# The Effect of Chronic Digitoxin Administration on the Contractile State of Normal and Nonfailing Hypertrophied Myocardium

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ABSTRACT To determine the effect of prolonged digitoxin administration on contractile function of nonfailing myocardium, right ventricular papillary muscle mechanics were examined after 6 or 24 wk of glycoside administration to control and pulmonary artery banded cats. Resting length-tension relations were not affected by digitoxin; however, isometrically developed force and the maximal rate of force development at the peak of the length-tension curve were increased in all treated groups.

In untreated animals, banding resulted in a 28% incidence of deaths from heart failure. 6 wk after constriction, contractile function was depressed whereas normal function was observed 24 wk after banding. Digitoxin significantly reduced mortality from heart failure and enhanced the recovery of contractile function; contractile function in the 6 wk banded treated group approached that of untreated control and 24-wk banded groups. The long-term effects of digitoxin on contractile function were not importantly related to the temporal association between banding and institution of glycoside administration. Development of myocardial hypertrophy was comparable in treated and untreated banded groups.

These results demonstrate that a significant positive inotropic effect persists in both normal and nonfailing hypertrophied myocardium during chronic digitoxin administration.

## INTRODUCTION

The efficacy of administering digitalis glycosides to patients with heart disease to prevent or delay the development of heart failure remains controversial. Although there is experimental evidence to support the "prophylactic" use of glycosides (1–4), results of these studies have not been sufficiently convincing to generate or justify widespread clinical acceptance of this use of digitalis. Furthermore, Katz has raised the theoretical possibility that maintenance of glycoside-induced positive inotropism in nonfailing myocardium for an extended period may be detrimental (5). In support of the latter it has been reported that prolonged administration of digitalis to normal hearts resulted in the development of myocardial hypertrophy (6). Surprisingly, it is unclear whether the inotropic effect of the glycosides on nonfailing myocardium, which has been demonstrated conclusively in acute studies (7–15), persists during prolonged glycoside administration; this is seemingly a prerequisite for either a beneficial or harmful effect under the latter condition. A chronic positive inotropic effect was not demonstrable in patients with heart disease after prolonged glycoside administration (16, 17), whereas a persistent inotropic effect was observed in a single animal study (18). However, in the patient studies, indirect methods for assessing changes in contractile state were employed, and in the latter study contractile state of normal hearts was examined after an average of only 8 days of digoxin administration. Thus, the effect of truly prolonged glycoside administration and, in particular, the effect on the nonfailing but diseased heart remains unanswered.

The present study was undertaken to provide further information in this area and the results demonstrate that prolonged digitoxin administration does produce a significant inotropic effect in both normal and nonfailing hypertrophied myocardium.

## METHODS

Adult cats (1.7–2.4 kg at entry) anesthetized with intraperitoneal pentobarbital (35 mg/kg) underwent main pulmonary artery constriction using a circular band 4.0 mm

