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Heart Rate Variability in Patients With Mild to Moderate Heart Failure: Effects of Neurohormonal Modulation by Digoxin and Ibopamine

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Objectives. **This study assessed the effects of digoxin and ibopamine on variables of heart rate variability in relation to neurohormonal activation.**

Background. **Analysis of heart rate variability can be used to study the autonomic dysfunction that characterizes chronic heart failure. In the Dutch Ibopamine Multicenter Trial, patients with heart failure were found to have increased neurohormonal activation with placebo therapy but not with digoxin and ibopamine therapy.**

Methods. **We studied 59 patients with mild to moderate heart failure (mean [±SEM] age 60 ± 1 years, mean ejection fraction 0.30 ± 0.01). Patients were randomized to double-blind treatment with digoxin (0.25 mg [n = 22]), ibopamine (100 mg three times a day [n = 19]) or placebo (n = 18); background therapy consisted of furosemide (up to 80 mg).**

Results. **After 3 months, plasma norepinephrine levels had increased with placebo, whereas they decreased with digoxin (+31 vs. −60 pg/ml, respectively, $p < 0.01$). With ibopamine, a nonsignificant decrease was observed (−27 pg/ml, $p = 0.10$). All variables of heart rate variability showed a deterioration in the placebo group. With digoxin, the percent differences between successive RR intervals >50 ms (pNN50) increased (+1.7 ± 0.9%, $p < 0.01$), along with absolute and normalized high frequency power (+40 ± 33 ms^2, $p < 0.05$ and +2.4 ± 1.7%, $p < 0.01$, respectively). These changes were observed during daytime hours only and were most pronounced in patients with the most impaired baseline heart rate variability. With ibopamine, nonsignificant trends similar to the changes with digoxin were observed.**

Conclusions. **In patients with early stages of heart failure, digoxin may prevent a progressive deterioration in heart rate variability, whereas ibopamine does not show statistically significant effects. The changes in heart rate variability with digoxin parallel an observed decrease in neurohormonal activation. Digoxin apparently enhances cardiac vagal tone in the setting of neuroendocrine activation.**

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It has been recognized that neurohormonal activation is one of the hallmarks of chronic heart failure and that the degree of neurohormonal activation is strongly correlated with the severity and prognosis of the syndrome (1,2). Furthermore, chronic heart failure is associated with autonomic dysfunction that is characterized by increased sympathetic and decreased parasympathetic activity (3). Analysis of heart rate variability can be used to study autonomic function noninvasively (4–6), and several studies have shown abnormalities of heart rate variability in patients with heart failure (7–12). The impairment of heart rate variability appears to be related to the degree of neurohormonal activation (7,10), which may have prognostic value (13). This concept therefore suggests that analysis of heart rate variability could be used to assess the severity of heart failure. At present, data on the effect of drug therapy on variables of heart rate variability in patients with heart failure are limited (14–17). Moreover, although it has been suggested that neurohormonal modulation by drug treatment may favorably affect heart rate variability in patients with heart failure, no placebo-controlled studies have compared the effects of pharmacologic treatment on both heart rate variability and neurohormonal activation.

In a recently reported double-blind, placebo-controlled trial (18), we assessed the efficacy and safety of treatment with digoxin and the oral dopamine agonist ibopamine in patients with mild to moderate heart failure. The data showed that during long-term follow-up, both digoxin and ibopamine prevented an increase in neurohormonal activation but placebo did not. The purpose of the present study was to assess the

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effects of both drugs on variables of heart rate variability and to investigate the relation of these effects to changes in neurohormonal activation.

Methods

Study design. The Dutch Ibopamine Multicenter Trial (DIMT) was a multicenter, double-blind, randomized, parallel-group comparison of ibopamine (100 mg three times daily), digoxin (0.25 mg once daily) and placebo in patients with mild to moderate heart failure. After a placebo run-in period of 7 to 10 days, patients received double-blind treatment. A double-dummy technique was used to ensure the blinding procedure. At the end of the placebo run-in period, and after 3 months of treatment, 24-h ambulatory Holter monitoring for analysis of heart rate variability and blood samples for determination of neurohormonal activation were obtained. The protocol was approved by the ethics committee of each participating center and was conducted in accordance with the revised Declaration of Helsinki. Before entry into the study, all patients gave written informed consent.

