Effects of Chronic Digoxin Administration on Left Ventricular Performance in the Normal Conscious Dog

By Felix Mahler, M.D., Joel S. Karliner, M.D., and Robert A. O’Rourke, M.D.

SUMMARY
The effects of chronic digoxin administration on left ventricular (LV) function were studied in six healthy conscious dogs, instrumented with high-fidelity LV manometers and endocardial ultrasonic diameter gauges. Studies were performed at an average of eight days after a therapeutic serum level of digoxin had been achieved by daily intramuscular injections. In the resting state, at matched heart rates and at unchanged LV end-diastolic pressures, LV systolic pressure increased after digoxin by a mean of 9 mm Hg (P < 0.008), while peak LV dP/dt was augmented by 38% (P < 0.006). Mean and maximal velocity of circumferential fiber shortening (VCF) increased by 22% and 21%, respectively (both P < 0.02), and LV systolic diameter excursion (ΔLV D) increased by 10% (P < 0.05) above control values. Intravenous propranolol did not alter these responses significantly. Elevation of LV systolic pressure to an average of 206 mm Hg by phenylephrine infusion did not change the previous basal augmentation of LV dP/dt and VCF produced by digoxin, but ΔLV D exceeded the control values by 25% as compared with the increase of 10% produced by digoxin alone (P < 0.02). Thus, chronic digoxin administration in the normal conscious dog elicits a potent positive inotropic effect in the resting state and markedly improves cardiac reserve as evidenced by enhanced LV performance during acute pressure overloading.

Additional Indexing Words:
Inotropic response Myocardial contraction patterns Propranolol
Left ventricular pressure overloading Acute dosage of drugs

There is considerable evidence that digitalis glycosides exert a positive inotropic effect not only on the failing or depressed myocardium but also on the nonfailing, normal heart. Using both invasive and noninvasive methods for the assessment of cardiac performance, it has previously been shown that an increased myocardial inotropic state can be induced in the nonfailing heart in unanesthetized human subjects after acute digitalis administration. However, in many acute studies performed on human subjects there has been a question as to whether the patients were entirely normal, and studies in animals have yielded results which are influenced by the administration of anesthetic agents. Vatner and coworkers demonstrated that the positive inotropic influence of intravenous ouabain on the left ventricle was considerably greater when anesthetized dogs were compared with animals in the conscious state, and they suggested that cardiac glycosides exert only a minor inotropic effect in the normal conscious animal. However, there is little information relative to the effects of chronic digitalis administration in the awake dog. We considered the possibility that different responses might occur when digitalis glycosides are given on a sustained, daily basis. Accordingly, the present study was designed to investigate the effects of chronically administered digoxin in the normal conscious dog, instrumented for measurement of left ventricular pressure and internal dimensions. Studies were performed both at rest and under conditions of acute pressure overloading.

Methods
Six mongrel dogs, ranging in weight from 15.9 to 30.9 kg [average 25.3 ± 3.1 kg (±SE)], underwent a left-sided thoracotomy in the fifth intercostal space under sterile conditions during Na-Thiomyl anesthesia. A high-fidelity micromanometer (Konigsberg P-20) and a silastic rubber catheter (inner diameter 1.1 mm) for pressure calibrations...
were inserted at the left ventricular apex through a stab incision. Two 4.5 mm ultrasonic crystals were positioned at opposing sites on the anterior and the posterior left ventricular endocardial surfaces in order to measure continuously the internal diameter of a transverse left ventricular chord. The pacing wires and ultrasound crystal leads and the left ventricular catheter were implanted subcutaneously in the neck where they could easily be exposed for subsequent studies. The dogs were permitted to recover from the operation for an average of three weeks and were trained to lie quietly on their right side on a table. At the time of each study they were vigorous and healthy and had normal temperatures and hematocrits ranging from 34 to 42% (mean 39 ± 2%). Measurements were recorded on an eight-channel forced ink pen oscillograph (Hewlett-Packard, Model 7868A). The output from the micromanometer was adjusted to the pressure measured through the fluid-filled catheter by means of a Statham P23dB transducer, which was directly calibrated with a mercury manometer; the zero reference point was at the level of the vertebral column. The tracings from the high-fidelity transducer were recorded at full scale and at high gain for accurate reading of diastolic pressure. The first derivative of the left ventricular pressure pulse (dP/dt) was obtained by electronic differentiation from the high fidelity pressure signal. The R-C differentiator (Hewlett-Packard), which has a linear frequency response to 100 Hz that decreases 3 dB at 250 Hz, was calibrated by a triangular wave. The signals from the ultrasonic diameter gauges were calibrated for diameter equivalents from 15 to 40 mm in steps of 5 mm. The error in LV diameter measurement induced by angular distortion up to 30° was less than 4% of the total measured distance.