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in internal diameter. The band was composed of silastic tubing through which was inserted a copper wire of appropriate length and a silk suture. After placement of the band around the main pulmonary artery the edges of the copper wire were approximated and the sutures tied. The circumference of the pulmonary artery was measured before constriction. The animals were then divided into two groups. One group received 75 μg/kg of digitoxin subcutaneously immediately after the chest had been closed and 15 μg/kg per day for 6 days of each week thereafter. The remaining animals did not receive the glycoside. Animals were reanesthetized 6 or 24 wk after banding, the chest opened, and right ventricular or right atrial pressure measured by a short catheter inserted through the right atrial appendage. Inadvertently, right ventricular pressure was measured in only a few 6-wk banded animals. Cardiac output was determined in duplicate by the dye dilution technique with injection of indocyanine green dye into the right atrium and sampling from a short catheter inserted into a carotid artery. The heart was then removed and the right ventricular papillary muscles dissected free and placed in a muscle chamber containing a solution of the following millimolar composition: $Na^+$, 144; $K^+$, 4.0; $Ca^{++}$, 2.5; $Mg^{++}$, 0.05; $H_2PO_4^-$, 1.0; $HCO_3^-$, 25; $Cl^-$, 128; and glucose 5.6. The solution was maintained at a temperature of 30°C and was bubbled vigorously with 95% $O_2$–5% $CO_2$. The nontendinous end of the papillary muscle was held in a plastic clip into which was inserted a short metal rod. The rod in turn passed through the bottom of the muscle chamber and was connected to a Statham force transducer (Model G1-4-250, Statham Instruments, Inc., Oxnard, Calif.). A short piece of braided silk suture was tied to the tendinous end of the muscle and secured to one arm of a lever attached to a rigid stand located above the bath. A micrometer located above the opposite arm of the lever and attached to the stand was employed as a stop to produce isometric contractions and to alter resting length by known amounts. The muscle was stimulated at a frequency of 12/min using field electrodes parallel to the long axis of the muscle. Stimuli of 5 m/s duration and 10% above threshold voltage were provided by an American Electronics stimulator (American Electronics Laboratories, Inc., Lansdale, Pa.). After the muscle had contracted for approximately 1 h at a light preload, generally 0.5 g, isometric length-tension relationships were determined by increasing muscle length by 0.1 mm increments from a point where active force was just apparent to that where active force first declined from its peak value. Resting muscle length was then fixed at the peak of the active length-tension curve. In addition to active force, the maximal rate of force development (dF/dt) [1] and time to peak force were also determined at this muscle length (Lmax, peak of active length-tension curve). Paired electrical stimulation was then instituted at a rate of 12 pairs/min. The interval between pairs was adjusted to produce a maximal contractile response. During continued paired electrical stimulation small increments of norepinephrine were added to the bath until no further increase in active force was observed: addition of norepinephrine generally produced only a slight additional increase in force. Preliminary observation demonstrated that the addition of calcium to the bath at this time did not result in a further augmentation of contractile force. Therefore, maximal contractile response with paired stimulation and norepinephrine is hereafter referred to as "maximal force index." All variables were recorded on a multichannel oscillograph at a paper speed of 100 mm/s. An operational amplifier was used to determine the maximal dF/dt. Muscle length at Lmax was measured using a calibrated reticle, and cross-sectional area was determined from this length and wet muscle weight by assuming cylindrical configuration and a specific gravity of 1.000.

The great vessels and atria were removed. The right ventricular-free wall was dissected from the left ventricle and septum and the wet weight of the ventricular specimens determined. Dry weight was also determined after exposure to 100°C for 24 h.

12 nonbanded cats received digitoxin in a manner identical to that described above and were studied after 6 wk of glycoside administration. 17 nonbanded untreated cats were studied in an identical manner after 6 wk of observation and an additional 9 cats after 24 wk.

After completion of this phase of the study and analysis of the results presented below, two groups of additional animals were studied 6 wk after banding. One group received digitoxin for the first 3 wk after banding after which glycoside administration was discontinued. The remaining animals were given digitoxin only during the last 3 wk of the 6-wk study period.

With one exception all statistical analyses were performed using analysis of variance as described by Snedecor (19). To determine the significance of difference in mortality between treated and untreated groups the chi-square method was employed.

## RESULTS

Pulmonary artery banding resulted in a reduction in cross-sectional area ranging from 55 to 85% (average 70%). Of 131 banded animals not given digitoxin, 37 died of congestive heart failure characterized by pleural effusions, ascites, and hepatomegaly. In contrast, only 9 of 64 digitoxin-treated animals died with these findings: the difference in mortality from congestive heart failure is statistically significant ($P < 0.05$). All but one death from heart failure occurred within 21 days of banding. 12 untreated and 14 treated animals were sacrificed 6 wk after banding, whereas 11 untreated and 12 treated animals were studied 24 wk after constriction. The remainder of the banded animals were utilized for other experiments (none before 6 wk after banding) or died of causes other than congestive heart failure. There was no significant difference between treated and nontreated groups in mortality from cause other than heart failure.

