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Does Digoxin Provide Additional Hemodynamic and Autonomic Benefit at Higher Doses in Patients With Mild to Moderate Heart Failure and Normal Sinus Rhythm?

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Objectives. **This study sought to examine the hemodynamic and autonomic dose response to digoxin.**

Background. **Previous studies have demonstrated an increase in contractility and heart rate variability with digitalis preparations. However, little is known about the dose-response to digoxin, which has a narrow therapeutic window.**

Methods. **Nineteen patients with moderate heart failure and a left ventricular ejection fraction <0.45 were studied hemodynamically using echocardiography and blood pressure at baseline and after 2 weeks of low dose (0.125 mg daily) and 2 weeks of moderate dose digoxin (0.25 mg daily). Loading conditions were altered with nitroprusside at each study. Autonomic function was studied by assessing heart rate variability on 24-h Holter monitoring and plasma norepinephrine levels during supine rest.**

Results. **Low dose digoxin provided a significant increase in ventricular performance, but no further increase was seen with the moderate dose. Low dose digoxin reduced heart rate and increased heart rate variability. Moderate dose digoxin produced no additional increase in heart rate variability or reduction in sympathetic activity, as manifested by heart rate, plasma norepinephrine or low frequency/high frequency power ratio. In addition, we did not find that either low or moderate dose digoxin increased parasympathetic activity.**

Conclusions. **We conclude that moderate dose digoxin provides no additional hemodynamic or autonomic benefit for patients with mild to moderate heart failure over low dose digoxin. Because higher doses of digoxin may predispose to arrhythmogenesis, lower dose digoxin should be considered in patients with mild to moderate heart failure.**

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In the 200 years since Sir William Withering popularized the use of digitalis preparations (1), we have only relatively recently elucidated many of its beneficial effects in patients with heart failure. Both hemodynamic (2–4) and functional (5–8) improvement have been achieved with digitalis, due in part to improved contractility (2) and relaxation (2) in the heart with systolic dysfunction. In addition, digoxin may reduce systemic sympathetic activity by a direct effect on baroreceptors (9–11). Despite these beneficial effects, digitalis has a neutral effect on mortality as demonstrated by the recently completed Digitalis Investigation Group (DIG) trial (12). However, the DIG trial suggested a trend toward a beneficial effect of digitalis on pump failure death but an adverse effect (although not statistically significant) on death due to other cardiovascular causes (including sudden death). These findings may be consistent with a narrow therapeutic range for digoxin, especially in patients who have reduced renal perfusion due to poor stroke volume (13–15). Such patients may easily become toxic from digoxin and suffer arrhythmias and sudden death.

Little data exist on the dose response of digitalis preparations. Several previous studies have suggested improved left ventricular function with higher doses of digitalis (16–24), and one study suggests no additional benefit of higher dose digoxin (25). However, these studies only examined systolic time intervals or ejection fraction, which are load- and heart-rate dependent indexes of left ventricular performance. Thus, alterations in load, such as a reduction in afterload, may account for such findings. Although digoxin reduces sympathetic activation (9–11,26) and increases parasympathetic activity (26), little data exist on the autonomic dose-response of digoxin. Because digoxin may have arrhythmic effects at higher doses, it is important to understand whether higher doses of digoxin result in hemodynamic or autonomic benefit. For this reason, we examined the hemodynamic and autonomic dose response to digoxin. Our hypothesis was that digoxin would

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Abbreviations and Acronyms

HRV = heart rate variability
NN>50 = number of successive beats differing by >50 ms
RMS-SD = root mean square of RR interval
SDANN = standard deviation of average normal RR intervals for successive 5-min segments
SDNN = standard deviation of RR interval

provide a dose-dependent increase in left ventricular performance, a reduction in sympathetic activity and an increase in parasympathetic activity.