Study group. Patients 18 to 75 years old with New York Heart Association functional class II or III heart failure and clinically stable for at least 2 weeks before the study were selected for inclusion in the trial. Chronic heart failure was characterized by clinical signs and symptoms and a radionuclide left ventricular ejection fraction ≤0.45 (obtained within the previous 2 months). In addition, patients had to be able to exercise for at least 4 min at 70 W on a bicycle ergometer. During the trial, furosemide (up to 80 mg/day) was allowed as background therapy, as well as short-acting nitrates. Triamterene was also permitted to control serum potassium levels. Other drugs for treatment of heart failure, including vasodilators and angiotensin-converting enzyme inhibitors, alpha- or beta-adrenergic blocking agents and calcium antagonists were not allowed. Patients were excluded from participation if they had heart failure due to hemodynamically significant valvular or congenital heart disease, active myocarditis, thyroid disease or hypertrophic obstructive cardiomyopathy. Further exclusion criteria were exercise-limiting angina pectoris; myocardial infarction or major operation within the previous 2 months; severe hypertension; atrial fibrillation or flutter; pacemaker therapy; a history of sustained ventricular tachyarrhythmias, chronic obstructive lung disease, severe hepatic or renal disease, insulin-dependent diabetes mellitus, psychiatric illnesses and use of monoamine oxidase inhibitors or (anti-)dopaminergic agents.

Neurohormonal levels. Venous blood for determination of plasma neurohormonal levels was drawn after 30 min of supine rest. Plasma norepinephrine, aldosterone and renin concentrations were analyzed in a central core laboratory. Plasma norepinephrine (19) and plasma renin (20) were measured as described previously; aldosterone was measured by a commercially available radioimmunoassay kit (Aldokit, Labservice Benelux, Apeldoorn, The Netherlands).

Table 1. Definitions of Variables of Heart Rate Variability

Variable	Definition
Time domain	
Mean NN (ms)	Mean value of all normal RR intervals during 24 h
SDNN (ms)	Standard deviation of all normal RR intervals during 24 h
CV (%)	Coefficient of variance, calculated as (SDNN/mean NN) × 100%
rMSSD (ms)	Root mean square of successive difference; square root of mean value of squared differences between successive normal RR intervals
pNN50 (%)	Percent differences between successive normal RR intervals >50 ms
Frequency domain	
TP(abs) (ms^2)	Total power (absolute units); energy in power spectrum between 0.0033 and 0.40 Hz
LF(abs) (ms^2)	Low frequency power (absolute units); energy in power spectrum between 0.04 and 0.15 Hz
HF(abs) (ms^2)	High frequency power (absolute units); energy in power spectrum between 0.15 and 0.40 Hz
LF(nu) (%)	Low frequency power (normalized units); calculated as {LF(abs)/[TP(abs) − Power <0.03 Hz]} × 100%
HF(nu) (%)	High frequency power (normalized units); calculated as {HF(abs)/[TP(abs) − Power <0.03 Hz]} × 100%
LF/HF ratio	Ratio of low to high frequency power

Analysis of heart rate variability. The 24-h ambulatory Holter recordings were analyzed on a Marquette 8000 Holter system (Marquette Electronics) by an experienced analyst (J.H.) and supervised by a single physician (J.B.). The analyses were performed without knowledge of the administered study medication. Recordings with >15% noise or ectopic beats were excluded from heart rate variability analysis. For calculation of variables of heart rate variability, a data base of RR intervals was transferred to a personal computer. Time and frequency domain variables were calculated from the time series of RR intervals (Table 1) and were computed over consecutive 5-min segments. Segments with >15% noise or ectopic beats were excluded from analysis. Before calculation of the frequency domain variables in the other segments, episodes with noise and ectopic beats were substituted by holding the previous normal RR interval constant throughout the entire period. Spectral analysis was performed using the discrete Fourier transform algorithm (21–23). During spectral analysis, the recordings were controlled for differences in actual heart rate. Low and high frequency components of the power spectrum were calculated in absolute units. Low and high frequency power were also expressed in normalized units analogous to calculations used in autoregressive models. Furthermore, the ratio of low to high frequency power which is considered a measure of sympathovagal balance, was calculated (6,23).