Comparison of ventricular weights, papillary muscle cross-sectional area, and hemodynamics among groups is presented in Table I.

Nonbanded control animals studied after 24 wk of observation had right ventricular-to-body weight ratios and left ventricular-to-body weight ratios significantly smaller than animals observed for 6 wk, as reported previously (20). These differences appear to be due to an increase in body fat during prolonged inactivity rather than any dimunition in mass of the heart since

[1] *Abbreviations used in this paper:* dF/dt, maximal rate of force development; Lmax, peak of active length-tension curve.

TABLE I

*Anatomic and Hemodynamic Data for All Groups**

| Group | No. | Body wt | RV wt/ Body wt | LV wt/ Body wt | RV wt/ LV wt | Papillary muscle cross-section | Cardiac output | RV PR Sys/dias | RA PR mean |
|---|---|---|---|---|---|---|---|---|---|
| | | *kg* | *g/kg* | *g/kg* | | *mm²* | *ml/min kg⁻¹* | *mm Hg* | *mm Hg* |
| Controls(6) | 17 | 2.8 ±0.1 | 0.71 ±0.04 | 2.35 ±0.10 | 0.31 ±0.01 | 1.1 ±0.06 | 158 ±14.7 | 23/2 ±1/0.2 | 2.8 ±0.4 |
| Untreated(24) | 9 | 2.8 ±0.1 | 0.58§ ±0.01 | 1.86§ ±0.05 | 0.31 ±0.01 | | | | |
| Controls(6) Treated | 12 | 2.8 ±0.2 | 0.69 ±0.05 | 2.19 ±0.10 | 0.32 ±0.02 | 1.2 ±0.10 | 183 ±18.0 | 31/3 ±4/0.3 | 3.5 ±0.3 |
| Banded(6) Untreated | 12 | 2.7 ±0.1 | 1.19‡ ±0.07 | 2.32 ±0.16 | 0.49‡ ±0.02 | 2.0‡ ±0.28 | 154 ±17.0 | 62/4 ($n$ = 3) | 2.5 ±0.4 |
| Banded(6) Treated | 14 | 2.3‡ ±0.1 | 1.15‡ ±0.05 | 2.26 ±0.08 | 0.53‡ ±0.03 | 2.1‡ ±0.22 | 160 ±15.2 | 57/3 ($n$ = 4) | 2.0 ±0.4 |
| Banded(24) Untreated | 11 | 3.1 ±0.2 | 1.08‡ ±0.08 | 2.03 ±0.09 | 0.53‡ ±0.03 | 1.8‡ ±0.20 | 121 ±12.5 | 59/3‡ ±8/1 | 2.6 ±0.6 |
| Banded(24) Treated | 12 | 3.1 ±0.2 | 0.99‡ ±0.08 | 1.91 ±0.06 | 0.52‡ ±0.04 | 1.9‡ ±0.20 | 189 ±16.2 | 60/3‡ ±7/1 | 3.1 ±0.5 |

* Values represent mean±SEM.

‡ Values significantly different from that of the respective nonbanded control group.

§ Values significantly different from that of untreated controls observed 6 wk.

(6) and (24), duration of observation or banding in weeks; RV, right ventricular; LV, left ventricular; RV PR, right ventricular pressure (systolic-diastolic); RA PR, right atrial pressure.

the liver-to-body weight ratios in the 24-wk control animals were also significantly less than those of the 6-wk controls. Right-to-left ventricular weight ratios in the control groups were identical. No statistically significant differences in any of the other measured variables were observed in the untreated 6 and 24-wk control groups, and these results were therefore combined. Administration of digitoxin for 6 wk to nonbanded animals did not result in a significant change in any of the measured anatomic variables when compared to the nontreated 6-wk control group. Hemodynamic variables in treated and nontreated control animals also were not significantly different.

