Diurnal Variation in Plasma Norepinephrine in Patients with Heart Failure

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Diurnal variation in plasma norepinephrine (PNE) levels is well documented in healthy individuals but not in patients with heart failure. Therefore, we attempted to determine variations in PNE levels over 24 hours, measured hourly, in six patients with an ejection fraction below 40% and a history of heart failure of longer than 3 months. Three controls without a history of heart failure also were evaluated. Both patients and controls had diurnal variations in PNE, with highest levels occurring during the day and lowest at night. When data in patients were evaluated by 6-hour time intervals the mean value for 6:00 A.M.–12:00 noon was approximately twice as high as 12:00 midnight–6:00 A.M. (689 ± 329 vs 338 ± 166 pg/ml, $p<0.05$, respectively). Patients also had significant peak to trough variation in PNE levels compared with controls (959 ± 396 vs 386 ± 84 pg/ml, $p<0.02$, respectively). These results suggest that significant intrapatient variations in PNE occur over 24 hours in patients with heart failure. These variations may have to be accounted for when evaluating and treating patients with heart failure.
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Plasma norepinephrine is a prognostic marker for mortality and disease severity in patients with heart failure.[1–3] However, in most trials, conclusions were based on norepinephrine levels obtained at only one time throughout 24 hours. This may not be appropriate, since subjects without heart failure have significant diurnal variations in plasma norepinephrine concentrations over 24 hours.[4, 5] Peak levels occur in the morning hours and trough concentrations during sleep at night. Furthermore, in patients with heart failure, diurnal variations in other variables occur, including blood pressure, heart rate, magnesium, and another neurohormone, atrial natriuretic peptide.[6–10] However, data are very limited with regard to diurnal variations in norepinephrine concentrations, which may have important implications for studying and treating these patients.

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Methods

Six patients with heart failure and three controls (patient spouses) were enrolled in this pilot study. Inclusion criteria for patients were a confirmed diagnosis of chronic heart failure of more than 3 months' duration and secondary to ischemic or idiopathic causes, and systolic dysfunction (left ventricular ejection fraction ≤ 40%) measured within the past year. All participants had an entrained sleep-wake cycle, with sleeping hours occurring between 12:00 midnight and 5:00 A.M. minimum. Controls

Table 1. Patient Demographics

Age (yrs)	Sex	Etiology of HF	NYHA Class	Ejection Fraction (%)	Concurrent Drugs
Patients with heart failure (n=6)					
58	F	ID	I	16	Furosemide, warfarin, KCl, digoxin
61	M	IS	II	40	Furosemide, nitroglycerin, KCl, ranitidine, aspirin
78	F	ID	II	26	Digoxin, bumetanide, warfarin, KCl, quinine, aspirin, spironolactone
65	F	IS	NA	23	Enalapril, aspirin, spironolactone, quinidine, KCl, lovastatin
59	M	ID	IV	14	Digoxin, enalapril, KCl, bumetanide, warfarin, insulin
60	F	ID	II	10	Bumetanide, enalapril, KCl, levothyroxine, ranitidine, warfarin, digoxin
Controls (n=3)					
64	M				Lisinopril
61	F				Estrogen, probucol, piroxicam
66	M				None

HF = heart failure; ID = idiopathic; IS = ischemic; NYHA = New York Heart Association; NA = not available.

were excluded if they had a history of heart failure or were receiving drugs that could alter their sleep-wake cycle.

Participants were admitted to the clinical research center. A peripheral venous catheter was placed in a forearm vein, and blood samples were drawn every hour for 24 hours into chilled Vacutainer tubes containing heparin to measure norepinephrine concentrations. All samples were obtained in a darkened room with subjects lying supine for a minimum of 20 minutes. Samples were immediately placed on ice, processed, and frozen at -70°C. Subjects were required to be in bed by 11:00 P.M. and out of bed at 7:00 A.M. Meals were provided at 8:00 A.M., noon, and 5:00 P.M.

Plasma norepinephrine concentrations were determined by high-performance liquid chromatography.[11] Interday and intraday coefficient of variation was less than 10%. Cosinor analysis was performed to determine if data showed a significant rhythmic variation with respect to time. Analysis of variance and Tukey's studentized range test were used to evaluate the data when placed in specific time periods. Regression analysis and unpaired *t* tests were employed where appropriate. A p value of 0.05 or less was considered the critical level. Data are reported as mean ± SD.

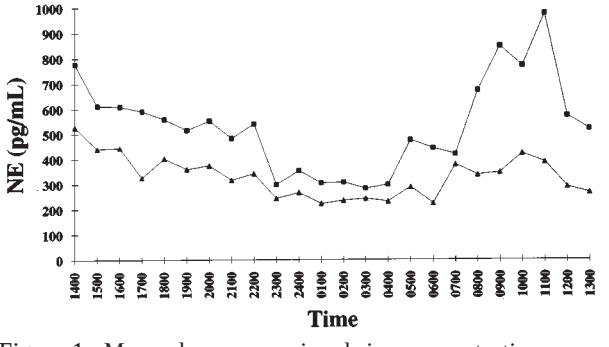

Figure 1. Mean plasma norepinephrine concentrations over 24 hours. Squares represent patients and triangles represent controls. NE = norepinephrine.