Statistical analysis. Statistical analysis was performed using SPSS-PC Version 5.01. Results are presented as mean value ± SEM. Differences between treatment groups were analyzed by comparing the change from baseline with use of

Table 2. Baseline Characteristics of the Three Treatment Groups

	Placebo (n = 18)	Digoxin (n = 22)	Ibopamine (n = 19)
Age (yr)	62 ± 1	60 ± 1	60 ± 1
Gender (%)			
Male	85	92	82
Female	15	8	18
Left ventricular ejection fraction	0.31 ± 0.01	0.28 ± 0.01	0.30 ± 0.02
New York Heart Association functional class (%)			
II	79	80	85
III	21	20	15
Cause of heart failure (%)			
Ischemic	77	73	85
Idiopathic	23	27	15
Hemodynamic data			
Systolic blood pressure (mm Hg)	134 ± 3	130 ± 3	135 ± 3
Diastolic blood pressure (mm Hg)	83 ± 2	81 ± 1	82 ± 1
Heart rate (beats/min)	82 ± 3	81 ± 2	80 ± 2
Furosemide use (mg/day)	26 ± 4	23 ± 4	31 ± 5
Plasma neurohormone levels*			
Norepinephrine (pg/ml)	391 (125–838)	463 (75–999)	422 (119–1,321)
Aldosterone (pg/ml)	90 (17–436)	104 (7–416)	97 (14–498)
Renin (ng/ml per h)	22 (3–112)	28 (4–82)	23 (4–58)
Heart rate variability			
Time domain variables			
NN (ms)	762 ± 24	764 ± 18	772 ± 18
SDNN (ms)	124 ± 9	119 ± 7	115 ± 6
CV (%)	16.5 ± 1.0	16.0 ± 0.8	15.2 ± 0.8
rMSSD (ms)	20 ± 2	21 ± 2	20 ± 2
pNN50 (%)	3.6 ± 1.0	3.4 ± 0.7	3.1 ± 0.9
Frequency domain variables			
TP(abs) (ms^2)	2,140 ± 290	2,356 ± 233	2,491 ± 355
LF(abs) (ms^2)	431 ± 82	442 ± 64	470 ± 99
HF(abs) (ms^2)	148 ± 40	153 ± 30	133 ± 30
LF(nu) (%)	56.5 ± 1.9	56.1 ± 2.0	55.7 ± 2.3
HF(nu) (%)	19.6 ± 1.7	20.3 ± 1.8	19.2 ± 1.6
LF/HF ratio	4.5 ± 0.6	4.3 ± 0.4	4.4 ± 0.6

*Median (range). Data presented are mean value ± SEM, unless otherwise indicated. Abbreviations as in Table 1.

analysis of variance and the Student *t* test. The Scheffé procedure was used in the analysis of variance to correct for multiple comparisons. For nonnormally distributed variables, the Kruskal-Wallis and Wilcoxon signed rank tests were used. All p values are reported for two-tailed tests, and an alpha <0.05 was considered statistically significant. Mean values of variables of heart rate variability were calculated for the entire 24-h period. To assess the differential effects of drug treatment during both daytime and nighttime, periods from midnight to 8 AM (nighttime) and from 8 AM to noon (daytime) were analyzed separately. Linear regression analysis was used to test the relation between values of variables of heart rate variability at baseline and after treatment.

Results

Study patients. Of the original DIMT study patients (18), Holter recordings for analysis of heart rate variability were available in 71 at baseline and after 3-month follow-up. Holter recordings could not be analyzed for heart rate variability in 12 patients because ectopic beats or noise accounted for >15% of the signal at baseline (7 patients [placebo in 2, digoxin in 2, ibopamine in 3] or during follow-up (5 patients [placebo in 3, ibopamine in 2]). Therefore, the remaining 59 patients constituted the study group and underwent heart rate variability analysis both at baseline and after 3 months. There were no significant differences at baseline among the three treatment groups, with respect to clinical characteristics and variables of heart rate variability (Table 2). Three patients had non–insulin-dependent diabetes mellitus (placebo in 1, digoxin in 1, ibopamine in 1). Heart failure was present for a median of 7.5 months. Comparison of the baseline characteristics of this subgroup with those of the original DIMT study cohort revealed no significant differences.