Banding resulted in an increase in right ventricular mass in all constricted animals as evidenced by a right-to-left ventricular weight ratio in each banded animal which exceeded the largest ratio in the controls. The ratio of right ventricular weight-to-body weight in the 24-wk banded groups was less than that observed in the 6-wk banded animals. However, the increase in this ratio in banded groups was similar when each was compared to its respective nonbanded control group observed for a comparable period of time. Right-to-left ventricular weight ratios among all banded groups were also insignificantly different. Thus the magnitude of right ventricular hypertrophy was not affected by digitoxin administration or the period of banding before study. Left ventricular weight-to-body weight ratios in the banded groups were not significantly different from their respective nonbanded control groups.

Right and left ventricular dry weight was approximately 25% of the wet weight, and no statistically significant differences among groups were observed.

Neither banding nor digitoxin administration resulted in a significant change in cardiac output or right atrial mean pressure. Right ventricular systolic pressure in the 24-wk banded groups was increased 2–2.5 times by banding, and the values in the treated and untreated banded groups were essentially identical. Although ventricular pressure was not measured in the majority of 6-wk banded animals, the similarity of the increase in right ventricular mass in the 6 and 24 wk untreated banded groups suggests that the loads were also similar. Furthermore, the similarity of right ventricular systolic pressure in 24-wk banded treated and nontreated animals indicate that digitoxin did not effect the load. These observations plus the similar increases in right ventricular systolic pressure in the few

TABLE II
*Functional Data from Nonbanded Control Animals**

| Group | Resting force at Lmax | Active force at Lmax | dF/dt | TTPF | Maximal force index |
|---|---|---|---|---|---|
| | $g/mm^2$ | $g/mm^2$ | $g/mm^2$ $sec^{-1}$ | $m/s$ | $g/mm^2$ |
| Controls | 1.2 | 5.1 | 31.9 | 243 | 8.1 |
| Untreated | ±0.1 | ±0.3 | ±1.4 | ±6.8 | ±0.4 |
| Controls | 1.2 | 6.2‡ | 38.6‡ | 260 | 7.8 |
| Treated | ±0.2 | ±0.5 | ±2.6 | ±10.3 | ±0.6 |

* Values represent mean±SEM.
‡ Value significantly different from the respective untreated value ($P \leq 0.05$).
TTPF, time to peak isometric force development at Lmax.

6-wk banded animals in which measurements were obtained provide strong evidence that the loads in all banded groups were comparable.

None of the banded animals had evidence of congestive heart failure at the time of sacrifice and liver-to-body weight ratios among groups, although not presented, were not statistically different from their respective control groups. Furthermore, the lowest cardiac output in any constricted animal exceeded the lowest value found in the controls (76 ml/min $kg^{-1}$).

There were no significant differences in papillary muscle cross-sectional area among banded groups. However, the value for each banded group was significantly greater than the controls ($P \leq 0.05$). Inasmuch as the detrimental effect of increasing papillary muscle size on muscle function has been well demonstrated (21), it was not possible to compare meaningfully data from control and banded animals. Therefore, papillary muscle function data from nonbanded and banded animals is presented separately in Tables II and III, respectively. However, a valid comparison of data from nonbanded and banded animals is possible by using only data from banded muscles whose cross-sectional area did not exceed that of the largest nonbanded muscle, i.e., 2.0 $mm^2$. Comparison of this data is presented in Fig. 1–3. When selected in this manner, average cross-sectional area of the banded muscle was not significantly different from that of the control groups (Fig. 1). Also, there were no significant differences in right-to-left ventricular weight ratios among these groups of selected hypertrophied muscles and those from the entire group of banded animals.

*Control animals (Table II).* Both peak active force and the maximal dF/dt were increased by an average of 21% in the digitoxin-treated animals ($P < 0.05$ for both). In contrast the mean values for resting force at Lmax, time to peak active force and maximal force index were not significantly different.