Mean velocity of circumferential fiber shortening (VCF), expressed in circumferences per second (circ/sec), was calculated as the systolic excursion of the diameter signal (∆LVD, mm) divided by ejection time in seconds (from peak left ventricular dP/dt to the systolic nadir of the diameter tracings) and by end-diastolic diameter (EDD, mm). We have utilized the term “circumferential fiber shortening” to describe dimensional alterations in the LV circumference measured by the ultrasound crystals, although we recognize that these changes reflect the interaction of myocardial fiber bundles with varying orientations to the circumference. Maximum (max) VCF was obtained by differentiating the diameter signal (fig. 1). In four animals highly significant correlations (all r > 0.95) were obtained between ∆LVD and stroke volume, the latter being derived from dye dilution curves (cardiogreen). These correlations were obtained during induced variations in heart rate by atrial pacing and in EDD by volume expansion, thus confirming that alterations in ∆LVD correspond to changes in stroke volume derived by the conventional dye dilution method, a finding previously described by Bishop and Horwitz and O’Rourke and coworkers, who used electromagnetic flowmeters to analyze beat-to-beat variations in stroke volume. For atrial pacing, a constant current stimulator (Nuclear-Chicago Model 7150) was used.

After recovery from operation, two control studies were performed in each dog on different days. For each control study data were obtained while the dogs were in a resting circulatory state and exhibiting spontaneous sinus rhythm. The heart rate was increased by atrial pacing (five dogs) or small doses of atropine (one dog) to comparable values in each dog (average, 104 beats/min) in order to abolish any effects on cardiac performance produced by variations in heart rate. The difference between the measurements of LVSP, LV dP/dt, mean VCF, and ∆LVD obtained during the two control atrial pacing studies in each dog was less than 10%. At least one study utilizing a pressure load was carried out in the control state in each animal by means of a phenylephrine infusion (0.1-0.2 mg/min). During this intervention, atrial pacing or atropine prevented decreases in heart rate related to the baroreceptor reflex. To insure sufficient venous return during each phenylephrine administration and to avoid wide variations in the values for left ventricular end-diastolic pressure in the individual dogs prior to the pressure load, a rapid infusion of 150–250 ml of lactated Ringer’s solution was given before the administration of phenylephrine. During at least one control study in each dog 0.25–0.5 mg/kg of propranolol was injected intravenously. This dose was sufficient to prevent the positive inotropic and chronotropic effects of a bolus of 0.002–0.004 mg of isoproterenol. Atrial pacing or atropine was again employed to prevent alterations in heart rate produced by this intervention.

Digoxin (Lanoxin, Burroughs-Wellcome Co.) was administered by intramuscular injection at a dose of 0.005–0.01 mg/kg body weight twice a day over eight to ten days. To confirm the adequacy of the dose in each dog, serum digoxin levels were measured by a modification of the radioimmuno-assay technique described by Smith et al. (human therapeutic range 0.5 to 2.0 ng/ml). Three to five studies were performed in each animal during the period of digoxin administration. At the time of optimal digoxin effect, as judged by the serum level, at least two phenylephrine infusions and one study with intravenous propranolol were carried out. All studies were performed at least four hours after digoxin administration. One to four weeks after cessation of the chronic digoxin administration, each dog was restudied to demonstrate the reproducibility of the control state. In three of the animals the effects of acute intravenous digoxin on LV function were examined 30 to 60 min after a bolus of 1.0 mg. For statistical comparisons, a paired t-test was used, calculated by a program for an EAI computer (Model 640).