Methods

Patient selection. Nineteen men (mean [±SD] age 64 ± 12 years), all with normal sinus rhythm, were enrolled in the study. On the basis of clinical findings, 13 patients were in New York Heart Association functional class II, and 6 were in functional class III. The etiology of heart failure was coronary artery disease in 11 patients, presumed alcoholic cardiomyopathy in 4, hypertension in 1, valvular heart disease in 1 and idiopathic in 2. The four patients with presumed alcoholic cardiomyopathy were no longer actively drinking. Mean left ventricular ejection fraction as measured by multiple gated acquisition before study entry was 0.28 ± 0.09 (range 0.14 to 0.43). Fifteen patients completed both the echocardiographic and Holter portions of the trial. Echocardiography was technically difficult in three patients, and only Holter data were collected. One patient had excessive ventricular ectopic beats, and only echocardiographic data were collected.

All but one patient were receiving a constant dose of angiotensin-converting enzyme inhibitor throughout the study (captopril in nine, ramapril in four, benazepril in three, enalapril in two). The one patient not receiving an angiotensin-converting enzyme inhibitor was taking hydralazine and isosorbide dinitrate. Seventeen patients received diuretic drugs throughout the study, and the dose of these drugs did not change. No patient had received digoxin for at least 3 months before study entry. Five patients were receiving isosorbide dinitrate, two were receiving amlodipine, one was receiving diltiazem, two were receiving metoprolol, and one was receiving amiodarone. No patient was taking a sympathomimetic agent, such as a bronchodilator. Apart from digoxin, no medication changed during the study period in any patient. No patient had a myocardial infarction within the previous 3 months. All patients had a creatinine level <2.0 mg. One patient had diabetes mellitus and was excluded from the Holter analysis to avoid any possible confounding problem with diabetic autonomic dysfunction.

Study protocol. The study was approved by the Institutional Review Board for Ethical Treatment of Patients at the Dallas Veterans Affairs Medical Center, Dallas, Texas. Furthermore, all patients gave written informed consent before the study.

At baseline, patients had serum digoxin and plasma norepinephrine levels measured after 30 min of supine rest. During the same visit, the baseline echocardiographic assessment of the left ventricular stress-shortening relation was performed (27). Briefly, echocardiographic images were collected in the standardized short- and long-axis views before and after small doses of intravenous nitroprusside were infused to lower systolic blood pressure. Left ventricular dimensions, fractional shortening and wall stress were measured by echocardiography at three levels of afterload. Twenty-four hour Holter monitoring was then performed for measurement of heart rate variability (HRV). The patients were then treated with 0.125 mg/day of oral digoxin for 2 weeks.

After 2 weeks of 0.125 mg of digoxin (and then 2 weeks of 0.25 mg), the patients returned for repeat measurement of serum digoxin and plasma norepinephrine levels. Repeat measurements of wall stress and fractional shortening were obtained in a similar manner, as previously described. In addition, 24-h Holter monitoring was again performed to measure HRV variables. Because digoxin has a narrow therapeutic window, doses higher than 0.25 mg/day were not used so as to maintain patient safety.

Echocardiographic data. All subjects underwent two-dimensional echocardiography in the left lateral decubitus position using a Vingmed CFM750 instrument with a 3.25-MHz transducer (Vingmed Sound, Horten, Norway). Parasternal long-axis and midventricular parasternal short-axis images were acquired and recorded on 0.5-in. VHS videotape for subsequent analysis. Repeat images were obtained before each incremental increase in the infusion rate of nitroprusside and were also recorded on 0.5-in. VHS videotape. Patients underwent continuous electrocardiographic monitoring, and blood pressure was recorded at 1-min intervals using an automated cuff.

The left ventricular stress-shortening relation was measured using methodology previously published from our laboratory (28). All echocardiographic images were interpreted by an observer (P.A.G.) who had no knowledge of the patient's digoxin dose. Fractional shortening (FS) was measured in the parasternal long-axis view using the following formula:

$$FS\% = LVID_d - LVID_s/LVID_d \times 100,$$

where $LVID_d$ = left ventricular internal diameter at end-diastole; and $LVID_s$ = left ventricular internal diameter at end-contraction. Fractional shortening was normalized for heart rate by dividing fractional shortening by the square root of the RR interval to yield the heart rate-corrected fractional shortening. This was done to help eliminate the confounding factor of heart rate effects.