Results

Participant demographics are shown in Table 1. Five of six patients were receiving diuretics, and five were receiving angiotensin-converting enzyme inhibitors and/or digoxin. All patients had maintained a stable drug regimen for at least 2 weeks before the study. No subjects were receiving drugs that could alter sleep patterns.

The overall mean norepinephrine concentrations were 532 ± 316 pg/ml for patients and 330 ± 173 pg/ml for controls ($p<0.001$). Mean hourly norepinephrine levels for patients and controls are illustrated in Figure 1. Levels in both groups showed similar overall changes, with lowest concentrations occurring during sleep and highest while awake, with a surge in morning hours. A significant cosinor rhythm was observed in eight of the nine subjects, suggesting diurnal variation in concentrations. When the data were evaluated by time intervals (Table 2), the highest mean levels of norepinephrine occurred between 6:00 A.M. and noon in patients and between noon and 6:00 P.M. in controls. In fact, in patients with heart failure, the mean value for 6:00 A.M.–noon was twice as high as that for midnight–6:00 A.M., which was statistically significant ($p<0.05$).

When mean norepinephrine levels were

Table 2. Mean Norepinephrine Levels (pg/ml) over 6-Hour Intervals

Time	Patients	Controls
6:00 A.M.–noon	689 ± 329	349 ± 147
Noon–6:00 P.M.	613 ± 249	382 ± 166
6:00 P.M.–midnight	492 ± 206	341 ± 222
Midnight–6:00 A.M.	338 ± 166[a]	248 ± 127

[a]$p<0.05$ compared with 6:00 A.M.–noon.

correlated with levels at each time point, regression values were for the most part high (Figure 2). The highest values occurred in the afternoon between noon and 6:00 P.M. (0.78–0.98). When peak levels were correlated with each time point, the correlations were overall lower except in the morning to early afternoon (9:00 A.M.–1:00 P.M.; Figure 3).

In addition to diurnal variations, large intrapatient variability in concentrations was seen especially in patients with heart failure. The mean difference in peak to trough concentrations in this group was significantly higher than in controls (959 ± 396 vs 386 ± 84 pg/ml, $p<0.02$, respectively). Mean values for the hour-to-hour variation were 153 ± 105 pg/ml in patients and 84 ± 50 pg/ml in controls ($p<0.01$). For patients, the lowest hour-to-hour variation occurred during sleep and the highest between 8:00 A.M. and noon (Figure 4).

Discussion

The results of this study reveal that patients with mild heart failure have diurnal variations in plasma norepinephrine, with the highest concentrations occurring in the morning hours and the lowest at night. This is similar to control subjects. However, patients had greater variation in concentrations within 24 hours than controls, as demonstrated by differences in peak to trough concentrations and hour-to-hour variations. Levels measured at each time point appear to reflect overall mean norepinephrine levels but do not routinely reflect peak levels.

Such variations in patients and controls are similar to what was reported in subjects without heart failure.[4, 5] One group investigated norepinephrine levels in patients with heart failure over 24 hours.[12] However, interpretation of this study is difficult since mean values at each time point were not reported and cosinor analysis appeared not to be employed. This study did suggest that patients with heart failure had less daytime variability than controls, although, it appears that patients in that study had a higher mean amplitude (difference between peak and trough concentrations)[13] than controls. The mean amplitude values we calculated were 217 ± 479 pg/ml for patients and 44 ± 24 pg/ml for controls, approximately a 4-fold difference, which is similar to our findings.

Levels we obtained during waking hours were highly correlated with the 24-hour mean level. This suggests that levels may be measured at any time during waking hours without regard to diurnal variation. Another group found a similar correlation between the level at 8:00 A.M. and the overall mean level (r=0.78) but did not test other time points.[12] However, we found that levels at each time period were not highly correlated with peak levels except for a few time points in the morning and early afternoon (9:00 A.M.–1:00 P.M.). Thus a single level measured at any time point may not be adequate to reflect peak levels. Unfortunately, it is difficult to interpret these findings for the clinical setting since it is not known whether mortality or morbidity is better

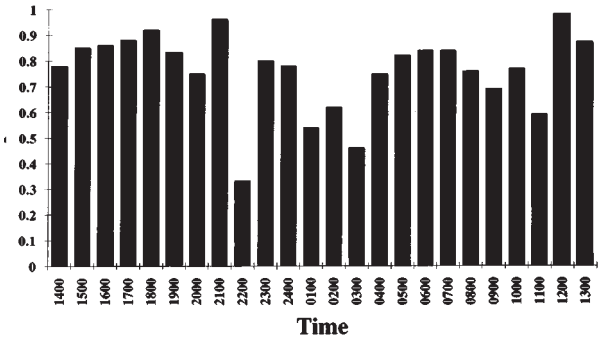

Figure 2. Correlation coefficients between overall mean norepinephrine concentrations and concentrations at each measured time point in patients. r = correlation coefficient.

