Effects of Chronic Digitalization on Cardiac and Renal Na$^+$ + K$^+$-Dependent Adenosine Triphosphatase Activity and Circulating Catecholamines in the Dog

Bohdan R. Nechay, Robert E. Jackson, Michael G. Ziegler, Susan L. Neldon, and Jon D. Thompson

SUMMARY To extend our understanding of the mechanism of action of digitalis drugs, we studied electrocardiograms (ECGs), renal function, plasma concentrations of catecholamines, and myocardial and renal Na$^+$ + K$^+$-dependent adenosine triphosphatase (Na$^+$ + K$^+$ ATPase) activity in chronically digitalized dogs. Five healthy, male, mongrel dogs received a therapeutic regimen of digoxin (0.1 mg/kg on day 1 in three divided doses followed by 0.025 mg/kg per day) orally for 2-4 months. This resulted in plasma digoxin concentrations of 1.1 to 4.7 ng/ml as determined by radioimmunoassay. Six control dogs received daily gelatin capsules by mouth. ECGs monitored throughout the study showed no changes. Digitalized dogs had elevated plasma norepinephrine concentrations (347 vs. 137 pg/ml in controls) and no change in plasma epinephrine concentrations. Digitalized dogs had elevated glomerular filtration rates (0.74 vs. 0.94 ml/min per g of kidney) without significant changes in renal handling of electrolytes and water. All of the above studies were done without the aid of restraining drugs or infusions. The animals were killed with an overdose of pentobarbital for in vitro studies. In digitalized dogs, microsomal Na$^+$ + K$^+$ ATPase-specific activity was 26 to 33% lower in the renal cortex, medulla, and papilla, and 46% lower in the cardiac left ventricle than in control dogs. Digitalization did not alter the osmolalities of renal tissues. We conclude that chronic reduction of Na$^+$ + K$^+$ ATPase activity by one-third does not cause abnormalities in renal handling of electrolytes and water, and inhibition of Na$^+$ + K$^+$ ATPase in the left ventricular muscle by one-half is associated with no obvious ECG changes in the dog. Further, elevated plasma norepinephrine concentrations may contribute to both the therapeutic and the toxic effects of digitalis.


THE cardiac glycosides are potent inhibitors of Na$^+$ and K$^+$-dependent adenosine triphosphatase [Na$^+$ + K$^+$ ATPase, E.C. 3.6.1.3 (Skou, 1965)]. There is a controversy, based on acute experiments performed in various heart preparations, as to whether the inhibition of Na$^+$ + K$^+$ ATPase results in the positive inotropic effect or is just a manifestation of cardiotoxicity (Smith and Haber, 1973; Akera and Brody, 1978; Hoffmann and Bigger, 1980). Low concentrations of cardiac glycosides stimulate Na$^+$ + K$^+$ ATPase preparations, and this effect may be responsible for the therapeutic action of digitalis (Palmer and Nechay, 1964). Little is known about the chronic effects of digitalis glycosides on Na$^+$ + K$^+$ ATPase. Bonn and Greeff (1978) reported increased Na$^+$ + K$^+$ ATPase activity in guinea pig hearts after 24 days of digitoxin administration, but they did not study cardiac function. Ku et al. (1977) found dog myocardial Na$^+$ + K$^+$ ATPase inhibited by arrhythmogenic doses of digoxin administered for 30 days.

Although it is generally assumed that the diuretic effect of digitalis is secondary to its effect on the heart (Moe and Farah, 1975), an iv dose of digoxin may initiate a slight but definite Na"Cl" diuresis independent of cardiac output (Farber et al., 1951). In acute animal experiments, large doses of cardiac glycosides inhibit renal Na$^+$ + K$^+$ ATPase activity, and consequently reduce the reabsorption of Na"Cl", increase urinary Na""/K"" ratio, and abolish the ability of the kidney to concentrate and dilute urine (Nechay, 1977). Bonn and Greeff (1978) found renal Na" + K" ATPase activity unchanged in guinea pigs after 24 days on digitoxin, but they did not examine renal function.