Meridional wall stress (MWS) was calculated using the following formula:

$$MWS = P(LVID_s)/4h\ (1 + h/LVID_s),$$

where P = systolic (cuff) blood pressure; $LVID_s$ = left ventricular end-systolic dimension; and h = posterior wall thickness (29).

Table 1. Hemodynamic/Echocardiographic Dose-Response of Digoxin

	Baseline (mean ± SD)	Low Dose Digoxin (mean ± SD)	Moderate Dose Digoxin (mean ± SD)	p Value (ANOVA)
Digoxin level (ng/ml)	0.0 ± 0.0	0.8 ± 0.5*	1.5 ± 0.7*†	<0.0001
HR (beats/min)	81 ± 13	70 ± 18	72 ± 15	0.064
Systolic blood pressure (mm Hg)	126 ± 16	137 ± 22	134 ± 22	0.088
LV end-diastolic dimension (cm)	5.6 ± 0.8	5.6 ± 0.6	5.3 ± 0.8	0.111
LV end-systolic dimension (cm)	5.1 ± 0.8	4.9 ± 0.7	4.7 ± 0.9*	0.049
Fractional shortening (%)	9.1 ± 5.3	12.9 ± 6.9	12.5 ± 6.6	0.123
Fractional shortening (HR corrected)	0.33 ± 0.18	0.43 ± 0.22	0.42 ± 0.22	0.22

*$p < 0.05$ versus baseline by Scheffé F test. †$p < 0.05$ versus low dose digoxin by Scheffé F test. ANOVA = analysis of variance; HR = heart rate; LV = left ventricular.

Measurement of HRV. All Holter recordings were made on a 8500 model Marquette recorder and were analyzed in blinded manner by an experienced Holter technician using a DelMar 363 scanner. DelMar installed a selectable acquisition formation for Marquette recorders on the Delmar scanner to ensure accuracy of analysis of the Marquette recordings on the Delmar scanner. The heart period variability spectrum was computed using fast Fourier transformation, as described fully elsewhere (30,31).

Determinations of frequency domain included measurements of low and high frequency power. Low frequency power (0.05 to 0.15 Hz) has been shown to be a marker of sympathetic and parasympathetic HRV; furthermore, high frequency power (0.15 to 0.35 Hz) was used as a marker of parasympathetic modulation of heart rate (32–35).

Time domain variables obtained included the standard deviation of the RR interval (SDNN), root mean square of the RR interval (RMS-SD) and the number of successive beats differing by >50 ms (NN>50). SDNN has been shown to be closely correlated with total power of HRV and has been shown to be a predictor of mortality after myocardial infarction (36,37). In addition, both RMS-SD and NN>50 have been shown (38) to be highly correlated with high frequency power and can be used as a marker of parasympathetic activity (38).

Measurement of plasma norepinephrine. After a 21-gauge intravenous catheter was inserted, patients were placed in the supine position for 30 min. Blood was then collected in a heparinized tube and placed immediately on ice. Within 15 min, the blood was centrifuged at 4°C for 15 min at 1,000 ± 100*g*. The plasma was then frozen at −70°C until it could be sent for analysis. Analysis was performed by Smith, Kline, Bio-Science Laboratories using high pressure liquid chromatography with electrochemical detection.

Statistical analysis. Repeated measures analysis of variance was used to determine the effects of increasing doses of digoxin on HRV and hemodynamic variables. Significant differences among the digoxin dose levels were tested using Scheffé multiple comparisons. The natural logarithm of high and low frequency power was used in the statistical analysis because these variables were positively skewed. A p value <0.05 was considered statistically significant, and descriptive statistics are provided as mean value ± SD.

