frequency of a quartz crystal controlled oscillator. A voltage proportional to transit time was recorded and calibrated in terms of

crystal separation. In this manner a measure of the internal diameter of the left ventricle was continuously recorded.

The signals were directly coupled to a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 100 mm/sec. A cardiometer triggered by the signal from the pressure pulse provided instantaneous and continuous records of heart rate. Continuous records of dP/dt and dD/dt were derived from the left ventricular pressure and diameter signals; Philbrick operational amplifiers (Philbrick/Nexus Research, Dedham, Mass.) were connected as differentiators. A triangular wave signal with known slope (rate-of-change) was substituted for pressure and diameter signals to directly calibrate the left ventricular dP/dt and velocity channels.

The action of ouabain on myocardial force-velocity relations was assessed by determining its effects on the velocity of shortening and intraventricular pressure at an identical ventricular diameter. When, at any given instantaneous myocardial diameter or length (isolength point), the velocity of shortening rises, a shift in myocardial force-velocity relations which reflects a positive inotropic effect is considered to have occurred. All isolength points were obtained during the first one-third of ejection. In addition, developed pressure, i.e., $(dP/dt)/P$, was examined. The latter was calculated as the quotient of dP/dt and left ventricular pressure minus end-diastolic pressure, the same level of pressure which occurred during the isovolumetric contraction period both before and after ouabain. These techniques for evaluating the myocardial contractile state have been described in detail previously.^{8, 11–13} For statistical analysis of the data, both a paired *t*-test and group *t*-test¹⁴ were used.

Results

In Table 1 are summarized the control data for both the intact and denervated dogs. Control values for arterial pressure, left ventricular pressure, heart rate, and peak dP/dt of the denervated dogs were significantly higher than in the intact group, whereas control values for end-diastolic and end-systolic diameters and stroke volume were lower.

ARTERIAL PRESSURE

Ouabain increased mean arterial pressure in the intact dogs by 1 minute; the pressure reached a maximum of 11 ± 1 mm Hg above control of 90 ± 3 mm Hg at 3–5 minutes; and declined gradually but remained above control levels at 30 minutes (Fig 1). In the dogs with TABD, arterial pressure also was significantly elevated at 1 minute, at 3–5 minutes reached a maximum of 33 ± 4 mm Hg above a control of 107 ± 4 mm Hg, and remained above control at 30 minutes. The elevation in arterial pressure in the dogs with TABD was significantly greater than in intact dogs ($P < 0.001$).

HEART RATE

In intact dogs ouabain decreased heart rate within 1 minute after injection; at 3–5 minutes reached a minimum of -18 ± 2 beats/min below a control of 82 ± 2 beats/min ($P < 0.01$); and returned slowly toward control at 30 minutes (Fig. 1). In dogs with TABD, resting heart rate was

* Construction details are available from the authors.

TABLE 1 Control Values

	Intact	Denervated
Mean arterial pressure (mm Hg)	90 ± 3	107 ± 4*
Heart rate (beats/min)	82 ± 2	115 ± 6*
Cardiac output (liters/min)	2.40 ± 0.11	2.44 ± 0.06
Stroke volume (ml)	32.0 ± 3	25.0 ± 2*
Total peripheral resistance (mm Hg/ml per min)	0.037 ± 0.003	0.041 ± 0.003
End-diastolic diameter (mm)	36.3 ± 1.3	30.4 ± 2.5*
End-systolic diameter (mm)	27.5 ± 1.5	23.0 ± 2.3*
Left ventricular systolic pressure (mm Hg)	115 ± 4	141 ± 7*
Peak dP/dt (mm Hg/sec)	3160 ± 240	4090 ± 380†
$(dP/dt)/P$ (sec ⁻¹)	54 ± 3	60 ± 3
Isolength left ventricular velocity (mm/sec)	57 ± 9	66 ± 8

Results are expressed as mean ± SEM.

* Significantly different from intact ($P < 0.01$).

† Significantly different from intact ($P < 0.05$).

significantly higher at 115 ± 6 beats/min (Table 1), there was no significant reduction in heart rate during the peak pressor response, and the rate remained at resting control levels through the entire 30-minute period of observation.

SYSTEMIC HEMODYNAMICS

In intact dogs ouabain decreased cardiac output by a maximum -0.38 ± 0.06 liters/min from a control level of 2.40 ± 0.11 liters/min ($P < 0.01$) (Fig. 1). This coincided with the peak pressor response at 3–5 minutes and had returned almost to control levels by 15 minutes. Total peripheral resistance increased by 0.012 ± 0.002 mm Hg/ml per min from a control of 0.037 ± 0.003 at the time of the peak pressor effect, i.e., 3–5 minutes ($P < 0.001$), and returned toward control levels during the 30-minute period of observation.