The intravenous injection of cardiac glycosides causes an increase in blood pressure, systemic vascular resistance, and venomotor tone (Smith and Haber, 1973). These cardiovascular changes are partly mediated by an increase in sympathetic outflow (Gillis, 1969) stimulated by central actions of the drug (Pace and Gillis, 1976). The magnitude of
this sympathetic neuronal response to sub-arrhythmogenic doses of digitalis is unknown, and the sympathetic stimulatory effect is said to be transient, even though chronic studies have not been carried out (Moe and Farah, 1975). Although the methodology of prior studies, such as recording neuronal activity in sympathetic ganglia, is not applicable to chronic studies, plasma levels of catecholamines are relatively stable and thus provide an index of sympathetic nervous activity (Lake et al., 1976). Plasma norepinephrine is derived from release of this neurotransmitter by sympathetic neurons, and epinephrine is secreted by the adrenal medulla. We measured these compounds to see if the effect of digoxin on sympathetic nervous activity persists and is large enough to be of physiological significance.

We also examined the effects of chronic digoxin administration on renal function, electrocardiogram (ECG), and Na\(^+\) + K\(^+\) ATPase activity in the kidney and heart. Since cardiac glycosides have qualitatively similar effects on healthy and failing hearts (Smith and Haber, 1973), we have used healthy dogs to avoid the complications of disease. The dog was chosen as the experimental animal because therapeutic regimens of digoxin have been established (Detweiler, 1977), and the renal function (Pitts, 1974) and sensitivity of Na\(^+\) + K\(^+\) ATPase to cardiac glycosides (Nechay et al., 1975) are similar in dogs and humans.

**Methods**

Male, mongrel dogs, about 6–12 months of age, were quartered, two per run, in a large air-conditioned room and exercised daily. They were fed standard dog food and water intake was ad libitum, except during the kidney function tests. The surface area of the dogs was estimated using a nomogram (Smith, 1956).

Five dogs were digitalized with digoxin (Lanoxin) by mouth according to the method of Detweiler (1977), as follows: 0.1 mg/kg in three divided doses the first 24 hours and 0.025 mg/kg daily maintenance dose for 2–4 months. Radioimmunoassay for digoxin was performed with Corning Digoxin \(^{125}\)I Radioimmunoassay kit. Six control dogs received gelatin capsules (Lilly) by mouth. ECGs were monitored using modified limb leads on a Grass model 5D Polygraph throughout the study.

The experiments were designed thus: in vivo procedures did not employ any restraining drugs or infusions. One of us (R.E.J.) became sufficiently familiar with the dogs, through daily feeding, exercise, grooming, weighing, administration of drugs, playing, etc., so that they tolerated slight pain, such as from venipuncture, stomach intubation, or urethral catheterization, without acting frightened or attempting to escape. Initial renal function tests were performed in water-loaded animals after a minimum of 2 months of digoxin or placebo administration. From 1 to 8 weeks later, renal studies were repeated on water-deprived animals. Some of these dehydrated animals also were challenged with a salt load. Exogenous creatinine clearance was used to measure glomerular filtration rates (GFR). Blood samples were drawn into heparinized syringes from either brachial or saphenous veins, and plasma was separated in a clinical centrifuge. Urine was collected by catheterization using aseptic technique and the bladder was actively emptied by massage and injection of air with a syringe applied to the catheter tip.

**Water Diuresis Experiment**

Dogs were deprived of food, but not water, overnight prior to these experiments. After a blood sample was drawn for baseline studies, 3 g of creatinine in a sterile isotonic solution were injected subcutaneously in the upper neck region. Immediately after creatinine injection, 70 ml/kg of tap water were administered (in two equal portions 30 minutes apart) by a stomach tube. Thirty minutes later, the bladder was drained and this urine discarded. Subsequently, three consecutive 20-minute urine collections were made and blood drawn at mid-point of urine collection periods.