Results

Studies in the Resting State

Chronic Digoxin. Representative tracings before and after chronic digoxin administration during atrial pacing in the resting state are shown in figure 1. The average results and SEM from the group of six dogs are summarized in table 1. Spontaneous heart rate averaged 86 ± 8 beats/min and decreased to 83 ± 7 (NS) after chronic intramuscular administration of digoxin for an average of eight days. During this time, an average digoxin level of 1.58 ng/ml was achieved (range 0.5 to 2.7). At matched heart rates (average 104 before and 105 after digoxin administration), left ventricular systolic pressure increased from 128 ± 4 mm Hg by 9 ± 2 mm Hg (P < 0.008), while LVEDP and LVEDD were not significantly changed. However, ∆LVD increased by 10 ± 4% (P < 0.05) (fig. 2). Peak LV dP/dt was augmented by an average of 38 ± 5% over control values, increasing from 3120 ± 70 to

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Figure 1

Original tracings from one dog during control (left panel) and after chronic digoxin administration (right panel) during atrial pacing in the resting state. The traces (from top to bottom) are ECG; left ventricular pressure (LVP) (mm Hg) from an implanted micromanometer; dP/dt (mm Hg/sec), first derivative from LVP; left ventricular diameter (LVD) in mm from ultrasonic crystals; dD/dt, first derivative from LVD (maximum at arrow); LV diastolic pressure in expanded scale from LVP. A = systolic excursion of LVD; ET = ejection time.

4290 ± 160 mm Hg/sec (P < 0.0006). Mean and maximum VCF showed increases of 22 ± 4% and 21 ± 4%, respectively, compared with control values (both P < 0.02) (fig. 3). The studies 1–4 weeks after cessation of digitalis administration demonstrated values within ±10% of the initial control measurements.

Acute Digoxin. Thirty to sixty minutes after the intravenous injection of 1.0 mg digoxin, the spontaneous heart rate declined from 82 to 69 beats/min. At matched paced heart rates of 102 beats/min, LVSP increased by 10 mm Hg from an average control value of 152 mm Hg while LVEDP and LVEDD decreased slightly from 6 to 4 mm Hg and from 37.9 to 37.3 mm, respectively. However, ΔLVD remained unchanged. LV dP/dt was augmented by an average of 6% (range 0 to 8%), and both mean and maximum VCF increased by an average of 7% (range 0 to 12%), over control. The augmentation in these same animals after chronic digoxin administration, however, averaged 32% for dP/dt (range 23–41%) and 18% for VCF (range 13–22%).

Propranolol. A comparison of the effect of 0.25 mg (four dogs) or 0.5 mg (two dogs) of propranolol/kg body weight given intravenously in the control state and during digoxin administration is shown in table 1 and in figures 2 and 3. At comparable heart rates, the dose of propranolol utilized did not significantly affect LVSP, LVEDP, and LVEDD either in the control state or after digoxin, while LV dP/dt was reduced by 11% in the control state. The average LV dP/dt increase during digitalization was slightly less after propranolol (increase over control of 31% compared with 38%); however, this difference was not signifi-
Table 1

Hemodynamic Effects of Chronic Digoxin Administration

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*Atrial pacing.

Abbreviations: HR = heart rate; LVSP = left ventricular (LV) systolic pressure; LVEDP = end-diastolic pressure; LVEDD = end-diastolic diameter; ΔLVD = systolic excursion of the internal LV diameter; VCF = velocity of the circumferential fiber shortening; Max = maximum; C = control; D = after digoxin administration; av = average; se = standard error of the mean; P = significance level; NS = not significant; P > 0.05.
Hemodynamic parameters during the control state (C), after digoxin (D) administration, after propranolol (PR), and propranolol and digoxin administration (D + PR) are depicted. LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; ΔLVD = stroke excursion of the ultrasonic crystals. Figures above or below brackets indicate significance levels; NS = not significant (P > 0.05).

