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Effect of Long-Term Digoxin Therapy on Autonomic Function in Patients With Chronic Heart Failure

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Objectives. **This study was conducted to determine the effect of long-term digoxin therapy on autonomic function in patients with mild to moderate chronic heart failure.**

Background. **Chronic heart failure is characterized by increased sympathetic activity and decreased parasympathetic activity. Intravenous digitalis has been found to reduce sympathetic activity immediately in these patients, but whether short-term neurohormonal effects are sustained during long-term oral therapy has not been assessed.**

Methods. **We determined sympathetic activity in 26 patients with heart failure by measuring plasma norepinephrine levels and parasympathetic activity from variables of heart period variability derived from 24-h ambulatory electrocardiographic Holter recordings obtained before and after 4 to 8 weeks of digoxin therapy.**

Results. **After digoxin therapy, plasma norepinephrine decreased significantly from a mean ± SEM of 552 ± 80 to 390 ± 37 ng/ml. In addition, the RR interval increased significantly from 719 ± 19 to 771 ± 20 ms. High frequency power increased from 84 ± 24 to 212 ± 72 ms^2, and the root mean square of successive differences in RR interval increased from 20.3 ± 1.8 to 27.0 ± 3.4 ms, indicating a substantial increase in parasympathetic activity. Low frequency power, an index of baroreflex activity, was also significantly increased (239 ± 80 to 483 ± 144 ms^2) by digoxin therapy.**

Conclusions. **These results indicate 1) that long-term therapy with digoxin acts to ameliorate the autonomic dysfunction of patients with heart failure, and 2) that the short-term neurohormonal effects of digoxin are sustained during prolonged treatment with the drug.**

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Digoxin is widely used in the treatment of chronic heart failure. The benefit of digoxin in this condition has been supported by the results of several double-blind, placebo-controlled studies that have demonstrated salutary clinical effects of this drug in patients with chronic heart failure and normal sinus rhythm. These effects include improvement in exercise tolerance and functional capacity and a decreased need for hospital admission for worsening heart failure (1–4).

The clinical benefits observed with digoxin in patients with heart failure have traditionally been attributed to the hemodynamic improvements produced by this agent: that is, increases in cardiac output and left ventricular ejection fraction together with decreases in cardiac filling pressures and volumes (2,3,5). However, it is not clear that the clinical benefits of digoxin are related to its hemodynamic actions, because therapy with other positive inotropic agents (such as beta-adrenergic agonists and phosphodiesterase inhibitors) results in similar (if not greater) hemodynamic improvement yet has failed to produce favorable long-term outcomes in patients with heart failure (6–9). Therefore, the long-term benefits of digoxin in this condition may not be due solely to the drug's hemodynamic actions.

Considerable attention has recently been focused on additional pharmacologic actions of digoxin that are independent of its positive inotropic properties; for example, in contrast to other inotropic agents, digoxin reduces sympathetic activity in patients with heart failure. Single doses of digitalis inhibit the outflow of sympathetic impulses from the central nervous system, as determined from microneurographic recordings (10) and decreased levels of plasma norepinephrine (11). However, the long-term effects of digoxin on sympathetic activation in patients with heart failure have yet to be evaluated. As progression of disease and mortality in chronic heart failure may be directly related to the degree of sympathetic activation associated with the condition (12), long-term therapy with drugs that inhibit sympathetic activity may favorably influence clinical outcome.

In addition to sympathetic nervous system activation in chronic heart failure, there appears to be marked suppression of the activity of the parasympathetic nervous system (13). Both the increase in heart rate that occurs after the administration of atropine and the baroreceptor-mediated slowing of heart rate that occurs after the administration of phenylephrine are markedly less in patients with heart failure, than in

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normal control subjects (13). In normal subjects and in animals, digoxin enhances baroreceptor-mediated increases in vagal tone (14), sensitizes muscarinic receptors on the vagus (15) and enhances efferent acetylcholine-mediated vagal neural transmission (16). However, the effects of long-term digoxin therapy on parasympathetic activity have not been evaluated in patients with heart failure.

The aim of the present study, therefore, was to evaluate the effect of *long-term* digoxin therapy on the activity of both the sympathetic and the parasympathetic nervous system in patients with chronic heart failure to assess whether the short-term autonomic effects of the drug are sustained with long-term therapy.