Neurohormonal levels. After 3 months of treatment, plasma norepinephrine levels had increased in the placebo group (+31 pg/ml), whereas they had decreased in both the digoxin (−60 pg/ml, $p < 0.01$ vs. placebo) and ibopamine

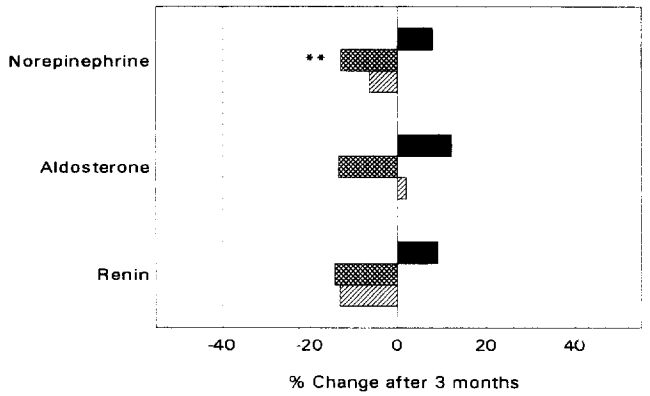

Figure 1. Change in plasma neurohormone levels after 3 months of treatment, expressed as percent of baseline values. **Solid bars** = placebo; **crosshatched bars** = digoxin; **hatched bars** = ibopamine. **p < 0.01 versus placebo.

groups (−27 pg/ml, p = 0.10 vs. placebo). After digoxin and ibopamine therapy, a trend was observed for changes in aldosterone and renin opposite to those in the placebo group; however, these changes did not reach statistical significance (Fig. 1).

Variables of heart rate variability. After 3 months of treatment, all time domain variables were decreased in the placebo group compared with baseline values (Table 3, Fig. 2). In contrast, an overall increase was observed in the digoxin group. Compared with the placebo group, the mean value of normal RR intervals increased significantly, as did the standard deviation of normal RR intervals (SDNN). The standard deviation adjusted for the change in mean value of normal RR intervals (i.e., coefficient of variance) showed no significant change. The root mean square successive differences (rMSSD) and percent difference between successive normal RR intervals >50 ms (pNN50) were significantly enhanced by digoxin. In