**Hydropenia Experiments**

Dogs were deprived of water, but not food, for 24 hours. A baseline blood sample was drawn. Creatinine was administered as described above. One hour later, the bladder was emptied and the urine discarded. To assure accurate measurements of urine formation at low rates, the two subsequent collection periods were increased to 90 minutes. Blood was drawn in the middle of each urine collection period.

**Salt-load Experiments**

Some dehydrated dogs were given a salt challenge after one urine collection period. One g of Na\(^+\)Cl\(^-\) (2% solution) per 20 kg of body weight was injected iv over 3–5 minutes. Two 60-minute urine collections were made with blood samples drawn in the middle of each period.

**In Vitro Experiments**

When kidney function studies were completed, dogs were killed with a 70 mg/kg iv dose of sodium pentobarbital prior to assay of renal and myocardial Na\(^+\) + K\(^+\) ATPase and renal tissue osmolalities. The heart and kidneys were removed rapidly. Kidneys were dissected on ice into cortex, outer medulla, and papilla, and two types of homogenates were made: (1) 0.5 g tissue and 1.5 ml of 0.25 M sucrose for tissue osmolality measurements, and (2) 2 g tissue and 18 ml of homogenizing medium for preparation of microsomes. Microsomes were also prepared from the cardiac left ventricle.

Methods for isolation of microsomes have been described previously (Nechay and Nelson, 1970). Briefly, tissue was added to 9 volumes homogeniz-
ing medium containing sucrose (0.25 M), disodium edetate (5 mM), sodium deoxycholate (0.1%), and Tris (to pH 6.8). These homogenates were used for obtaining microsomal fractions by differential centrifugation. The enzyme activity was measured by the rate of release of inorganic phosphate (P) from exogenous ATP at 37°C. The incubation mixture contained the enzyme (microsomal fractions), 100 mM NaCl, 20 mM KCl, 3 mM MgCl₂, 3 mM ATP, and histidine-imidazole buffer at pH 7.4. ATPase activity inhibited by 1 X 10⁻⁴ M ouabain represented Na⁺ + K⁺ ATPase activity. All enzyme measurements were done in duplicate and, at times, repeated again in duplicate. The duplicates varied by less than 5% and replicates by less than 20%.

A Wescor 5100 B Vapor Pressure Osmometer was used to measure osmolalities. The osmotic pressure of kidney tissues was estimated from osmolality measurements of tissue homogenates, after correcting for dilutions. Electrolytes were assayed on a Technicon Autoanalyzer 1. Creatinine was assayed according to the method of Smith (1956). Plasma levels of norepinephrine were measured by the radioenzymatic technique of Henry et al. (1975) as modified by Lake et al. (1976). This assay measures as little as 20 pg/ml of norepinephrine, and its accuracy and reliability have been confirmed by gas chromatography-mass spectroscopy (Ziegler et al., 1976). Plasma epinephrine was measured by the method of Durrett and Ziegler (1980). This technique also measures norepinephrine, and these determinations were always within 20% of the values measured by the prior technique.

Groups were compared by two-sample t-test (unpaired); a P value of 0.05 was accepted as the limit of significance. Results are expressed as mean ± SD.

Results

Plasma digoxin concentrations in dogs receiving the drug ranged from 1.3 to 2.4 ng/ml (mean = 1.9) when normally hydrated, and from 1.1 to 4.7 ng/ml (mean = 3.4) when dehydrated (P < 0.05). We noted no ECG changes in digitalized dogs, whether compared with untreated animals or with themselves prior to drug administration.

Digitalization did not alter renal handling of Na⁺, K⁺, Cl⁻, osmotic load, or water in hydrated, dehydrated, and salt challenged animals (Table 1). The water load was sufficiently large (70 ml/kg) to dilute urine to 65-70 mOsm, nearly the physiological limit. Twenty-four hours of water deprivation lead to urine of 1924-2107 mOsm, with a U/P ratio of 6.1 to 6.8, the upper limit for urinary concentration in the dog (Smith, 1956; Levitin et al., 1962). Plasma osmolalities and electrolyte concentrations were lowered markedly by water loading and increased markedly by dehydration, but were similar in control and digitalized animals.