A two-factor (digoxin dose and nitroprusside dose) repeated measures analysis of covariance was used to examine the effect of load as a covariate and digoxin dose on fractional shortening (using a stress-shortening relation). This analysis was performed using both fractional shortening with and without the correction for heart rate as dependent variables to eliminate the confounding factor of heart rate effects. Individual differences in stress shortening between baseline and low dose and moderate dose digoxin were examined by the Scheffé F test. Least squares mean estimates ±SD of fractional shortening for each digoxin dose level are presented and are compared using Bonferroni-adjusted *t* tests, that is, using $p < 0.017$ (0.05 divided by 3, for the number of comparisons made) to indicate statistical significance. These least squares mean values provide estimates of mean fractional shortening for each digoxin dose level at an average level of load; the digoxin dose level comparisons are statistically adjusted for the effect of load.

Results

Hemodynamic dose-response. Fifteen of the 19 patients studied had complete or technically satisfactory echocardiographic studies. The hemodynamic and echocardiographic dose-responses to digoxin in these patients are shown in Table 1. Serum digoxin levels increased from undetectable at baseline to 0.8 ± 0.5 at low dose digoxin ($p < 0.0001$ vs. baseline) to 1.5 ± 0.7 at moderate dose digoxin ($p < 0.0001$ vs. baseline; $p = 0.0001$ vs. low dose). At echocardiographic study, heart rate had decreased nonsignificantly, from 81 ± 13 to 70 ± 18 beats/min at low dose digoxin ($p = 0.064$), with no further decrease after moderate dose digoxin. Systolic blood pressure by cuff increased nonsignificantly from 126 ± 16 to 137 ± 22 mm Hg after low dose digoxin ($p = 0.088$), with no further increase after moderate dose digoxin. There were no significant changes in rest left ventricular end-diastolic dimensions with either low or moderate dose digoxin. However, end-systolic dimensions (uncorrected for afterload) decreased from 5.1 ± 0.8 to 4.9 ± 0.7 cm at low dose digoxin to 4.7 ± 0.9 cm