Maintenance of heart rate at control levels by atrial stimulation at the time of the peak pressor effect returned

cardiac output to control levels, while mean arterial pressure rose by 24 ± 4 mm Hg.

In dogs with TABD, ouabain did not produce a significant change in cardiac output from the control level of 2.44 ± 0.06 liters/min throughout the entire observation period (Fig. 1), and this was associated with no significant change in stroke volume. Total peripheral resistance increased by 0.018 ± 0.002 mm Hg/ml per min ($P < 0.001$) at 3–5 minutes from a control of 0.041 ± 0.003 ; it did not return to control levels as rapidly as it did in intact dogs, and at 30 minutes it was still significantly elevated above control by 0.005 ± 0.002 mm Hg/ml per min ($P < 0.05$). This increase was greater than that observed in intact dogs.

VENTRICULAR DYNAMICS

In intact dogs, ouabain increased left ventricular systolic pressure from a control of 115 ± 4 mm Hg by 12 ± 2 mm Hg at 3–5 minutes ($P < 0.01$) (Fig. 2); subsequently, pressure gradually returned toward control levels. End-diastolic diameter increased slightly, by $+0.29 \pm 0.20$ mm, but did not differ significantly from a control of 36.3 ± 1.3 mm (Fig. 2), while end-systolic diameter decreased by 0.51 ± 0.24 mm, but not significantly from a control of 27.5 ± 1.5 mm. By 15 minutes after injection of ouabain $dP/dt/P$ increased by 10 ± 2 sec⁻¹ from a control of 54 ± 3 sec⁻¹ (Figs. 1 and 2) and remained essentially at this level until the end of the 30-minute observation period. Isolength left ventricular velocity increased by a maximum of 12 ± 2 mm/sec from a control of 57 ± 9 mm/sec at 30 minutes (Figs. 1 and 2). Observations at times greater than 30 minutes indicated that myocardial contractility began to diminish.

If heart rate was restored to control levels by atrial stimulation during the peak inotropic effect there was no significant effect on the inotropic responses, although left ventricular dimensions were significantly smaller at the more rapid rate; end-diastolic size was 31.5 ± 1.5 mm and end-systolic size was 24.2 ± 1.4 mm. These values are comparable to those of dogs with TABD.

In dogs with TABD, left ventricular systolic pressure increased by 35 ± 4 mm Hg from a control of 141 ± 7 mm Hg (Fig. 2) ($P < 0.001$); this was a significantly greater increase ($P < 0.01$) than occurred in the intact dogs with

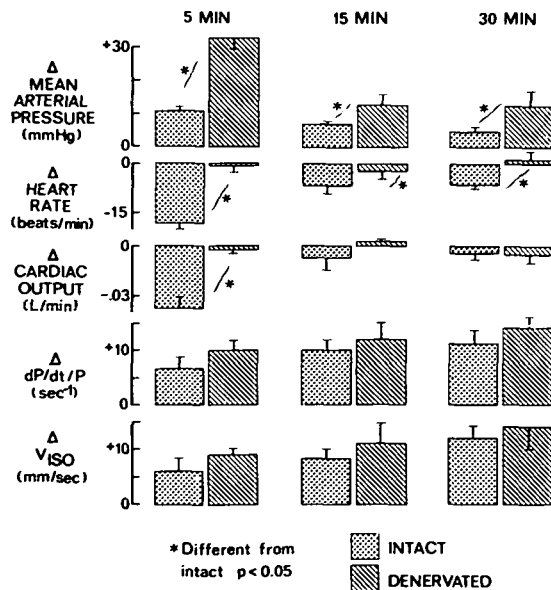


FIGURE 1 The average (\pm SEM) changes in mean arterial pressure, heart rate, cardiac output, $(dP/dt)/P$, and isolength left ventricular velocity (V_{ISO}) in intact dogs compared with denervated dogs at 5, 15, and 30 minutes after ouabain administration.

