Circ J 2004; **68:** 343 – 347

Very Low Frequency Power of Heart Rate Variability is a Powerful Predictor of Clinical Prognosis in Patients With Congestive Heart Failure

Mitsuyoshi Hadase, MD; Akihiro Azuma, MD; Kan Zen, MD; Satoshi Asada, MD*; Tatsuya Kawasaki, MD*; Tadaaki Kamitani, MD*; Shingo Kawasaki, MD*; Hiroki Sugihara, MD*; Hiroaki Matsubara, MD

Background The present study examined whether the very low frequency (VLF) power of heart rate variability (HRV) is predictive of clinical prognosis in patients with congestive heart failure (CHF).

Method and Results The study recruited 54 consecutive CHF patients with emergency admission because of exacerbation of pulmonary congestion. Holter monitoring was performed after improvement of pulmonary congestion. The frequency components of HRV were calculated in the frequency domain (VLF, low frequency (LF), high frequency (HF), total power (TP) and the ratio of LF to HF power). The left ventricular ejection fraction was calculated, and plasma brain natriuretic peptide (BNP) and norepinephrine were also measured at discharge. Within a mean follow-up period of 19.8±11.7 months, 18 patients experienced cardiovascular events; 7 patients died and 11 patients required rehospitalization because of worsening of CHF. In univariate analysis, diabetes mellitus (DM), BNP and New York Heart Association (NYHA) functional class were significant as risk factors for cardiac events. VLF power, LF power and TP were the strong predictors for cardiac events in HRV. In multivariate analysis, VLF power predicted cardiac events independently of LF power, TP, DM, BNP and NYHA functional class (chi-square = 6.24, p=0.01).

Conclusions VLF power is an independent risk predictor in patients with CHF. (*Circ J* 2004; **68:** 343 – 347)

Key Words: Congestive heart failure; Heart rate variability; Prognosis; Very low frequency power

Analysis of heart rate variability (HRV) is a noninvasive method of assessing the autonomic balance in the cardiovascular system[1,2] As many commercial devices now provide an automated measurement of HRV, the cardiologist seemingly has a simple tool for both research and clinical studies[3–6] Impaired regulation of the cardiac autonomic nervous system is one of the most important pathophysiologic changes in patients with congestive heart failure (CHF)[7,8] and several previous studies have suggested that HRV provides important prognostic information in these patients[9,10] It has been reported that the very low frequency (VLF) power spectral components of HRV are an independent risk stratifier for all-cause mortality and sudden death in patients with acute myocardial infarction[11,12] Similarly, Huikuri et al reported that the VLF power of HRV was the strongest independent predictor of ventricular tachycardia in patients with a prior myocardial infarction[13] However, it is not yet known whether the VLF power of HRV can predict cardiac events in patients with CHF and so the purpose of the present study was to determine the usefulness of the VLF as a predictor of prognosis in such patients.

(Received November 11, 2003; revised manuscript received January 6, 2004; accepted January 22, 2004)

*Department of Cardiology, Kyoto Prefectural University of Medicine, Kyoto and *Department of Cardiology, Matsushita Memorial Hospital, Osaka, Japan*

Mailing address: Mitsuyoshi Hadase, MD, Department of Cardiology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: hadase@msj.biglobe.ne.jp

Methods

Study Design

All CHF patients with normal sinus rhythm who were hospitalized for progressive heart failure from April 2000 to August 2003 were enrolled in this study. The diagnosis of CHF was based on a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion, documentation of left ventricular enlargement or dysfunction by physical examination, chest X-ray film, or echocardiography. All patients were prescribed standard medications including digoxin, angiotensin-converting enzyme inhibitors, diuretics, and β-blockers in various combinations. We followed the patients after hospital discharge following improvement of CHF. The endpoint of this study was a cardiac event defined as either cardiac death or readmission because of worsening of CHF.

HRV Analysis

All patients underwent 2-channel 24-h Holter ambulatory electrocardiographic (ECG) monitoring after improvement of pulmonary congestion or peripheral edema. A conventional estimate of rhythm disturbances was first performed using a MARS 8000 scanner version 4.0A of the arrhythmia analysis software (Marquette Medical Systems, Milwaukee, WI, USA). Second, spectral analysis of HRV was performed using a MARS 8000 HRV program version 4.0A as previously described[14,15] Briefly, after arrhythmia analysis, spectral plots were computed for every 5-min segment with a 1,024-point fast Fourier transformation and the power spectra were quantified. In the present study, we

Table 1 Basic Characteristics of the Patients With Congestive Heart Failure (CHF)