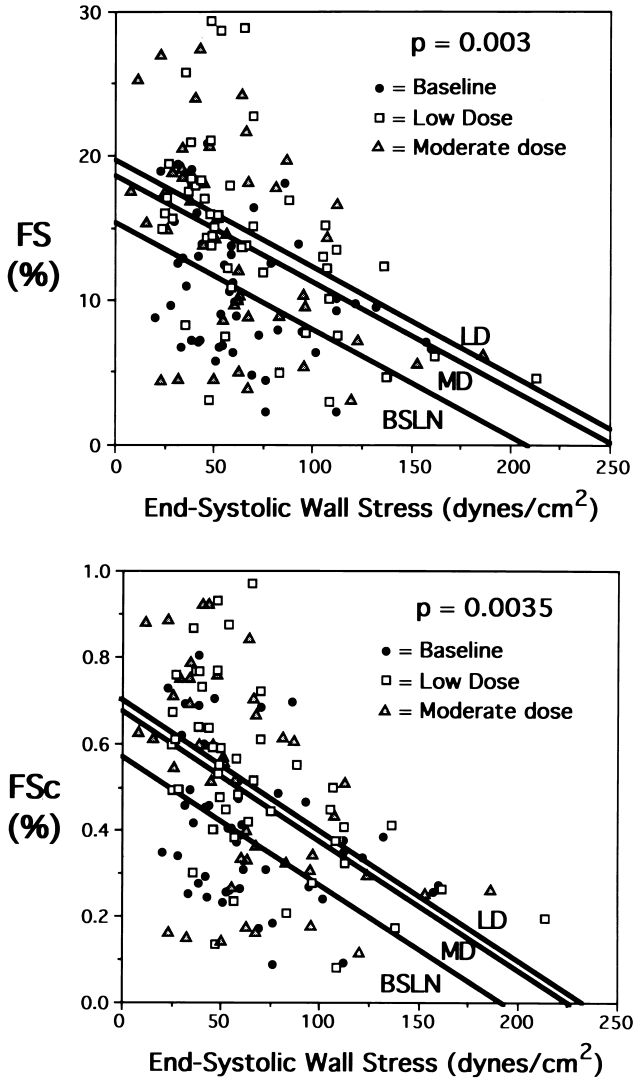

Figure 1. Fractional shortening (FS) (**top**) and heart rate-corrected fractional shortening (FSc) (**bottom**) are plotted against their covariate, end-systolic wall stress for baseline (BSLN) and low (LD) and moderate dose (MD) digoxin. Analysis of covariance demonstrated a significant effect of digoxin on these relations ($p = 0.003$ for fractional shortening, $p = 0.0035$ for heart rate-corrected fractional shortening). The Scheffé F test revealed an upward shift of this relation with low dose digoxin ($p = 0.012$ for fractional shortening, $p = 0.034$ for heart rate-corrected fractional shortening), with no additional effect with moderate dose digoxin.

at moderate dose digoxin ($p = 0.049$ for moderate dose vs. baseline). Fractional shortening (uncorrected for load) did not change significantly at low dose (from 9.1 ± 5.3% to 12.9 ± 6.9%) or at moderate dose (12.5 ± 6.6%) digoxin.

Figure 1 demonstrates the dose-response of the left ventricular stress–shortening relation with and without correction for heart rate. Analysis of covariance showed a significant interaction with digitalis with regard to fractional shortening as a function of its covariate, end-systolic wall stress ($p = 0.003$) and with regard to heart rate-corrected fractional shortening as a function of the same covariate, end-systolic wall stress ($p = 0.0035$). There was a significant upward shift of this relation with low dose digitalis compared with baseline ($p = 0.002$ for fractional shortening vs. end-systolic wall stress; $p = 0.017$ for heart rate-corrected fractional shortening vs. end-systolic wall stress). Moderate dose digoxin produced no further increase in performance compared with low dose digoxin, as shown in Figure 1 ($p = 0.88$ for fractional shortening vs. end-systolic wall stress at moderate vs. low dose; $p = 0.98$ for heart rate-corrected fractional shortening vs. end-systolic wall stress at moderate vs. low dose). These data suggest an improvement in performance with low dose digoxin and no further improvement with moderate dose digoxin.

Results of the least-squares mean estimates of mean fractional shortening for each digoxin dose level at an average level of load are shown in Table 2. A significant increase in fractional shortening ($p = 0.0059$) and a nearly significant increase in heart rate-corrected fractional shortening ($p = 0.029$) are present with low dose digoxin, with no further change after moderate dose digoxin.

Autonomic dose-response. The heart rate variability dose-responses to digoxin are shown in Table 3. Low dose digoxin significantly lowered average heart rate ($p = 0.006$) recorded over 24 h, from 87 ± 10 to 82 ± 10 beats/min, with no further change on moderate dose digoxin (p = NS for moderate vs. low dose).

In the time domain analysis, low dose digoxin increased HRV, as reflected by SDNN ($p = 0.028$) and the standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN) ($p = 0.012$), with no further increase after moderate dose digoxin. Digoxin at both low and moderate doses did not produce a change in RMS-SD or NN>50 (surrogate measures of parasympathetic activity).

In the spectral analysis, low dose digoxin did not increase high frequency power (parasympathetic) (5.8 ± 1.5 to 6.1 ± 1.4). There was no difference in moderate versus low dose digoxin in the high frequency range. In the low frequency spectrum, which reflects both sympathetic and parasympathetic activity, low dose digoxin produced a trend toward an increase in power ($p < 0.1$ low dose vs. baseline) that did not increase further with moderate dose digoxin. The ratio of low frequency to high frequency power and plasma norepineph-

Table 2. Least-Squares Mean Estimates of Fractional Shortening for Each Digoxin Dose at Average Level of Load

Digoxin Dose	Least-Squares Mean Estimate	SD	p Value	
			vs. Baseline	vs. Low Dose
FS (%)				
Baseline	10.6	7.1	—	0.0059
Low dose	14.6	7.2	0.0059	—
Moderate dose	13.7	6.5	0.027	0.526
FSc				
Baseline	0.40	0.25	—	0.029
Low dose	0.51	0.25	0.029	—
Moderate dose	0.49	0.23	0.06	0.73

FS = fractional shortening; FSc = heart rate corrected fractional shortening.