Studies During Phenylephrine Infusion

In figure 5 the average values of LVSP, LV dP/dt, and ΔLVD of the six dogs in the control state and after digoxin administration are related to different matched levels of LVEDP during phenylephrine infusion. Immediately before each phenylephrine infusion, LVEDP was increased by intravenous administration of Ringer's lactate solution to comparable levels in the control state and after digoxin. In addition, LVSP was not significantly different after digoxin compared with control values at equivalent levels of LVEDP. During the pressure load LV dP/dt fell slightly but remained at a significantly higher level after digoxin administration compared with the control at each level of LVSP (P < 0.005). At a matched LVSP of 206 mm Hg, LV dP/dt after digoxin exceeded the comparable control value by 31 ± 4% (P < 0.001), and mean and maximum VCF were augmented by 26 and 24%, respectively (P < 0.006, table 1). After digoxin ΔLVD remained significantly higher (P < 0.004) than control at each increment of systolic arterial pressure produced by phenylephrine. The decrease in ΔLVD from the resting state during the phenylephrine infusion was proportionally less after digoxin and insignificant; thus, at a LVSP of 206 mm Hg, ΔLVD exceeded the control values by 25 ± 4% compared to the increment of 10 ± 4% produced by digoxin without a pressure load (P < 0.02). The alterations produced by digoxin in the control state and during the pressure load are depicted in figure 4.

Discussion

The present experiments provide data concerning the effects of chronic digoxin administration in a setting analogous to that commonly seen in man, whereas previous investigations of the effects of digitalis glycosides on the hemodynamic and contractile properties of the left ventricle employed acute intravenous administration of digitalis preparations.1, 3, 4, 7–10 Our data indicate that chronic administration of digoxin in doses sufficient to produce therapeutic drug levels produces a marked increase in several measures of myocardial contractile state in the normal conscious dog. Peak LV dP/dt was augmented by 38%, while mean and maximum VCF each increased by an average of 22 and 21%, respectively. It should be pointed out that the persistent increase in
LVSP produced by digitalis\textsuperscript{13, 22} may have contributed to the differences between the parameters measured during the isovolumic and ejection phases of LV systole. While LV dP/dt is relatively unaffected by acute increases in afterload,\textsuperscript{23} it has been shown that VCF is sensitive to such alterations, VCF declining as afterload increases.\textsuperscript{24} However, our findings of an increase in LV stroke excursion after digoxin despite a significant increase in LVSP without alterations in LVEDP or LVEDD suggest that an enhancement in LV performance was present after chronic digoxin administration (table 1), since the extent of fiber shortening tends to be reduced by an increased afterload at a constant preload.\textsuperscript{25}

Studies in unanesthetized man concerning the effects of acutely administered digitalis have yielded data comparable to those obtained in the present study. In six patients with cardiac disease who did not have congestive heart failure, Murphy et al. described increases in LV dP/dt ranging from 18 to 135\% of control values with no change in stroke volume index.\textsuperscript{9} Using a catheter tip manometer system, Mason and Braunwald reported a mean increase in LV dP/dt of 32\% in the right and of 36\% in the left ventricle.\textsuperscript{8} Measuring at isolength points, Sonnenblick et al. found marked (75\%) increases in the velocities of markers sutured to the ventricular surface after intravenous ouabain.\textsuperscript{11} In the latter study, intraventricular pressure was raised by 23\% and stroke volume was unchanged. These measurements of contractility obtained in human subjects are directionally consistent and quantitatively similar to our own data, but differ from the findings in acute studies in conscious dogs.\textsuperscript{13} The modest hemodynamic augmentation in three of our conscious dogs after acute digoxin administration are consistent with the data of Vatner et al. who reported only minor increases in LV dP/dt and VCF in conscious dogs after intravenous injection of 20\,\mu g/kg of ouabain.\textsuperscript{13}