Methods

Study patients. We evaluated 26 patients (13 men) referred to the Heart Failure Center at Columbia-Presbyterian Medical Center for evaluation of chronic heart failure. Their mean age ± SEM was 55.5 ± 2.1 years. The cause of heart failure was idiopathic dilated cardiomyopathy in 16 patients, ischemic heart disease in 8, peripartum cardiomyopathy in 1 patient and hypertensive heart disease in 1 patient. Six patients were classified in New York Heart Association functional class I (asymptomatic) at study entry. Of these six patients, five had previously had heart failure but symptoms had disappeared with therapy. Twelve patients had functional class II symptoms and eight had class III symptoms. Mean left ventricular ejection fraction, as determined by radionuclide ventriculography, was 21.5 ± 1.6%. All patients were in clinically stable condition, had normal sinus rhythm and had no overt signs of fluid retention.

Twenty-one patients were receiving diuretic agents and angiotensin-converting enzyme inhibitors, four were receiving diuretic agents alone and one patient was not receiving background therapy. Patients not receiving angiotensin-converting enzyme inhibitors were unable to tolerate these agents (usually because of cough). Doses of diuretic therapy remained constant for ≥1 week before study entry and doses of angiotensin-converting enzyme inhibitors were stable for ≥2 weeks before study entry. No patient had previously received digoxin therapy, and none was currently receiving beta-blockers, calcium channel blockers, antiarrhythmic agents, bronchodilators or antihypertensive medications (except diuretic drugs).

No patient had a recent (<3 months) history of myocardial infarction, episode of unstable angina or stroke and none had heart failure due to hypertrophic or amyloid cardiomyopathy. All patients had a serum creatinine level <3.0 mg/dl and none had a concomitant condition that might produce autonomic dysfunction (e.g., diabetes mellitus).

Study design. The protocol was approved by the Institutional Review Board of the Columbia University College of Physicians & Surgeons and patients provided written, informed consent. At baseline, blood was collected for measurement of plasma norepinephrine, and 24-h Holter ambulatory electrocardiographic (ECG) recordings were performed to allow analysis of heart period variability. After completion of the Holter recording, digoxin therapy was initiated at a dose determined by the patient's age and renal function. These doses were 0.25 mg/day (in patients <70 years old with a serum creatine level <1.5 mg/dl), 0.125 mg/day (in patients <70 years old with a serum creatinine level >1.5 mg/dl or patients >70 years old with a serum creatinine level <1.5 mg/dl) and 0.125 mg every other day (in patients >70 years old with a serum creatinine level >1.5 mg/dl).

Digoxin therapy was continued for 4 to 8 weeks; concomitant therapy was maintained in unchanged doses.

At the end of the study period, as during the first visit, blood was collected for measurement of plasma levels of norepinephrine and serum digoxin, and a second 24-h Holter recording was obtained to assess measures of heart period variability.

Measurement of plasma norepinephrine. After placement of an intravenous cannula, patients rested supine for 30 min in a quiet, darkened room while blood was collected into prechilled lithium-heparin tubes for determination of plasma norepinephrine levels. All tubes were placed immediately on ice, centrifuged at 2,500 rpm at 4°C for 10 min, then immediately stored frozen at −70°C for later analysis. Samples were analyzed within 48 h of collection. Plasma norepinephrine was measured in a reference laboratory by high performance liquid chromatography with electrochemical detection (17).

Holter ECG recordings. Dual-lead ECG recordings (leads CM_2 and CM_5) were made on Marquette 8500 Holter recorders. These recorders contain a digital clock to provide a time signal that is continuously recorded on the tape. The Holter tapes were digitized on a Marquette series 8000 scanner. The signal was sampled at 128 Hz. Sampling was triggered by the timing track on the tape to correct for flutter and wow of the recording or playback tape transport. QRS complex recognition and arrhythmia detection were done automatically by template matching. This system generates a beat by beat annotation of the ECG with a consistent and accurate time stamp for each QRS complex and classifies each complex as normal sinus, atrial or ventricular premature complex or noise. The decisions made automatically by the computer were reviewed and corrected by an experienced technician and then by a cardiologist. The digitized ECG, QRS trigger list and report data were then transferred over a high speed direct memory access link to a Sun Microsystems 4/75 computer where additional editing on the sorted intervals and further analysis, including time and frequency domain analysis of heart period variability, were performed. Each completed analysis, comprising 50 megabytes of digitized ECG and a QRS trigger list, was stored on laser disk. The 24-h heart period power spectrum was computed by using a fast Fourier transform on data for the entire 24-h period (18,19). Low frequency power (0.04 to 0.15 Hz) reflects modulation of both sympathetic and parasympathetic tone by baroreflex activity, whereas high frequency power (0.15 to 0.40 Hz) reflects modulation solely of parasympathetic tone by breathing. Both low and high frequency power were computed by integrating over their frequency intervals. In addition, the ratio of low to high frequency