Table 3. Autonomic Dose Response to Digoxin (mean ± SD)

	Baseline	Low Dose Digoxin	Moderate Dose Digoxin	p Value (ANOVA)
Time Domain Analysis of HRV				
HR (beats/min)	87 ± 10	82 ± 10*	81 ± 12*†	0.006
SDNN (ms)	88 ± 32	106 ± 37*	103 ± 42†	0.028
SDANN (ms)	77 ± 30	95 ± 32*	93 ± 40*†	0.012
RMS-SD	29.4 ± 16.7	32.1 ± 16.3	29.1 ± 8.7†	0.57
lnNN>50	8.4 ± 1.0	8.6 ± 0.7	8.4 ± 0.7†	0.56
Spectral Analysis of HRV				
lnHFP	5.8 ± 1.5	6.1 ± 1.4	6.1 ± 1.2†	0.27
lnLFP	5.9 ± 1.7	6.3 ± 1.3	6.4 ± 1.4†	0.074
LFP/HFP	1.2 ± 0.4	1.3 ± 0.6	2.0 ± 2.6†	0.33
PNE (ng/ml)	347 ± 148	362 ± 177	362 ± 178†	0.89

*$p < 0.05$ versus baseline by Scheffé F test. †p = NS versus low dose by Scheffé F test. HFP = high frequency power; HRV = heart rate variability; LFP = low frequency power; NN>50 = number of pairs of adjacent NN intervals differing by >50 ms in entire recording; PNE = plasma norepinephrine; RMS-SD = square root of mean of sum of squares of differences between adjacent NN intervals; SDANN = standard deviation of averages of NN intervals in all 5-min segments of entire recording; SDNN = standard deviation of all NN intervals; other abbreviations as in Table 1.

rine, surrogate measures of sympathetic autonomic activity, did not change with either low or moderate dose digoxin.

Discussion

The results of the present study demonstrate both a hemodynamic and an autonomic benefit of digoxin at low dose (0.125 mg daily), with no clinically significant additional benefit at moderate dose (0.25 mg daily). To our knowledge, this is the first long-term study to examine the dose-response of digoxin using a relatively load-independent index of performance. Additionally, we believe that this is the first study to examine the dose-response of digoxin on autonomic activity.

Dose-ranging hemodynamic results. Several previous investigators have found a hemodynamic dose-response to digoxin (16–24) whereas others have not (25). However, several of these studies were short-term intravenous studies (16–19,21,22) with uncertainty regarding the steady state kinetics of the drug and measured glycoside levels transiently in the toxic range. In addition, ventricular function was measured by systolic time intervals (16–20,23) or ejection fraction (24,25), which are load- and heart rate-dependent measurements. In addition, the study by Gheorghiade et al. (24) did not examine patients before digoxin administration to assess whether a majority of its beneficial effects occurred at low dose. To eliminate these limitations, we studied the dose-response to digoxin before any administration of drug, at low and moderate doses. We chose not to administer high dose digoxin for patient safety. We also chose to use a relatively load-independent index of ventricular function, a stress–shortening relation before and after correction for heart rate changes.

In contrast to Gheorghiade et al. (21), but like Ware et al. (25), we did not find additional hemodynamic benefit of digoxin at higher dosages. There are several reasons for the differences between our study and that of Gheorghiade et al.: 1) The patients from the Gheorghiade et al. study were studied after 12 weeks of therapy compared with our 2 weeks. Although digoxin should be at an equilibrium state by 2 weeks, long-term beneficial changes due to remodeling could have taken longer to evolve, resulting in some improvement in ejection fraction. 2) Measurement of ejection fraction by radionuclide methods may have been more sensitive than our use of fractional shortening by echocardiography, especially because it encompasses global performance changes as opposed to a more regional view with echocardiography. In contrast, ejection fraction does not take load or heart rate into account, factors that may alter the result. Our assessment is relatively independent of both heart rate and afterload. 3) It is unlikely that differences in digoxin dosing can account for the discrepancy because serum levels in the two studies were comparable. In addition, it is doubtful that differences in patient cohorts or background therapy could account for the different findings of the two studies because the patient demographics (including age) and background medications were similar in the two trials.