The only consistent change in renal function following digitalis was an increased GFR. When expressed per unit of body surface area, GFR was insignificantly elevated in digitalized animals (Table 1). However, GFR per unit of kidney weight (ml/min per g of kidney) was 27% higher (P < 0.05) in digitalized dogs than in controls (Table 2). Since the kidney weight can be determined more precisely than the body surface area, the latter mode of expression should more accurately define the magnitude of GFR.

Plasma, for measurement of catecholamines, was obtained from animals with normal water balance on days when no other experimental procedures were done, to assure as little excitement as possible. The mean norepinephrine concentration was about 2.5 times higher in digitalized (347 ± 63 pg/ml) than in control (137 ± 32 pg/ml) dogs (P < 0.01). There were no differences in epinephrine concentrations between the two groups (control 135 ± 87; digitalized 113 ± 67 pg/ml).

In vitro studies (Table 2) show that digitalization did not alter the weight of the kidneys. In keeping with an unimpaired ability of the kidney to concentrate urine, the osmolalities of medulla and papilla were equally high in digitalized and control dogs. Although renal cortical tissue is known to be 300 mOsm (Pitts, 1974), the values by our methods were about 400 mOsm, suggesting that tissue homogenization freed structural particles which did not contribute to the osmotic pressure in the intact cell.

Microsomal Na⁺ + K⁺ ATPase-specific activity was 30% lower in cortex, 26% in medulla, and 33% in papilla of digitalized dogs than in kidneys of control dogs. Renal Mg²⁺ ATPase specific activity was the same in both groups. Specific activity of microsomal Na⁺ + K⁺ ATPase derived from left ventricular muscle of the heart was 46% lower in digitalized than in control dogs. Mg²⁺ ATPase-specific activity of the same preparations remained unchanged. Studies of Na⁺ + K⁺ ATPase obtained from kidney medulla and heart of digitalized dogs revealed uniformly depressed enzyme activity at all levels of Na⁺ (10-150 mM), K⁺ (2-20 mM), and MgATP (1-3 mM) tested (data not shown). This suggests that the properties of the uninhibited portions of the enzyme remained unchanged.

Discussion

The relatively short half-life of digoxin in the dog, about 22 hours (Ku et al., 1977) vs. 36 hours in humans, accounts in part for the fact that digitalizing doses of digoxin are several times higher in this species than in humans. It appears that the dog may also tolerate somewhat higher plasma digoxin concentrations than humans, even though Na⁺ + K⁺ ATPase preparations of the two species are similarly sensitive to ouabain in vitro (Nechay et al., 1975). According to a veterinary pharmacology text (Detweiler, 1977), healthy beagles generally do not exhibit toxic ECG changes at serum digoxin levels of up to 2.5 ng/ml. Levels of 2.5 to 6.0 ng/ml cause moderate changes, and levels over 6 ng/ml cause severe toxicity. We observed no ECG changes...
at plasma digoxin concentrations ranging from 1.1 to 4.7 ng/ml. There are no published data on plasma digoxin concentrations during the therapy of congestive heart failure in the dog. The upper limit for therapeutic plasma concentration of digoxin in humans is 2.0 ng/ml (Hoffman and Bigger, 1980).

Ku et al. (1977) studied plasma digoxin concentrations, ECGs, and myocardial Na\(^+\) + K\(^+\) ATPase activity in dogs digitalized for 30 days. They found no ECG changes in their non-toxic group with an average plasma digoxin of 2.0 ng/ml, until they administered 60 μg/kg of digoxin iv. This raised plasma levels of digoxin to about 8 ng/ml and produced first-degree heart block. In their toxic group, with an average digoxin level of about 6 ng/ml, various forms of heart block occurred. These dogs were also given 60 μg/kg of digoxin iv before they were killed. There was about 75% reduction in myocardial Na\(^+\) + K\(^+\) ATPase activity when data for both groups were combined. We found 46% of the Na\(^+\) + K\(^+\) ATPase activity inhibited in the left ventricle of the heart, when plasma digoxin concentration averaged 3.4 ng/ml. Thus, the arrhythmogenic level of inhibition of myocardial Na\(^+\) + K\(^+\) ATPase activity appears to be between 46 and 75%, according to our results and the studies of Ku et al. (1977). Ku et al. (1977) also produced evidence that the uninhibited Na\(^+\) + K\(^+\) ATPase, or Na\(^+\) pump activity, remained unchanged during chronic digoxin treatment. This is in agreement with our observations that the uninhibited enzyme was not altered.