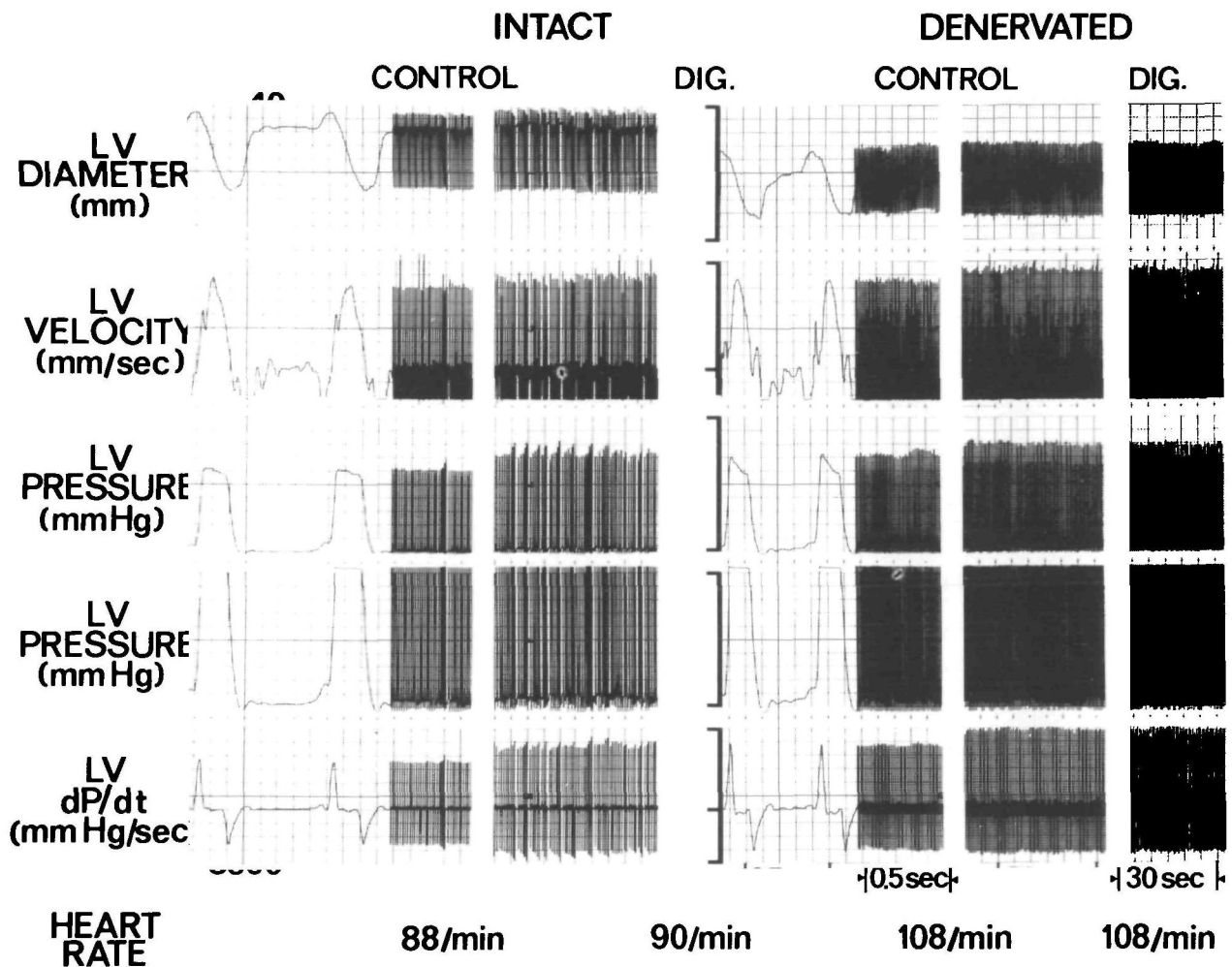


FIGURE 2 Typical waveforms recorded from the same dog before and after ouabain when the animal was intact (left panels) and after total arterial baroreceptor denervation (right panels). The records of instantaneous left ventricular (LV) diameter, velocity, pressure, and dP/dt are shown at a fast and slow paper speed during the control period and during the peak inotropic response. This dog exhibited as large an increase in the inotropic state as was observed in this study. Dig. = digitalis.

spontaneous rhythm or with heart rate constant. As in the intact dogs, ouabain produced little change in left ventricular diameter. $dP/dt/P$ increased by $14 \pm 2 \text{ sec}^{-1}$ above a control of $60 \pm 3 \text{ sec}^{-1}$, while isolength left ventricular velocity increased by a maximum of $14 \pm 4 \text{ mm/sec}$ from a control of $66 \pm 8 \text{ mm/sec}$. The peak increases in $dP/dt/P$ and isolength left ventricular velocity were slightly greater in dogs with TABD than in intact dogs. The differences, however, were not significantly greater (Fig. 1). Moreover, if percent change from control was examined, differences in inotropic responses between intact and TABD dogs would have been even smaller.