It is unclear why left ventricular performance does not increase more at moderate digoxin dosages. The lack of further increase in performance is not a function of heart rate or afterload alterations because these factors are accounted for by our analysis. In addition, the lack of reduction in left ventricular end-diastolic dimension suggests that preload is not significantly changed. Thus, other factors must account for this phenomenon. Although other investigators (26) have found an increase in parasympathetic activity with digoxin, we did not. Thus, we cannot account for the lack of incremental improvement in left ventricular performance with moderate dose digoxin by augmented parasympathetic activity. Further evaluation of this phenomenon, perhaps by examining the effect of digoxin on neurohormones that may affect contractility (e.g., angiotensin II, endothelin-1, cytokines) and on biologic function of the myocytes (39), is warranted.

Dose-ranging autonomic results. Both the reduction in heart rate and the increase in SDNN and SDANN at low dose, with no further changes at moderate dose, suggest that the majority of benefit of increasing heart rate variability is at low dose.

We found a much more modest change in parasympathetic activity than did Krum et al. (26). High frequency power did not increase significantly with low dose digoxin ($p = 0.27$). In addition, RMS-SD and NN>50 did not change. These data suggest that parasympathetic activity did not change significantly in our patients. The finding that moderate dose digoxin did not further increase high frequency power over low dose digoxin suggests that increasing the dose of digoxin will not produce further augmentation of parasympathetic activity. The increase in low frequency power ($p = 0.074$ for low dose vs. baseline), an index of baroreflex activity, was consistent with

the previous study of Krum et al. (26). However, there was no additional benefit of moderate dose over low dose digoxin in our study.

Sympathetic activity, as reflected by both the ratio of low to high frequency power and by plasma norepinephrine did not change at low or moderate dose digoxin. The study by Krum et al. (26) demonstrated a reduction in plasma norepinephrine from 552 ± 80 to 390 ± 37 ng/ml without any change in the ratio of low to high frequency power. Another clinical trial (10) found that digoxin resulted in a median reduction in plasma norepinephrine of 98 from 339 pg/ml at baseline. The differences between our study and that of previous investigators is unclear but is probably not due to differences in baseline neurohormonal activation. Our baseline plasma norepinephrine level of 369 ± 174 ng/ml is in between the baseline levels found in these comparison trials (10,25). In addition, the patients in the study by Krum et al. were younger, included women and did not include patients taking other agents, such as beta-adrenergic blocking agents and calcium antagonists, and this may have accounted for some difference.

Clinical implications. The use of inotropic medications to treat congestive heart failure has generally resulted in an increase in mortality (40,41) despite their beneficial effects on hemodynamic variables and functionality (8,42,43). This increase in mortality seems to be due to an increase in sudden death in some cases (44).

Digoxin appears to be a unique inotropic agent because it has no adverse effect on mortality (12), which may be due to a balance between beneficial neurohormonal (9–11,26) and toxic arrhythmogenic effects (13–15). Our study has shown that most of the beneficial effects occur at low dose, with little additional hemodynamic or autonomic benefit at higher dose. However, higher dose digoxin may predispose to toxic rhythm problems, especially in older patients who are more likely to have impaired renal function and therefore are likely to be more prone to heightened digitalis levels and digitalis toxicity (45,46). The subgroup analysis of the DIG study examining digoxin levels and risk of sudden death should help to determine whether higher doses of digoxin provide little additional benefit but higher risk of death.

Study limitations. The present study did not address the use of higher dose digoxin to treat patients in atrial fibrillation. In such patients, digoxin may have the additional benefit of rate control. In addition, because patients in functional class IV were not studied, we can make no conclusions about the dose-response effects of digoxin in the sickest patients. Because patients in functional class IV may have the greatest degree of dysautonomia, higher doses of digoxin may be more efficacious in these patients, although this efficacy has yet to be proved.