We found that a 26 to 33% chronic inhibition of renal Na\(^+\) + K\(^+\) ATPase caused no statistically significant changes in urinary output of electrolytes and water. This is consistent with the lack of saluretic response in acute experiments when the renal enzyme is inhibited less than 40% by ouabain (Nechay, 1977). Perhaps the presence of other mechanisms for conservation of electrolytes and water by the kidney (Nechay, 1977) may compensate for the inhibition of the Na\(^+\) + K\(^+\) ATPase.

The concentration of digoxin causing 50% inhibition of microsomal Na\(^+\) + K\(^+\) ATPase isolated

### Table 1 Effect of Chronic Digitalization on Renal Function in Different States of Water Balance

<table>
<thead>
<tr>
<th>Renal functions</th>
<th>Water diuresis</th>
<th>Hydrogena</th>
<th>Hydrogena + salt load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control(n = 5)</td>
<td>Digitalized(n = 5)</td>
<td>Control(n = 5)</td>
</tr>
<tr>
<td>Animal wt (kg)</td>
<td>18.5 ± 1.3</td>
<td>21.3 ± 1.5</td>
<td>20.8 ± 1.6</td>
</tr>
<tr>
<td>Animal surface (m(^2))</td>
<td>0.90 ± 0.05</td>
<td>1.00 ± 0.05</td>
<td>0.94 ± 0.05</td>
</tr>
<tr>
<td>Urine flow (ml/min per m(^2))</td>
<td>6.8 ± 0.4</td>
<td>6.1 ± 0.5</td>
<td>0.29 ± 0.02</td>
</tr>
<tr>
<td>GFR (ml/min per m(^2))</td>
<td>70 ± 1.5</td>
<td>78 ± 1.5</td>
<td>68 ± 1.2</td>
</tr>
<tr>
<td>Plasma osmolality (mOsm)</td>
<td>281 ± 1.5</td>
<td>276 ± 1.5</td>
<td>312 ± 1.5</td>
</tr>
<tr>
<td>Urinary osmolality (mOsm)</td>
<td>65 ± 1.5</td>
<td>70 ± 1.5</td>
<td>1924 ± 1.5</td>
</tr>
<tr>
<td>Uosm/Poxm</td>
<td>0.24 ± 0.05</td>
<td>0.26 ± 0.05</td>
<td>6.3 ± 0.2</td>
</tr>
<tr>
<td>Cosm (ml/min per m(^2))</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>14 ± 1.2</td>
</tr>
<tr>
<td>C(\text{Na}) (ml/min per 100 ml) of glomerular filtrate</td>
<td>7.8 ± 1.5</td>
<td>7.3 ± 1.5</td>
<td>-1.7 ± 1.8</td>
</tr>
<tr>
<td>Plasma Na(^+) (mM)</td>
<td>141 ± 1.4</td>
<td>137 ± 1.4</td>
<td>153 ± 1.5</td>
</tr>
<tr>
<td>Urinary Na(^+) (mM)</td>
<td>1 ± 0.2</td>
<td>1 ± 0.2</td>
<td>57 ± 1.2</td>
</tr>
<tr>
<td>% of filtered Na(^+) excreted</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.01</td>
<td>0.48 ± 0.02</td>
</tr>
<tr>
<td>Plasma K(^+) (mM)</td>
<td>4.1 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>Urinary K(^+) (mM)</td>
<td>5 ± 0.2</td>
<td>3 ± 0.2</td>
<td>145 ± 0.1</td>
</tr>
<tr>
<td>Plasma Cl((\text{mM}))</td>
<td>102 ± 1.5</td>
<td>104 ± 1.5</td>
<td>116 ± 1.5</td>
</tr>
<tr>
<td>Urinary Cl((\text{mM}))</td>
<td>3 ± 0.2</td>
<td>5 ± 0.2</td>
<td>92 ± 0.2</td>
</tr>
<tr>
<td>Plasma Ca (mM)</td>
<td>2.5 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Plasma P (mM)</td>
<td>1.4 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
</tbody>
</table>