Table 1. Heart Period Variability Before and After 4 to 8 Weeks of Digoxin Therapy

Heart Period Variability Measures	Before Digoxin	After Digoxin	p Value*
Average normal RR interval for 24 h (ms)	719 ± 19	771 ± 20	0.0014
24-h standard deviation of normal RR intervals (ms)	90 ± 9	115 ± 10	0.0147
Root mean square successive difference	20.3 ± 1.8	27.0 ± 3.4	0.0517
Percent of adjacent normal RR intervals >50 ms	4.9 ± 1.0	8.0 ± 1.8	0.0041
Total power (<0.40 Hz) (ms^2)	9,896 ± 2,193	16,698 ± 3,371	
Natural logarithm total power	8.7 ± 0.2	9.4 ± 0.2	0.0006
Low frequency power (0.04–0.15 Hz) (ms^2)	239 ± 80	483 ± 144	
Natural logarithm low frequency power	4.5 ± 0.3	5.4 ± 0.3	0.0004
High frequency power (0.15–0.40 Hz) (ms^2)	84.2 ± 24.1	212 ± 72	
Natural logarithm high frequency power	3.7 ± 0.3	4.5 ± 0.3	0.0057
Ratio of low to high frequency power	2.4 ± 0.2	3.1 ± 0.5	0.1021

*p values compare values before and after digoxin, as analyzed by paired *t* test. Because frequency domain measures of heart period variability were positively skewed, these data were natural logarithm transformed before parametric analysis. Data presented are mean value ± SEM.

power, which has been proposed as a marker of sympathovagal balance (20), was calculated. Time domain measures of parasympathetic activity—specifically the root mean square of successive differences and the percent of heart period differences >50 ms—were also measured. These time domain measures are highly correlated with one another as well as with high frequency power (21) and can therefore be used interchangeably as measures of parasympathetic activity. In addition, the 24-h standard deviation of normal RR intervals, a marker of overall heart period variability, was measured. Although not a pure measure of parasympathetic activity, it has been found (22) to be predictive of mortality in patients after myocardial infarction.

Statistical analysis. The effect of digoxin on sympathetic and parasympathetic activity was assessed by comparing posttreatment with pretreatment values for plasma norepinephrine and Holter-derived measures of heart period variability.

Previous studies have demonstrated that the distributions of the frequency domain measures of heart period variability are positively skewed (23). Because of this skewness, the frequency domain data in the present study were transformed to their natural logarithms to achieve a normal distribution; this transformation permitted parametric statistical analysis.

Differences in values at baseline and during digoxin therapy were tested for statistical significance by using the paired *t* test. In addition, possible associations between changes in plasma norepinephrine and Holter measures after digoxin therapy were evaluated for statistical significance by linear regression analysis. All results are expressed as mean value ± SEM.

Results

Digoxin was administered to all 26 patients for a total of 4 to 8 weeks (mean 4.6); the mean serum digoxin levels was 1.1 ± 0.1 ng/ml at the end of the study period.

Plasma norepinephrine levels decreased significantly after digoxin therapy by 42% from 552 ± 80 to 321 ± 37 ng/ml ($p < 0.05$). The decrease in plasma norepinephrine was greatest in those patients who had the highest plasma norepinephrine levels before treatment ($r = 0.70$ for the correlation of pretreatment plasma norepinephrine vs. change in plasma norepinephrine, $p < 0.001$).

There was a modest, statistically significant increase in 24-h average RR interval during digoxin therapy from 719 ± 19 ms to 771 ± 20 ms, corresponding to a slowing of heart rate from 83 to 79 beats/min with the drug (Table 1). The high frequency (0.15 to 0.40 Hz) component of the 24-h heart period variability power spectrum increased significantly during therapy with digoxin ($p < 0.01$), indicating a substantial increase in cardiac parasympathetic activity (Table 1, Fig. 1). In addition, the low frequency power spectrum also increased significantly during digoxin therapy ($p < 0.001$), despite the decrease in plasma norepinephrine (Table 1, Fig. 1). Furthermore, the time domain measures of heart period variability that reflect cardiac parasympathetic activity (i.e., root mean square of successive RR interval differences and percent of heart period differences >50 ms) also increased during digoxin therapy in these patients (by 33% and 63% respectively (Table 1, Fig. 2). Despite the substantial increase in high frequency power during digoxin therapy, there was no significant change in the ratio of low to high frequency power ($p = 0.10$), reflecting concomitant increases in low frequency power.