*Banded animals (Table III).* In 6-wk banded animals, peak active force, maximal dF/dt, and maximal force index were all significantly greater statistically in treated than in nontreated animals; the increases averaged 40%, 71%, and 24%, respectively. In the 24-wk banded animals, peak active force and maximal dF/dt were greater in treated animals by an average of 18 and 23%, respectively. However, neither of these increases were significant statistically. Maximal force index was essentially identical in 24-wk banded groups. No statistically significant differences in time to peak active force development were observed among banded groups.

*Nonbanded controls vs. banded animals (Fig. 1–3).* No significant differences in resting force over a range of 85 to 103% of Lmax were observed among groups. Active force development at Lmax in the 24 wk banded treated and nontreated groups was essentially identical to that of the respective nonbanded control groups.

In contrast, peak active force in the 6 wk banded nontreated group was significantly less than that of the nontreated control animals ($P < 0.05$). In the 6 wk banded treated group, peak active force was comparable to that of untreated controls.

Changes in dF/dt were similar (Fig. 2). 24 wk banded treated and untreated groups had values insignificantly different from their respective controls, whereas 6 wk banded untreated animals had values significantly less than untreated controls ($P < 0.05$). However, dF/dt in the 6 wk banded treated group was identical to that of untreated controls.

Maximal force index (Fig. 3) in the 24 wk banded treated and untreated groups also was not significantly different from their respective controls, whereas the value in the 6 wk banded untreated group was less than in untreated controls ($P < 0.01$). Maximal force in the

TABLE III
*Functional Data from Banded Animals**

| | Resting force at Lmax | Active force at Lmax | dF/dt | TTPF | Maximal force index |
|---|---|---|---|---|---|
| | $g/mm^2$ | $g/mm^2$ | $g/mm^2$ $s^{-1}$ | $m/s$ | $g/mm^2$ |
| Banded(6) | 1.3 | 3.1 | 18.6 | 269 | 4.7 |
| Untreated | ±0.1 | ±0.4 | ±3.0 | ±7.9 | ±0.5 |
| Banded(6) | 1.1 | 4.6‡ | 33.7‡ | 267 | 5.8‡ |
| Treated | ±0.1 | ±0.5 | ±2.7 | ±8.3 | ±0.4 |
| Banded(24) | 1.0 | 4.0 | 23.4 | 260 | 6.3 |
| Untreated | ±0.1 | ±0.5 | ±2.8 | ±10.2 | ±0.5 |
| Banded(24) | 1.2 | 4.7 | 28.7 | 286 | 6.2 |
| Treated | ±0.1 | ±0.6 | ±3.1 | ±7.8 | ±0.5 |

* Values represent mean±SEM.
‡ Value significantly different from the respective untreated value ($P \leq 0.05$).
TTPF, time to peak isometric force development at Lmax.