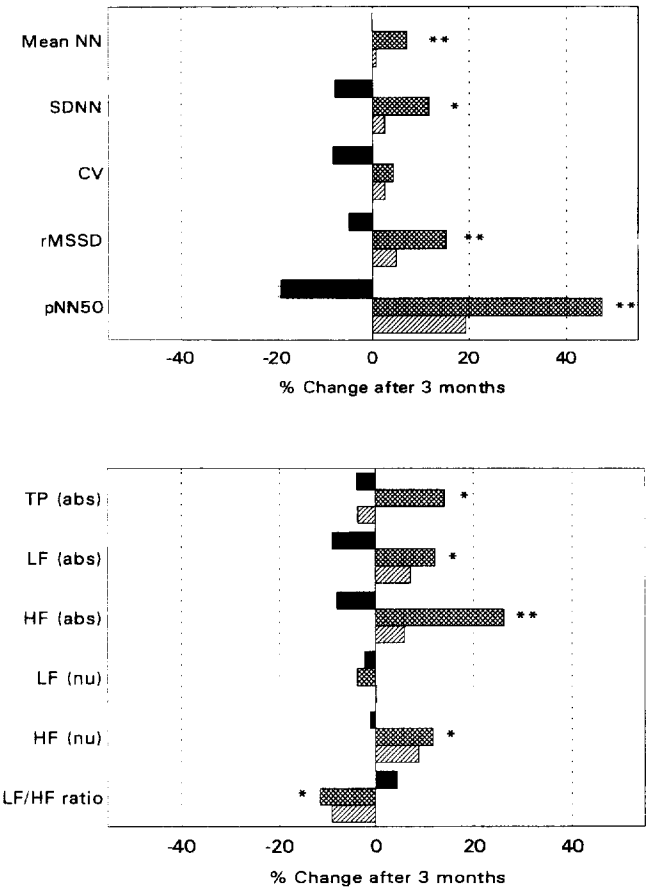

Figure 2. Change in time domain (**top**) and frequency domain variables (**bottom**) of heart rate variability after 3 months of treatment, expressed as percent of baseline values. abs = absolute units; CV = coefficient of variance; HF = high frequency power; LF = low frequency power; NN = normal RR intervals; nu = normalized units; pNN50 = percent difference between successive normal RR intervals >50 ms; rMSSD = root mean square of successive difference; SDNN = standard deviation of normal RR intervals; TP = total power. Symbols as in Figure 1. *p < 0.05, **p < 0.01 versus placebo.

Table 3. Changes in Variables of Heart Rate Variability After 3 Months of Treatment

Variable	Placebo (n = 18)	Digoxin (n = 22)	Ibopamine (n = 19)
Time domain			
Mean NN (ms)	−1 ± 10	+55 ± 11*	−6 ± 12
SDNN (ms)	−10 ± 6	+14 ± 7†	−3 ± 8
CV (%)	−1.4 ± 0.7	−0.7 ± 0.8	+0.4 ± 1.1
rMSSD (ms)	−1 ± 1	+3 ± 2*	−1 ± 2
pNN50 (%)	−0.7 ± 0.6	−1.7 ± 0.9*	+0.6 ± 0.7
Frequency domain			
TP(abs) (ms^2)	−84 ± 159	+332 ± 125†	−92 ± 270
LF(abs) (ms^2)	−39 ± 48	+54 ± 32†	+34 ± 93
HF(abs) (ms^2)	−12 ± 22	+40 ± 33*	−8 ± 43
LF(nu) (%)	−1.3 ± 1.0	−2.1 ± 1.3	+0.1 ± 1.4
HF(nu) (%)	−0.2 ± 0.9	+2.4 ± 1.7†	+1.7 ± 1.3
LF/HF ratio	+0.2 ± 0.3	−0.5 ± 0.3†	−0.4 ± 0.3

*p < 0.01, †p < 0.05 versus placebo. Data presented are mean change relative to baseline ± SEM. + = increase; − = decrease; abbreviations as in Table 1.

the ibopamine group, similar but nonsignificant trends opposite to the decrease in the placebo group were observed.

Spectral analysis of heart rate variability showed a decrease in all variables in the placebo group similar to the change in time domain variables, except for a small increase in the ratio of low to high frequency power. In the digoxin group, total power, and low and especially high frequency power showed a significant increase (absolute units). Normalized high frequency power also showed a significant increase, whereas normalized low frequency power showed a nonsignificant trend to decrease. The ratio of low to high frequency power was significantly reduced after digoxin. In the ibopamine group, again, less pronounced and nonsignificant changes were observed. Comparison of the individual changes in plasma neurohormone levels and variables of heart rate variability revealed no significant correlations, either in the total group or in any of the three treatment groups.

Table 4. Differential Effects of Digoxin on Heart Rate Variability During Nighttime and Daytime

Variable	Nighttime Baseline	3 mo	Daytime Baseline	3 mo
Time domain				
Mean NN (ms)	842 ± 22	907 ± 25*	717 ± 19	772 ± 23†
rMSSD (ms)	23 ± 2	24 ± 2	20 ± 1	23 ± 2*
pNN50 (%)	3.8 ± 0.9	5.4 ± 1.3	2.9 ± 0.7	4.9 ± 1.2‡
Frequency domain				
TP(abs) (ms^2)	2,736 ± 297	2,906 ± 380	2,070 ± 269	2,605 ± 348*
LF(abs) (ms^2)	520 ± 76	567 ± 88	389 ± 71	479 ± 83‡
HF(abs) (ms^2)	186 ± 45	207 ± 34	117 ± 22	175 ± 34*
LF(nu) (%)	52.9 ± 2.2	51.0 ± 1.9	58.0 ± 2.0	56.5 ± 1.8
HF(nu) (%)	22.3 ± 2.2	24.3 ± 2.1	18.9 ± 1.6	21.7 ± 1.8‡
LF/HF ratio	4.2 ± 0.5	3.6 ± 0.4	4.5 ± 0.4	3.9 ± 0.3

*$p < 0.01$, †$p < 0.001$, ‡$p < 0.05$ versus baseline. Data presented are mean value ± SEM. Abbreviations as in Table 1.