Serum digoxin level was the only variable measured that was correlated with the parasympathetic response to digoxin therapy. Serum digoxin levels correlated directly with changes in parasympathetic activity as determined from measures of heart period variability; that is, patients with the highest serum digoxin levels had the largest increases in high frequency power ($r = 0.59$, $p < 0.05$). In contrast, serum digoxin levels were not correlated with changes in plasma norepinephrine level during digoxin therapy. In addition, there was no correlation between age, functional class or left ventricular ejection fraction assessed at baseline and autonomic responses to therapy. Changes in sympathetic activity as determined by

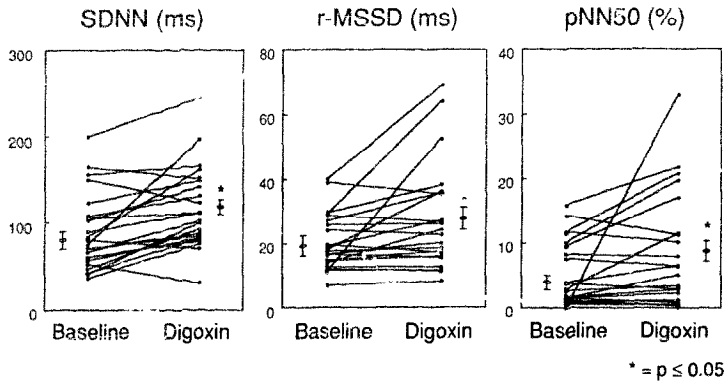

Figure 1. Effect of long-term digoxin therapy on time domain measures of 24-h heart period variability in patients with chronic heart failure. With digoxin therapy, values for standard deviation of successive RR intervals (SDNN), root mean square of successive RR interval differences (r-MSSD) and percent adjacent RR intervals >50 ms (pNN50) increased ($p \leq 0.05$) with respect to baseline values.

changes in plasma norepinephrine levels during therapy with digoxin were not correlated with changes in parasympathetic activity as determined from heart period variability measures.

Discussion

The present study demonstrates that long-term therapy with digoxin results in a significant increase in parasympathetic activity and a decrease in sympathetic activity in patients with chronic heart failure.

Several well validated measures of beat to beat variations in normal RR intervals are available to assess parasympathetic nervous system activity in humans (24–26). With these techniques, parasympathetic withdrawal has been found (13,27) to be a prominent component of the autonomic dysfunction that accompanies chronic heart failure, thereby confirming similar conclusions obtained by established techniques (13). However, the role of digoxin in modulating parasympathetic activity has not been extensively studied in patients with heart failure. The present findings demonstrate significant and persistent increases in parasympathetic activity during long-term digoxin therapy as indicated by the substantial increases in high frequency power, root mean square of successive RR interval differences and percent of heart period differences >50 ms. These results are consistent with observations (28) of substantial increases in parasympathetic activity with long-term administration of this drug to normal subjects.

Sympathetic activity, as determined from measurement of plasma norepinephrine levels, was significantly reduced by long-term digoxin therapy in these patients. Previous studies of short-term administration of digoxin in patients with chronic heart failure have demonstrated both acute peripheral vasodilation (29) and reductions in sympathetic nerve traffic (10) and plasma norepinephrine levels (11). The present data confirm that these effects are sustained during long-term therapy with digoxin, and are consistent with a recent report (30).

Measurement of heart period variability in our study demonstrated an increase in low frequency power with long-term digoxin therapy. Low frequency RR interval rhythms are jointly mediated by fluctuations of vagal and sympathetic nerve activity (24,31) and are attributed to the modulation of heart rate by baroreflex mechanisms (32). Because plasma norepinephrine levels decreased with digoxin therapy in the present study, the increase in absolute low frequency power noted in our study is unlikely to be accounted for by increases in sympathetic activity. Moreover, because low frequency power has been demonstrated (32) to be correlated with the degree of baroreflex-mediated vagal stimulation, our finding of increased low frequency power may reflect baroreflex sensitiza-