Although this was not a double-blind, placebo-controlled trial, assessment of Holter monitoring and echocardiograms was performed by independent observers, in blinded manner, who were unaware of the dose of digoxin for each patient or the time of assessment. Because the hypothesis of the study was not to show digoxin efficacy, which has been previously demonstrated (6–8), each patient was his own control.

The use of fractional shortening as opposed to a more global assessment of shortening may be less sensitive to smaller or more regional changes in shortening. However, this may be a special problem in assessing patients with coronary artery disease. This methodology has been used in previous studies in humans with good reproducibility (27,28). Despite the fact that we did not use a more global assessment of shortening, we were able to detect changes in performance between baseline and low dose digoxin using this technique. If there were any undetected additional changes in shortening between low and moderate dose digoxin, these changes were probably not clinically significant.

The use of a cuff systolic blood pressure instead of end-systolic pressure to determine systolic wall stress is less accurate than using intraventricular pressure. However, because this was a noninvasive study, the use of cuff blood pressure was more practical. In addition, we have examined the relation of invasively determined end-systolic and peak systolic pressure in 25 patients with heart failure and found a close correlation (peak systolic pressure 19.46 mm Hg, end-systolic pressure 1.349 mm Hg, $r^2 = 0.86$, $p < 0.0001$) (unpublished data).

The Holter monitor studies were performed after the echocardiographic study. Because nitroprusside increases sinoaortic baroreflex activation, we waited at least 10 to 15 min after the echocardiographic studies to place the Holter monitors. In all patients, blood pressure and heart rate had returned to baseline values when the Holter monitors were placed. Moreover, because the baseline, low dose and moderate dose digoxin studies were all performed in an identical manner, any changes over time would reflect the digoxin effect and not the nitroprusside effect. In addition, plasma norepinephrine was drawn before echocardiographic study and was thus independent of any nitroprusside effect.

Although many of our patients were taking other medications that could affect the autonomic nervous system, such as angiotensin-converting enzyme inhibitors, diuretic drugs and beta-blockers for background therapy, the patients were all in stable condition during this background treatment for at least 3 months before study entry, and no change in medication (other than digoxin) was made during the study period. Thus, although these medications can alter the adrenergic nervous system, the addition of digoxin to this stable background therapy provides a "real-world" test of the effects of digoxin. However, a repeat study with no other background therapy is warranted.

Five patients had underlying conditions that could impair baroreflex mechanisms. One patient had diabetes and was excluded from Holter analysis, and four had some history of hypertension but were included in the analysis. When the diabetic patient was added to the analysis, or the four patients with hypertension were excluded, the Holter results were unchanged.

The results of the present study reflect a 2-week treatment period with each dose of digoxin. We cannot exclude the

possibility that longer term effects of digoxin on remodeling, left ventricular function and the autonomic nervous system would have been present had we studied these patients after several months of therapy. However, the findings of a hemodynamic and autonomic benefit at 2 weeks of therapy suggests that benefit can be detected early. In addition, previous studies (9) in humans have shown that baroreflex mechanisms may be reset within minutes with a rapid acting digitalis. If any bias existed in the present study due to late effects, it was toward moderate dose digoxin because this measurement was made after an additional 2 weeks of digoxin therapy. In addition, large amounts of remodeling have not been reported as a consequence of digoxin therapy. Thus, this was probably of minimal importance.

Conclusions. The results of this study suggest that moderate dosages of digoxin may not have a significant hemodynamic or autonomic advantage over low dose digoxin in patients with moderate heart failure in normal sinus rhythm. Because digoxin has a narrow therapeutic index and higher dosages may predispose to arrhythmias, the use of low dose digoxin may be preferable. This is especially true because patients with heart failure often have fluctuating renal perfusion and thereby have altered kidney function, which may predispose to toxicity.

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