The effects of digoxin on variables of heart rate variability during nighttime and daytime are shown in Table 4. Compared with that at baseline, the mean value of normal RR intervals was significantly prolonged during both nighttime and daytime. However, significant changes in variables of heart rate variability were observed during daytime hours only. The rMSSD and pNN50 values, which showed lower values at baseline during the day than at night, were significantly enhanced in the daytime hours during digoxin treatment. Similar changes were observed in frequency domain variables. Both absolute and normalized high frequency components were significantly enhanced with digoxin treatment during the daytime, but changes in heart rate variability after placebo and ibopamine treatment were not significant during either nighttime or daytime.

Comparison of the baseline values of heart rate variability and the subsequent change during treatment revealed an inverse relation for several variables in the digoxin-treated patients. A statistically significant negative correlation was observed for rMSSD, normalized low frequency power, absolute and normalized high frequency power and the ratio of low to high frequency power (Table 5). In the ibopamine-treated patients, a statistically significant negative correlation was found for the ratio of low to high frequency power only ($r = -0.48$, $p = 0.045$), not for the other variables. No significant trends were observed in the placebo group. Scatterplots of the correlation between the ratio of low to high frequency power and at baseline and after 3 months of treatment for the placebo, digoxin and ibopamine groups are shown in Figure 3.

Table 5. Correlation Between Variables of Heart Rate Variability at Baseline and After 3 Months of Treatment in the Digoxin Group ($n = 22$)

	r Value	p Value
rMSSD (ms)	−0.53	0.012
HF(abs) (ms^2)	−0.53	0.011
LF(nu) (%)	−0.51	0.017
HF(nu) (%)	−0.49	0.022
LF/HF ratio	−0.68	< 0.001

Only significant correlations are listed; r values obtained using least squares linear regression analysis. Abbreviations as in Table 1.

Discussion

To our knowledge, the present study is the first to report placebo-controlled data on the effects of treatment with digoxin and ibopamine on variables of heart rate variability in heart failure. In patients with mild to moderate heart failure, treatment with digoxin was found to prevent the progressive deterioration in variables of heart rate variability that was observed in placebo-treated patients. In addition, digoxin prevented the increase in neurohormonal activation that was observed in the placebo group. An important novel finding in our study is that digoxin treatment enhances variables of heart rate variability associated with cardiac vagal tone especially during daytime, when sympathetic tone is known to be increased and parasympathetic tone is decreased (24). Furthermore, the treatment effect is inversely correlated with a number of variables of heart rate variability at baseline, and digoxin therefore seems to exert its effect on autonomic control, especially when these variables are impaired. As mentioned earlier, there were no changes in exercise capacity and symptom scores after 3 months of digoxin treatment, which makes it unlikely that differences in activity can explain the observed differences in heart rate variability (18). These effects indicate a modulating influence on autonomic tone, which agrees with earlier reports of the neurohormonal-modulating effects of digoxin (24–26). Furthermore, our results are concordant with the recently published study of Krum et al. (17) in patients with chronic heart failure. After treatment with digoxin, they also found a significant decrease in plasma norepinephrine levels combined with a significant enhancement of parasympathetic activity. However, a placebo control group was not included in their study. After ibopamine,