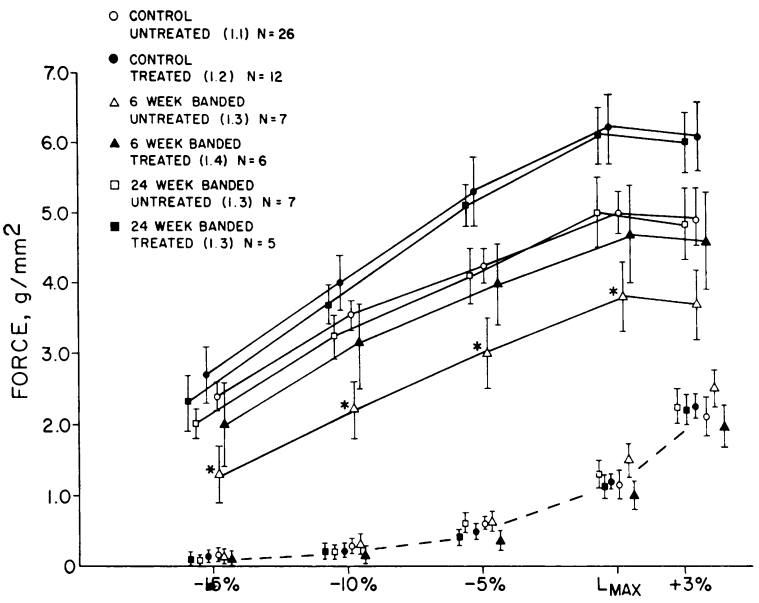


FIGURE 1 Comparison of length-tension relations of papillary muscles from nonbanded animals and muscles of comparable cross-sectional area from banded animals. Figures in parenthesis represent cross-sectional area of papillary muscles. Values represent mean±SEM. *, denotes value significantly different ($P \leqq 0.05$) from the respective nonbanded group.

6 wk banded treated group, although greater than in the untreated banded group, remained significantly less than in the untreated controls ($P < 0.05$).

Results from the banded animals given digitoxin for only 3 wk are presented in Table IV. No significant differences in right-to-left ventricular weight ratios were observed between these groups or when compared to other banded groups. Papillary muscle cross-sectional area was significantly larger in the on-off group than in the off-on animals. However, it was possible to obtain meaningful information since the size of the papillary muscles in the on-off group was quite comparable to that of the entire group of 6 wk banded untreated animals, whereas that of the off-on group was similar to that of the 6 wk banded treated animals with papillary muscles less than 2.0 mm². To facilitate this comparison data from these 6-wk banded groups are reproduced in Table IV. Animals in which digitoxin was discontinued 3 wk after banding had values of peak force, maximal dF/dt, and maximal force index comparable to the group which did not receive the glycoside during the entire 6-wk study period. In contrast, contractile function of animals treated only during the last 3 wk was comparable to that of muscles of similar size from banded animals treated for 6 wk.

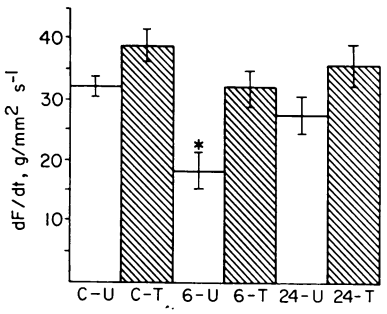


FIGURE 2 Comparison of maximal rate of force development at Lmax among groups of papillary muscles included in Fig. 1. C, controls: 6, 6-wk banded; 24, 24-wk banded; U, untreated; T, digitoxin treated; and * denotes value significantly different ($P \leqq 0.05$) from the respective nonbanded group.

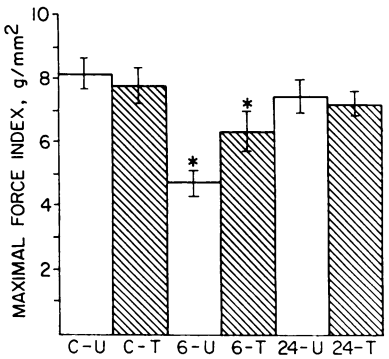


FIGURE 3 Comparison of maximal force index among groups of papillary muscles included in Fig. 1. For abbreviations see Fig. 2. *, denotes value significantly different ($P \leqq 0.05$) from the respective nonbanded group.

TABLE IV

*Comparison of Anatomic and Functional Data in Banded Animals Receiving Digitoxin for 3 or 6 Wk*