Since the effects of acute intravenous digitalis administration appear to differ quantitatively from those of chronic therapy, the possible influence of the mode of drug administration relative to such conflicting results deserves comment. The augmented contractility and increased peripheral resistance produced by acute digitalis administration can cause autonomic reflex alterations which may moderate the ultimate response to this agent, reflex inhibition of cardiac sympathetic tone obscuring the direct inotropic effect of digitalis.\textsuperscript{26} These reflex responses, in turn, may be influenced by other factors such as barbiturate anesthesia during acute experiments.\textsuperscript{27} To some extent, the larger rise in systemic arterial pressure and the greater augmentation of contractile indices after acute administration of ouabain intravenously to dogs under general anesthesia\textsuperscript{19} could be explained by such alterations in cardiac reflex activation. There is evidence that autonomic reflexes can be altered by a sustained rise in systemic arterial pressure; a peripheral resetting of the baroreceptor response occurs, and the operating range of the baroreceptors shifts to the new elevated pressure level.\textsuperscript{30-32} In rats rendered hypertensive acutely, such a resetting of the baroreceptors occurred within 48 hours.\textsuperscript{30} Although our data indicate that after chronically administered digoxin, systolic arterial pressure as well as contractile indices are augmented, whether a decreased baroreceptor reflex responsiveness after 8 to 10 days of digoxin administration unmasks the inotropic effects of the glycoside remains to be proved. It is difficult to estimate the quantity of glycoside present at the active membrane site 30 min after administration even if early serum levels of the drug are high, since tissue equilibrium, organ distribution, and the final ratio of tissue to serum concentration of the drug have not been reached.\textsuperscript{31} On the other hand, it is known that serum levels of digoxin, obtained approximately eight hours after administration, bear a meaningful relation to the tissue concentration.\textsuperscript{31} Therefore, it is possible that the discrepant response
observed after acute intravenous ouabain compared with chronic digoxin could be related to a difference in the amount of active glycoside actually present at the membrane site of the heart muscle cells. Furthermore, despite several conflicting reports, there is evidence that digitalis-specific receptor sites appear to be present deep within the intact plasma membrane rather than at the cell surface.\textsuperscript{32-34} It seems possible that these receptor sites may tend to become more completely saturated after chronic glycoside administration.

A blocking dose of propranolol did not alter the change in contractile state produced by digoxin. This observation is in accord with the view that the mode of action of digitalis is independent of catecholamine release.\textsuperscript{5, 35-37} However, the further augmentation of LV performance induced by acutely infused digitalis after pretreatment with propranolol, which has been noted by others,\textsuperscript{7-13} was avoided in our study by the use of chronic glycoside administration.

During intravenous infusions of phenylephrine LVSP reached equal values both in the control state and after digoxin from matched levels of left ventricular filling pressure (fig. 5). Early in the course of the pressure load a slight decrease in LV $dP/dt$ was consistently present, suggesting a withdrawal of sympathetic tone, probably due to baroreceptor stimulation. A virtually identical decline, however, was present in the control state as well as after digoxin. In the control state, intravenous phenylephrine produced a significant reduction in stroke excursion. This finding corresponds to other reports in which stroke excursion measured by endocardial ultrasonic crystals and stroke volume measured by electromagnetic flowmeters or thermodilution techniques, respectively, consistently declined during angiotensin infusions in conscious dogs.\textsuperscript{10, 38} However, after digoxin administration, this decrease was smaller and not significantly different from the control state. In the nonfailing heart, basal cardiac output is not limited by myocardial contractility, but rather is regulated by the balance of preload, afterload, and venous return.\textsuperscript{39, 40} During each phenylephrine infusion, the heart had to work against a high systemic arterial pressure from a comparable preload in both the control state and after digoxin. Under these conditions the inotropic state appeared to be the limiting factor with respect to alterations in stroke excursion. Thus, the marked enhancement of the LV inotropic state induced by digoxin administration prevented a decline in the extent of fiber shortening during phenylephrine infusion as compared with control (fig. 5). That the sensitivity of the heart to pressure loading may vary with the level of inotropic state is suggested by the marked decrease in stroke volume observed in patients with dilated hearts in response to angiotensin infusion.\textsuperscript{41}

We conclude that the effect of sustained digoxin administration on the normal heart in the basal, conscious state consists mainly of a major increase in LV contractility. The potent enhancement in functional myocardial reserve demonstrated by the response to acute pressure overload may have clinical implications with regard to the question of prophylactic digitalization of the nonfailing heart. Thus, whenever an acute pressure overload is to be expected, as during anesthesia and surgery, or during chronic pressure stress, as in aortic stenosis, such therapy appears to have a rational basis.

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