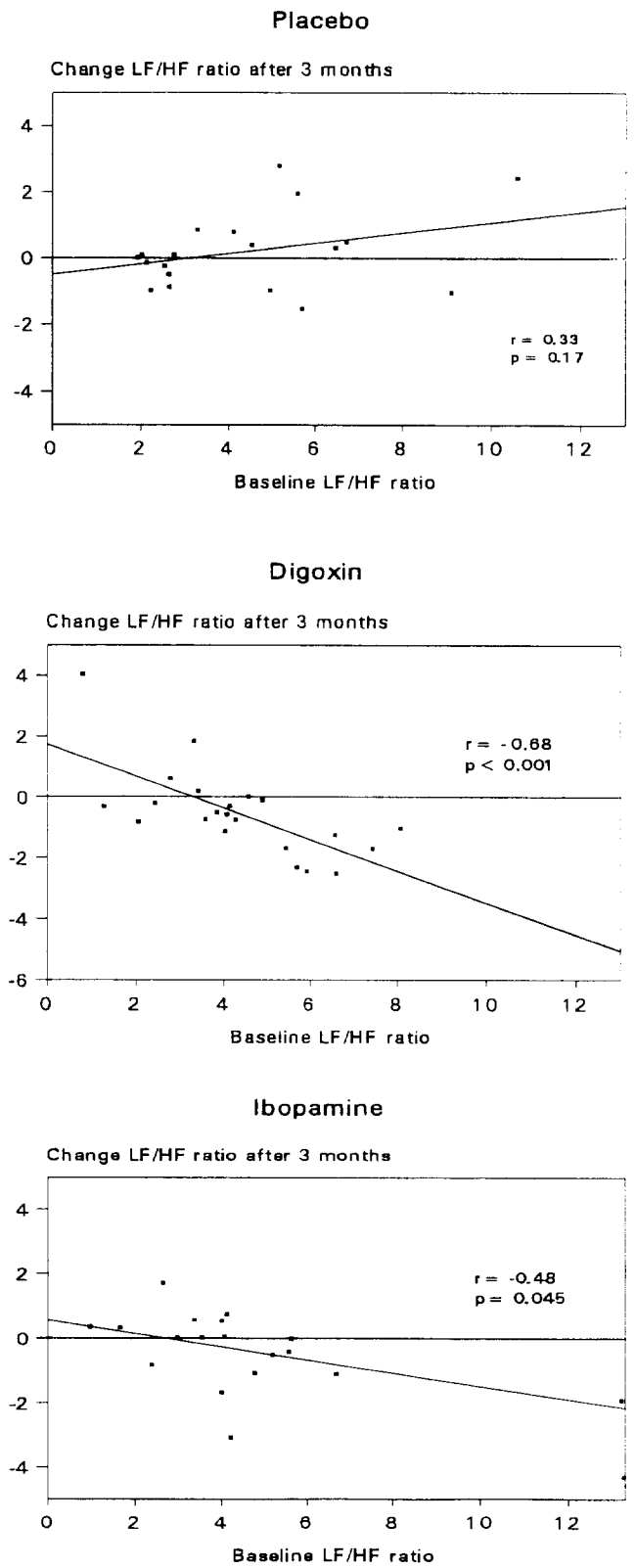

Figure 3. Scatterplot of correlation between low frequency/high frequency (LF/HF) ratio at baseline and change after 3 months of treatment in the placebo, digoxin and ibopamine groups.

only nonsignificant trends opposite to the deterioration in the placebo group were observed, both in variables of heart rate variability and in neurohormonal activation.

Variables of heart rate variability. Compared with the decline in the placebo group after 3 months in our study, digoxin significantly improved variables of heart rate variability. Ibopamine did not show a statistically significant effect on these variables. The variables associated with cardiac vagal control (rMSSD, pNN50 and high frequency power) showed a significant increase with digoxin compared with placebo. These results indicate a parasympathomimetic effect of digoxin in patients with heart failure, which confirms the findings in experimental studies (26,27). Furthermore, our data are in agreement with the findings of Kaufman et al. (28), who showed that short-term treatment with digoxin in healthy volunteers induced increases in variables of heart rate variability parameters up to 51%, particularly in indexes of vagal modulation. Similar to the findings of Ferguson et al. (27), we found a small but significant increase in the mean normal-to-normal interval, that could be considered a direct result of the shifted sympathovagal balance. The observed increase in absolute high frequency power may in part be explained by this increase in the mean normal-to-normal interval and parallels the observed increases in SDNN and total power. Still, high frequency power shows also a significant increase expressed in normalized units. Furthermore, the increase in absolute and normalized high frequency power during the day was significant. Absolute low frequency power also showed a significant increase, but normalized low frequency power showed a trend to decrease. Because the ratio of low to high frequency power showed a trend to decrease, the digoxin-induced changes in variables of heart rate variability can be considered to reflect a shift in sympathovagal balance toward enhanced cardiac vagal tone (29).