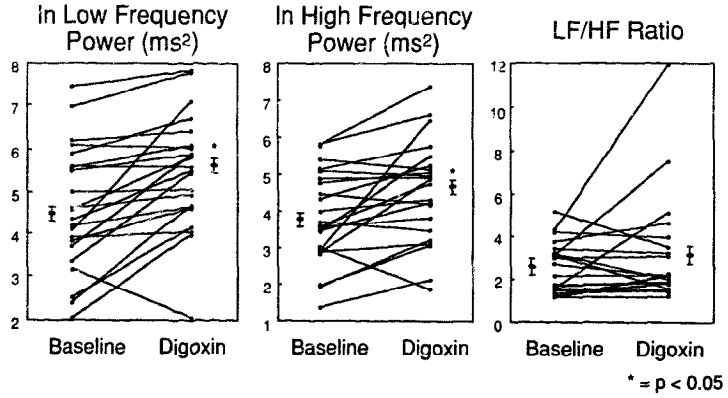

Figure 2. Effect of long-term digoxin therapy on frequency domain measures of 24-h heart period variability in patients with chronic heart failure. With digoxin therapy, natural logarithm low and high frequency power increased significantly ($p \leq 0.05$) with respect to baseline values. The low frequency/high frequency (LF/HF) ratio was unaltered by digoxin therapy.

tion, thereby supporting previous observations that digoxin sensitizes cardiac and aortic baroreceptors (15,33).

The changes we observed in autonomic function with long-term digoxin therapy are particularly noteworthy given the characteristics of our study group. Our patients had relatively mild heart failure as assessed by New York Heart Association functional class. Because severity of disease is closely correlated with degree of sympathetic activation, plasma norepinephrine levels would not be expected to be greatly elevated at baseline or to be significantly reduced by therapy in such patients. Nevertheless, long-term therapy with digoxin in this group did result in significant reductions in sympathetic activity as measured by plasma norepinephrine levels. Patients with the highest baseline norepinephrine levels had the greatest decreases in plasma norepinephrine. This finding could be accounted for, in part, by regression toward the mean; however it is also consistent with the suggestion that the degree of sympathoinhibition with digoxin is related to the degree of neurohormonal activation (34). Furthermore, most patients were receiving angiotensin-converting-enzyme inhibitors, drugs that themselves decrease sympathetic (35) and increase parasympathetic (36) activity in patients with heart failure. Despite the presence of these agents as background therapy, long-term digoxin therapy further decreased sympathetic and increased parasympathetic nervous system activity. This finding may be of some importance as angiotensin-converting enzyme inhibitors are now standard therapy for patients with chronic heart failure.

Limitations of the study. There was no control group in this study. However, the variables measured—plasma norepinephrine and Holter-derived measures of heart period variability—are not affected by placebo therapy (26,30,37,38). Plasma norepinephrine levels were measured under strictly controlled conditions in the present study and these levels have been found to be highly reproducible over time (39). The day to day stability of Holter-derived measures of heart period variability is also well established, especially in patients with left ventricular dysfunction (26). It is therefore unlikely that changes observed in the present study were due to effects other than therapy with digoxin.

Clinical implications. The increase in parasympathetic activity demonstrated with digoxin therapy in this study may have favorable prognostic implications in heart failure. In patients with left ventricular dysfunction after myocardial infarction, low parasympathetic nervous system activity (as assessed by heart period variability measures derived from 24-h Holter monitoring) is associated with increased mortality as compared with that of patients with high levels of parasympathetic activity (40). In animal models of sudden cardiac death (41), high levels of parasympathetic activity are protective against sudden arrhythmic death. Therefore, one can speculate that drugs that increase parasympathetic activity will exert a favorable influence on clinical outcome.

Reductions in sympathetic activity may also be of favorable prognostic significance. Sympathetic nervous system activity has been found to be directly related to patient prognosis in patients with heart failure (12). Those with the greatest degree of sympathetic activation, as determined by plasma norepinephrine levels, have been found to have the highest mortality rate. This relation may not necessarily be causal; however, excess catecholamine secretion does have profound direct toxic effects on the myocardium and may potentiate arrhythmias (42). A National Institutes of Health cooperative study and Veterans Affairs Administration study (Digoxin Intervention Group [DIG] Study) is currently investigating these theoretically beneficial effects of digoxin on mortality in patients with heart failure.

Conclusions. The present study demonstrates that digoxin causes significant reductions in sympathetic activity together with large increases in parasympathetic modulation of RR intervals in patients with mild to moderate congestive heart failure. The effects of digoxin therapy on autonomic function persisted for the 4 to 8 weeks of our study; thus, the beneficial neurohormonal effects of digoxin previously described during short-term therapy are sustained during long-term treatment with the drug.

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