| Group | No. | RV wt/ LV wt | Papillary muscle cross-section | Resting force at Lmax | Active force at Lmax | dF/dt | TTPF | Maximal force index |
|---|---|---|---|---|---|---|---|---|
| | | | $mm^2$ | $g/mm^2$ | $g/mm^2$ | $g/mm^2\ s^{-1}$ | $m/s$ | $g/mm^2$ |
| On-off | 5 | 0.56 ±0.05 | 2.1 ±0.2 | 1.0 ±0.2 | 2.8 ±0.4 | 15.6 ±0.9 | 251 ±8.4 | 5.1 ±0.3 |
| Banded(6) Untreated | 12 | 0.49 ±0.02 | 2.0 ±0.3 | 1.3 ±0.1 | 3.1 ±0.4 | 18.6 ±3.0 | 269 ±7.9 | 4.7 ±0.5 |
| Off-on | 5 | 0.60 ±0.03 | 1.1 ±0.2 | 1.0 ±0.2 | 5.1 ±0.9 | 31.6 ±6.5 | 257 ±8.4 | 6.8 ±1.2 |
| Banded(6) Treated | 6 | 0.53 ±0.06 | 1.4 ±0.1 | 1.0 ±0.2 | 4.7 ±0.8 | 31.2 ±3.0 | 282 ±10.8 | 6.2 ±0.6 |

On-off and off-on refer to animals receiving digitoxin during only the first 3 wk and last 3 wk, respectively, of the 6-wk banding period.
For method of selecting data from 6-wk treated and untreated animals see Results section.
For other abbreviations see Tables I and II.

In four treated control animals digitoxin serum levels were determined by radioimmunoasay 7, 14, and 21 days after commencing the study. The values averaged 15, 46, and 54 ng/ml, respectively.

## DISCUSSION

The results of this study clearly demonstrate that the positive inotropic effect of digitoxin persists in both normal and nonfailing hypertrophied myocardium during 6 wk of glycoside administration. Furthermore, the data suggest that maintenance of this effect for 24 wk in the nonfailing heart is not detrimental. Although statistically peak active force and maximal dF/dt were not significantly different in the 24 wk banded treated and untreated animals, the larger values occurred in the treated animals, and the magnitude of the increase was essentially identical to that in the treated control group (Fig. 1 and 2).

The inotropic effect of digitoxin was manifest by an increase in peak active force and maximal rate of force development in all groups, whereas maximal force index was not significantly increased in either 24-wk banded or control groups. This latter observation is not surprising since Beiser et al. have demonstrated that the maximal increase in contractile force produced by catecholamines is greater than that produced by digitalis glycosides (22). Furthermore, in the same study, the combination of the two did not result in greater contractile force than occurred with catecholamines alone. However, in our 6-wk banded animals, maximal force index was significantly greater in the treated than in the nontreated group although the percent increase above peak active force was comparable.

We previously reported that sudden sustained pulmonary artery banding in the cat resulted in depression of contractile state 6 wk after banding with subsequent recovery of normal contractile function by 24 wk after constriction (20). In the present study values for peak force and maximal dF/dt in the 6 wk banded treated group were comparable to those of untreated nonbanded animals indicating that digitoxin significantly enhanced the rate of recovery of myocardial function after banding. However, contractile function was not completely restored in this banded group since maximal force index remained significantly less than that of untreated controls. This suggests that a decrease in maximal force may be a more sensitive indicator of depressed contractile state than a decrease in active force or maximal dF/dt at Lmax. Others previously have emphasized the usefulness of maximal force development as a measure of contractile function (23).

In this animal model myocardial wall stress is probably greatest during the early period after pulmonary artery constriction, i.e., before significant myocardial hypertrophy has occurred. Because it seemed possible that the presence of digitoxin during this period could produce a long-term effect on contractile function unlike that which would occur with later administration of the glycoside, we examined the effect of the glycoside in banded animals treated for only 3 of the 6 wk. This data demonstrates that it was not necessary to institute digitoxin treatment at the time of acute loading to obtain an inotropic effect quantitatively similar to that

which resulted when glycoside administration was begun much later. Neither did administration of digitoxin at the time of acute loading result in any sustained enhancement of contractile function if the glycosides were subsequently discontinued. However, since all deaths from heart failure occurred early after banding prompt administration of digitoxin was necessary to reduce mortality from heart failure in this particular model.