There are no previous reports on the effects of ibopamine on variables of heart rate variability. In the present study, trends opposite to those in the placebo group were observed in ibopamine-treated patients for both variables of heart rate variability and neurohormonal activation. In the present study, none of these changes reached statistical significance; but previous data (18,30,32) suggest a significant decrease in neurohormone levels during treatment with ibopamine compared with placebo. Because this study was carried out in patients with mild disease, and the sample size was limited, further studies will be needed to better establish the effects of ibopamine on heart rate variability.

The effects of drug therapy on variables of heart rate variability in patients with heart failure have been addressed in three previous studies (14–16). Angiotensin-converting enzyme inhibitors (14,15) were found to improve overall heart rate variability especially in association with vagal control. In a study by Coumel et al. (16), beta-blockers also improved the imbalance of the autonomic nervous system, as was shown by changes in the heart rate variability spectrum. However, the effect of treatment on neurohormonal activation was not evaluated in those previous studies. Nevertheless, because

both drugs have been shown to reduce neurohormonal activation (33), our results are basically in accord with the aforementioned studies (14–16).

Neurohormonal activation. There is now accumulating evidence that neurohormonal activation is not simply a marker of the severity of heart failure, but that it may actually contribute to the progression of the disease and therefore may have prognostic significance (33,34). As a consequence, drugs that possess neurohormonal-inhibiting properties, such as angiotensin-converting enzyme inhibitors (35,36), digoxin (18,25), beta-blockers (37) and oral dopaminergic agents (18,30–32), have recently gained increasing attention. Indeed, the former two drugs appear to be beneficial in the long-term treatment of patients with heart failure. It has been suggested (33,38) that a neurohormonal modulating effect of these drugs may be more important than a beneficial hemodynamic influence. Neurohormonal activation may lead to progressive autonomic impairment and baroreceptor dysfunction (39), and it may be hypothesized that reversal of neurohormonal activation may correct these abnormalities.

Furthermore, it should be emphasized that our study was performed in patients with mild disease. In these patients, treatment with digoxin improved the progressive disturbance in parasympathetic control of the heart that was observed in placebo-treated patients. In patients with a roughly similar, "early," degree of heart failure, Binkley et al. (15) also showed augmentation of cardiac vagal tone after treatment with an angiotensin-converting enzyme inhibitor. Both studies suggest that drug treatment may be beneficial early in the disease process of heart failure, because it may restore the observed derangement in autonomic control.

Other studies (7,10) have shown that impairment of heart rate variability and autonomic function in heart failure are correlated with the degree of neurohormonal activation. Although our data suggest that this neurohormonal effect may be responsible for the observed improvement in heart rate variability, no direct correlations between individual changes in variables of heart rate variability and plasma neurohormone levels were found. This result agrees with a recent report from Adamopoulos et al. (11), who showed that in patients with heart failure, an overall decrease in neurohormonal activation was related to an overall improvement in variables of heart rate variability but that no significant individual correlations were present. In fact, they concluded that specific variables of autonomic function reflect different aspects of circulatory control (11).

Clinical implications. Improvement in heart rate variability by drug treatment may be important irrespective of changes in neurohormonal activation because recent studies (13) indicate that impaired heart rate variability is independently related to an adverse prognosis in patients with heart failure. Although we did not investigate the prognostic value of this change in heart rate variability, the drug-induced improvement in heart rate variability in the present study may shed new light on the value of digoxin in this syndrome. The benefit of digoxin treatment has been questioned in patients with heart failure who are in sinus rhythm (40). Our finding that digoxin apparently affects heart rate variability under circumstances associated with neuroendocrine activation may well be compatible with reports (40) indicating that patients with more severe heart failure derive benefit from digoxin treatment. The observed negative correlation between heart rate variability at baseline and after treatment also suggests that analysis of heart rate variability may be used to identify patients with heart failure who will benefit from drug treatment. Further studies will be needed to evaluate the clinical consequences of these findings.

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