For experimental protocol, see Methods. Since the data for digitalized and control dogs were not different, only the mean values are shown.

* Plasma samples obtained several minutes before the water load was administered had the following values: 300 mOsm, 147 mM Na\(^+\), 4.7 mM K\(^+\), 1.2 mM Ca\(^+\), 1.6 mM P.

† Exogenous creatinine clearance.

### Table 2 In Vitro Determinations on Kidneys and Heart Removed from Chronically Digitalized Dogs

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Control(n = 6)</th>
<th>Digitalized(n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney wt (g/m(^2))</td>
<td>92 ± 0.2</td>
<td>91 ± 0.2</td>
</tr>
<tr>
<td>GFR((\text{ml/min per g of kidney}))</td>
<td>0.74 ± 0.07</td>
<td>0.94 ± 0.15</td>
</tr>
<tr>
<td>Kidney tissue osmolality (mOsm)</td>
<td>392 ± 1.5</td>
<td>417 ± 1.5</td>
</tr>
<tr>
<td>Cortex</td>
<td>542 ± 1.5</td>
<td>563 ± 1.5</td>
</tr>
<tr>
<td>Outer medulla</td>
<td>1299 ± 1.5</td>
<td>1199 ± 1.5</td>
</tr>
<tr>
<td>Papilla</td>
<td>44 ± 8</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>Microsomal ouabain-sensitive ATPase (μmol P/hr per mg protein)</td>
<td>172 ± 12</td>
<td>128 ± 12</td>
</tr>
<tr>
<td>Kidney cortex</td>
<td>12 ± 3</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Kidney outer medulla</td>
<td>13 ± 3</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Kidney papilla</td>
<td>22 ± 27</td>
<td>27 ± 27</td>
</tr>
</tbody>
</table>

Kidneys were removed from water-deprived dogs after an iv overdose of pentobarbital. Three dogs in each group also received an iv salt load in the final part of experiment. For more details, see Methods. Only mean values are given when the data for digitalized and control groups are not different.

* Exogenous creatinine clearance.

† Mean values ± 1 S.D. with \(P < 0.05\).
from dog heart and kidney is $5 \times 10^{-7}$ M in the presence of 4 mM K$^+$ (data not shown). This is about 100 to 500 times more than the plasma concentrations of the drug found in this study (1.1 to 4.7 ng/ml = 1 to 6 $\times 10^{-8}$ M). Thus, an accumulation of digoxin by binding to the heart and kidney enzyme (Akera and Brody, 1978) is necessary to account for the observed enzyme inhibition in these organs.

The mechanism for the increased GFR by digoxin may be related to increased plasma concentration of norepinephrine. Norepinephrine causes a decrease in renal blood flow with an increase in filtration fraction; GFR may be increased, suggesting a preferential constriction of the postglomerular arterioles (Stein, 1976).

Although not statistically significant, the urineto-plasma osmolality ratio was 5-8% higher in digitalized dogs than in controls during hydropenia. If true, this might be due to reduced medullary and papillary blood flow caused by increased circulating norepinephrine. Reduced blood flow would increase papillary tissue hypertonicity by slowing the wash-out of osmotically active particles (Pitts, 1974).