The significant reduction in mortality from congestive heart failure is in agreement with previous studies (3). Importantly, all but one death from heart failure occurred within 21 days of banding, the single exception occurring in the nontreated group, and in a number of banded animals the period of observation has now exceeded a year. Therefore, changes in contractile function between 6 and 24 wk after banding cannot be attributed to "selection," i.e., survival for 24 wk only in those animals with lesser depression of contractile function. Conversely, we do not believe that the administration of digitoxin to banded animals affected our results by delaying death from heart failure beyond 24 wk in animals which otherwise would have died within the first 3 wk. Such an occurrence would be expected to result in animals whose contractile function was even less than that of nontreated surviving ones rather than enhanced function as observed in treated animals.

The results of this study differ from those of previous investigations in which the magnitude of left ventricular hypertrophy in response to pressure loading was reduced in rats given digitoxin (3, 4). No significant differences in the magnitude of right ventricular hypertrophy were observed among our banded treated and nontreated groups. The reason for this disparity is unclear but it is of interest that digitoxin has been reported to retard the development of left ventricular hypertrophy but not the development of right ventricular hypertrophy in rats exposed to prolonged hypoxia (24). In addition, determination of serum digitoxin levels revealed that the "loading" dose we selected resulted in a relatively low serum level at the end of the 1st wk of treatment. It is possible that the presence of larger amounts of glycoside during the early period after banding might have produced somewhat different results. Digitoxin administration to control animals did not result in a significant increase in ventricular mass in contrast to the observations of others (6).

The dose of digitoxin was selected on the basis that the dog and cat respond similarly to the glycoside and this dose is a therapeutic one in the former animal (25). In addition, we administered 30 $\mu$g/kg per day of digitoxin as a maintenance dose to five normal animals. Four animals died within 2 wk and no definite cause of death could be established at autopsy. An additional five animals received a maintenance dose of 20 $\mu$g/kg per day. Four animals developed anorexia and progressive weight loss which was reversed when the glycoside was discontinued. Thus, 15 $\mu$g/kg appears to be near the maximal maintenance dose that can be administered to these animals. However, as noted above, our "loading" dose was probably not optimum.

Comparison of our results with those of acute studies revealed certain similarities in the myocardial response to the glycosides. As reported by others in acute studies (26), the inotropic effect of digitoxin was quantitatively greater in our animals with depressed function, i.e. the 6 wk banded group, than in those with normal function. Interestingly, the 21% increase in peak force and maximal dF/dt in our treated control animals is identical to the increase in an index of contractile state reported in acute in vivo studies in normal animals (26). These increases are also comparable to those reported by Mahler, Karliner, and O'Rourke after 8 days of digoxin administration to normal dogs (18). However, time to peak force, a reflection of the duration of active state (27), was not reduced in our chronically treated animals in contrast to previous reports in acutely studied papillary muscles (28). This raises the possibility that some alteration in the basic mechanism responsible for the inotropism does occur during chronic glycoside administration.

The average cross-sectional area of the papillary muscles from banded animals was larger than optimum, and some degree of hypoxia was probably present (29, 30). Although the use of smaller muscles would have been desirable, it is difficult to obtain hypertrophied muscles less than 1.0 $mm^2$ in cross-sectional area. To obtain data from a significant number of muscles it was therefore necessary to use larger ones. However, we believe our conclusions are valid since we limited our comparisons to muscles of similar cross-sectional area.

The hazard of extrapolating our data to the clinical situation is apparent since our model employs sudden sustained right ventricular loading, a condition unlike the more common forms of pressure-induced human heart disease in which a slowly progressive load is applied to the left ventricle. A definitive answer concerning the usefulness of "prophylactic" digitalization must therefore await the development of a more suitable animal model. Nevertheless, we have demonstrated that a significant positive inotropic effect persists during prolonged glycoside administration to the nonfailing heart, and that persistance of this effect for a protracted period is not detrimental to contractile function.

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