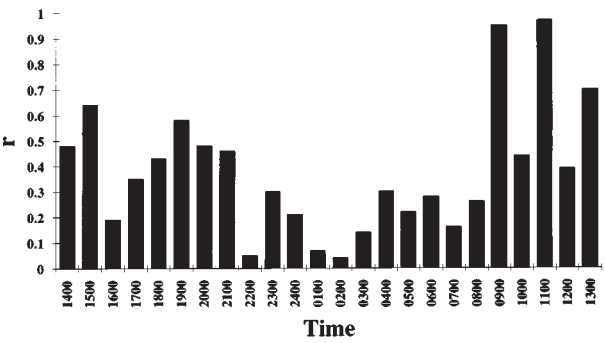

Figure 3. Correlation coefficients between peak norepinephrine concentrations and concentrations at each measured time point in patients. r = correlation coefficient.

correlated with 24-hour mean levels or peak levels in patients with heart failure. At this time, since previous studies evaluating the relationship between norepinephrine levels and outcomes examined only one level, it may be reasonable to conclude that they reflected a patient's mean level when evaluated over 24 time points.

However, the results of this study raise an important question as to whether mean or peak norepinephrine concentrations are the most important with regard to outcomes in patients with heart failure. Since a single level is likely not to reflect peak concentrations, only one measurement may not be adequate for quantifying peak concentrations. It should be noted that overall, most cardiovascular events occur in the morning hours and may be related in part to a surge in catecholamine levels during that time.[13, 14] Thus quantifying peak norepinephrine concentrations may be more important than quantifying mean concentrations.

Another concern raised by this study, despite the high correlation between time points and mean levels, is the high hour-to-hour variability in levels. Since the correlation between mean levels and individual time points is not equal to 1, a norepinephrine level measured at one time point may suggest one prognosis and at the next time point another prognosis. This concern is especially apparent in the morning hours when the highest hour-to-hour variation occurred. Theoretically, based on current practice of measuring only one level, a patient's prognosis may change depending on what time of day the level is drawn. Future studies in which norepinephrine concentrations are determined may have to take into account this variation by measuring several levels over 24 hours.

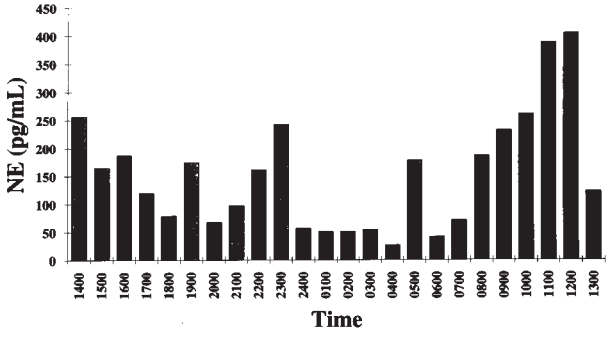

Figure 4. Mean difference in norepinephrine concentrations measured from one time point to the next in patients. NE = norepinephrine.

In addition to the diurnal variations in norepinephrine levels observed in this study, blood pressure, heart rate, and magnesium and atrial natriuretic peptide concentrations are associated with diurnal variations in patients with heart failure.[6–10] However, in some cases, the magnitude of these variations may be less than in controls. Limited data suggest that for blood pressure, heart rate, and atrial natriuretic peptide, as the severity of heart failure worsens, as determine by functional class or ejection fraction, the variability in these values decreases.[6, 10] This may explain some of the differences between our study and an earlier one,[12] since that group evaluated only patients with classes III and IV heart failure, whereas five of our six patients had class I or II disease. However, this finding does not explain why one patient did not show a significant cosinor rhythm for norepinephrine concentrations. Perhaps other unknown factors contribute to norepinephrine variability in patients with heart failure.

This study has several limitations including the small number of subjects. However, our findings are consistent with other reports with regard to diurnal variations in plasma norepinephrine, so the number of patients evaluated, methods, and results are probably appropriate.[4, 5] Another limitation is that the patients had mild disease. Potentially, patients with more severe heart failure may have less variability than we observed. In addition, the study enrolled a heterogeneous population consisting of patients with both ischemic and idiopathic cardiomyopathies, which limits interpretation of data. Not all patients were taking the same drugs, which also theoretically affect our results and contribute to the variability; however, most patients were receiving standard therapy. Furthermore, no available data suggest that drugs, including β-blockers, alter overall circadian patterns. Drugs may limit peak or trough variation in a circadian pattern, but the overall pattern remains intact. Digoxin theoretically may increase variability in norepinephrine levels over that in patients not receiving the agent, if it restores sympathetic and parasympathetic balance.

The diurnal variations and hour-to-hour variations in norepinephrine levels in patients with mild heart failure may have to be accounted for when evaluating norepinephrine for prognostic purposes, in designing research trials, and potentially for prescribing optimal drug therapy.

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