Kopin et al. (1978) have noted how difficult it is to obtain blood samples from rats without stressing the animals so much that their catecholamine levels increase enormously. In contrast, the dogs used in our studies grew familiar with one of us (R.E.J.) and acted eager for human contact, even when it involved experimental manipulations. The dogs had low norepinephrine and epinephrine levels, well within the normal range for human subjects (Lake et al., 1976). Epinephrine levels did not differ between control and digitalized dogs, which suggests that both groups were under similar minimal stress.

The dogs receiving digitalis had much higher levels of norepinephrine. Digitalis could increase norepinephrine levels by two mechanisms, diminished clearance or enhanced release. The digitalis interacts with Na$^+$ + K$^+$ ATPase in the neuronal membrane and affects norepinephrine re-uptake parallel to its effects on ATPase activity. In very low doses, when ATPase activity is stimulated, norepinephrine uptake is stimulated (Sharma et al., 1980). Higher doses of digitalis, associated with therapeutic (Sharma et al., 1980) or toxic (Helke, 1978) effects, inhibit Na$^+$ + K$^+$ ATPase activity and norepinephrine uptake. Since Na$^+$ + K$^+$ ATPase activity was inhibited in cardiac and renal tissue from these dogs, it seems likely that norepinephrine uptake was similarly inhibited.

Digitalis also enhances norepinephrine release. Gillis et al. (1969, 1972) have shown, in nerve recordings, that digitalis can influence preganglionic cardiac sympathetic nerve activity. Toxic doses increased sympathetic nerve activity markedly, and this increase was associated with ventricular arrhythmias. Spinal cord section prevented the sympathetic activity and arrhythmias, thus indicating a central origin for the increase in sympathetic activity (Gillis et al., 1972; Levitt, 1973).

The interactions of cardiac glycosides with norepinephrine, in the heart and in blood vessels, assumes new importance since digitalis increases norepinephrine levels. Both agents have positive inotropic effects on the myocardium. Norepinephrine liberation, however, is not a requirement for the inotropic effect of digitalis (Smith and Haber, 1973). Digitalis can increase peripheral resistance (Smith and Haber, 1973) by causing release of norepinephrine (Nakajima, 1977). Norepinephrine and high doses of digitalis cause vasoconstriction (Flaim, 1979). The similar actions of digitalis and of norepinephrine on blood vessels are more than additive. Low concentrations of digitalis, that do not directly affect smooth muscle, potentiate the effects of norepinephrine on vascular smooth muscle (Flaim, 1979) and markedly increase the maximal response to norepinephrine in arteries and veins (Mikkelsen, 1979; Mikkelsen et al., 1979). This combined effect of increased norepinephrine levels, and enhanced response to norepinephrine, is probably clinically important, since digitalis elevates total systemic arteriolar resistance in conscious normal subjects (Smith and Haber, 1973).

Increased norepinephrine levels may be important in the genesis of digitalis-induced cardiac arrhythmias. Exogenous infusions of norepinephrine lower the dose of digitalis necessary to produce cardiac arrhythmias (Morrow, 1967). Reduction in sympathetic outflow by spinal cord section prevents digitalis induced tachyarrhythmias (Gillis et al., 1972). Propranolol is clinically useful in the treatment of digitalis-induced ventricular arrhythmias. Both digitalis and norepinephrine can cause ventricular arrhythmias, and each appears to enhance the arrhythmogenic properties of the other.

Patients with congestive heart failure have elevated norepinephrine levels (Thomas and Marks, 1978). Some of that increase may be due to digitalis and to diuretic therapy (Lake et al., 1979; Ziegler, 1980). However, successful therapy of congestive heart failure with digitalis may diminish circulatory distress, and thereby decrease sympathetic tone (Smith and Haber, 1973). Thus, digitalis treatment can decrease congestive heart failure and relieve excess sympathetic tone and the propensity for arrhythmias, or, if used without benefiting a patient's congestive failure, can enhance sympathetic tone and cause cardiac arrhythmias. The increase in norepinephrine levels that can accompany digitalis administration is important to consider when using the drug because both agents can increase vascular tone, cause arrhythmias, and potentiate the arrhythmogenic properties of the other.

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