Discussion

To examine the role of the arterial baroreceptors in modifying the response to cardiac glycosides, we studied the conscious dog because general anesthesia interferes with baroreceptor control of the circulation^{7, 8} and modifies the normal response to a cardiac glycoside.⁸ In the conscious dog, a relatively large dose of ouabain produced a peak pressor response after about 3–5 minutes and this was

associated with modest bradycardia and reduction in cardiac output which gradually returned to control levels by 15–30 minutes. Indices of myocardial contractility, i.e., $dP/dt/P$ and isolength left ventricular velocity, increased significantly although slightly. These increases in myocardial contractility are relatively small compared to those found for the conscious dog after administration of other inotropic agents^{15, 16} or, after exercise; in these instances contractility may increase 5-fold.¹⁷ They are small also in relation to changes induced by administration of ouabain after myocardial depression had occurred because of either general anesthesia⁸ or chronic heart failure.¹⁸

To explain the relatively modest positive inotropic effect of ouabain on the nonfailing heart, it has been proposed that the power of its direct inotropic effect is obscured by baroreceptor-activated reflex withdrawal of cardiac sympathetic tone.⁸ Arterial baroreceptors are stimulated after administration of cardiac glycosides in at least two ways: First, as has been shown recently, cardiac glycosides cause direct stimulation of the afferent carotid sinus and aortic nerves^{3–5} and thus enhance “barosensitivity” of the animal.

Second, they elevate arterial pressure by causing systemic vasoconstriction, and this is expected to excite baroreceptor afferent pathways.³⁻⁵ The arterial baroreceptor reflex then would be expected to buffer the rise in pressure, in part by reducing myocardial contractility and, thus, to oppose the direct effects of the cardiac glycoside.³⁻⁶ The results of our study suggest that baroreceptor reflex activation plays a minor role in blunting the positive inotropic effect of a cardiac glycoside in the intact, conscious dog, since the maximum dose of ouabain that could be used without eliciting toxic effects induced only slight inotropic effects in the absence of arterial baroreceptors. These results are consistent with those of a previous study from this laboratory in which the carotid sinus baroreceptor reflex was found to exert only a minimal effect in the control of myocardial contractility and stroke volume but to exert important effects in the regulation of arterial pressure and cardiac rate.¹³ Thus, under physiological conditions, baroreceptor control of myocardial contractility appears to be relatively ineffective.

Although inotropic responses were not markedly different between the two groups of dogs, those with TABD responded to ouabain with a 3-fold greater increase in pressure, indicating that arterial baroreceptors do play an important role in buffering the pressor response to the cardiac glycoside. The 3-fold difference in peak pressor response between intact dogs and dogs with TABD is similar to that described for responses to intravenous methoxamine;¹⁹ this finding suggests that cardiac glycosides do not exert a major action in "sensitizing" the arterial baroreceptors.⁸ If the latter phenomenon were important, a greater difference in arterial pressure response should have been observed in response to ouabain than to methoxamine, because methoxamine is not known to exert a direct effect on the arterial baroreceptors.

The responses of cardiac output to the cardiac glycoside were different in the presence and absence of arterial baroreceptors. However, even with TABD, ouabain did not increase cardiac output in the conscious dog. The initial, transient reduction in cardiac output which was observed could have been due either to venous pooling^{2, 20} or to the attendant bradycardia. In normal, anesthetized canine preparations, digitalis has been reported to produce generalized venoconstriction,² which is particularly marked in the hepatic veins and leads to pooling of blood in the portal venous system; this, consequently, leads to a diminished venous return²⁰ and ultimately contributes to the decreased cardiac output observed after ouabain administration. If this mechanism were important, then controlling the heart rate by atrial stimulation should not have prevented the reduction in cardiac output, whereas if the bradycardia were responsible, in the face of a constant heart rate cardiac output should not have decreased. This latter relationship was, in fact, found. These results suggest that the mechanism of diminished venous return plays little role in reducing cardiac output after ouabain administration, as observed in the intact, conscious dog. The finding that end-diastolic size, an indication of cardiac preload, did not diminish in any group of conscious dogs studied supports this conclusion.

The precise mechanism for the cardiac slowing induced by digitalis remains controversial. In our experiments, removal of the carotid sinus and aortic nerve afferent pathways abolished the bradycardia seen in intact dogs, even though the vagus nerves were intact; this result is in agreement with those of Heymans et al.^{21, 22}

In summary, arterial baroreceptor reflexes play a minor role in attenuating the inotropic action of a cardiac glycoside. Even in the absence of arterial baroreceptor afferent pathways, ouabain did not exert an inotropic action sufficiently powerful to elevate cardiac output. The major role of the arterial baroreceptor reflex in the response to ouabain involves (1) substantial attenuation of the pressure response, and (2) mediation of the reflex bradycardia and reduction in cardiac output that normally occurs in the conscious dog without heart failure. This latter observation implies that splanchnic pooling is not an important mechanism mediating the reduction in cardiac output which results from administration of ouabain to the conscious dog.

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