	CHF with events	CHF without events	p value
	n=18	n=36	
Age (years)	72.0±9.1	68.0±12.6	0.20
Female	10 (56%)	13 (36%)	0.20
Complication			
Systolic hypertension	13 (72%)	19 (53%)	0.17
Hyperlipidemia	7 (39%)	11 (31%)	0.56
Diabetes mellitus	10 (56%)	8 (22%)	0.024
Medication			
β-blockers	11 (61%)	18 (50%)	0.45
ACE-inhibitors	10 (56%)	27 (75%)	0.18
Ca-antagonists	7 (39%)	12 (33%)	0.70
Diuretics	16 (83%)	31 (83%)	0.77
Digitalis	7 (39%)	8 (22%)	0.24
Established risk predictor			
NYHA fuctional class	2.7±0.8	2.1±0.8	0.011
LVEF	40.0±19.6	44.3±19.1	0.53
BNP	500±568	180±263	0.034
NE	577±410	468±238	0.32

CHF patients with cardiac events had a higher incidence of diabetes mellitus than patients without events.
CHF, congestive heart failure; ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; NE, norepinephrine.

Table 2 Relation Between Heart Rate Variability and Cardiac Events

Variable	CHF with events	CHF without events	p value
VLF In (ms^2)	5.16±0.93	6.19±0.98	0.0007
LF In (ms^2)	3.84±1.16	4.78±1.18	0.0087
HF In (ms^2)	3.75±1.08	4.21±1.05	0.14
TP In (ms^2)	5.99±0.89	6.89±0.94	0.0017
LF/HF	1.05±0.23	1.15±0.17	0.10

The values of VLF power, LF power and TP were significant for cardiac events ($p<0.05$). VLF, very low frequency; LF, low frequency; HF, high frequency; TP, total power; LF/HF, low-frequency/high-frequency ratio.

Table 3 Multivariate Analysis of Selected Variables for Cardiac Events

Variable	Chi-square	p value
VLF In (ms^2)	6.24	0.01
LF In (ms^2)	2.21	0.13
TP In (ms^2)	4.20	0.04
Diabetes mellitus	3.43	0.06
NYHA functional class	1.70	0.19
BNP (pg/ml)	2.29	0.13

VLF power and BNP remained independent and VLF power was the most powerful predictor for cardiac events.
VLF, very low frequency; LF, low frequency; TP, total power; NYHA, New York Heart Association; BNP, brain natriuretic peptide.

computed the 24-h power spectral density and calculated the power within 3 frequency bands: very low frequency (VLF: 0.0033–0.04 Hz); low frequency (LF: 0.04–0.15 Hz), which reflects modulation of sympathetic or parasympathetic tone by baroreflex activity[16] and high frequency (HF: 0.15–0.40 Hz), which reflects modulation of vagal tone, primarily by breathing.[17,18] In addition, we calculated the total power (TP: 0–0.40 Hz) and the ratio of LF to HF power, a measure that has been used as an indicator of sympathovagal balance,[2] making a total of 5 frequency bands that were measured.

New York Heart Association (NYHA) Functional Class, LVEF, BNP and NE

The NYHA functional class was quantitatively estimated using the specific activity scale question.[19] Resting ECG-gated ^{99m}Tc perfusion imaging, the neurohormonal measurements and the specific activity scale questionnaire were examined after improvement of pulmonary congestion at approximately the same time as the Holter recording.

Resting ECG gated ^{99m}Tc perfusion imaging was obtained 30 min after injection of 600 MBq of ^{99m}Tc perfusion tracer (^{99m}Tc single photon emission computed tomography image). Images were gated at 16 frames/cycle. The left ventricular ejection fraction (LVEF) was automatically calculated from the resting ECG gated ^{99m}Tc perfusion imaging as a parameter of ventricular function using previously validated and commercially available automated software (QGS, Cedars-Sinai Medical Center, Los Angeles, CA, USA).[20]

Participants were allowed to rest in the supine position in a quiet room for 30 min in the morning after intravenous cannulation. Blood was collected for analysis of brain natriuretic peptide (BNP) and norepinephrine (NE). The sample was separated within 20 min, and the plasma was stored at –20°C before transport on dry ice to the assay laboratory. Assays for BNP and NE were conducted according to established methods.[21,22]

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and were assessed using an unpaired Student's t-test. Categorical variables are reported as absolute and relative frequencies, and were compared using a chi-square test. The difference in the grading of the NYHA functional class was tested with a Mann-Whitney U test. Multivariate regression analysis was performed on the variables with $p<0.05$ in univariate analysis and used to identify independent predictors for cardiac events. To analyze the predictive value of variables, we constructed receiver operating characteristic curves and determined the suitable cutoff point where sensitivity is as nearly equal to specificity as possible. The event-free curve was compared with Kaplan-Meier analysis using the log-rank test. Results of all prognostic analyses were presented as relative risks with corresponding 95% confidence intervals. A p-value <0.05 was considered statistically significant. Statistical analysis was performed with StatView 5.0 (SAS Institute).

Results

Patient Recruitment and Follow-up

A total of 65 patients were recruited and follow-up data were available for 63 (94%). Two patients dropped out because they stopped having medical check-ups. Of the 63 patients, 9 were excluded because of in-hospital death. the final study group comprised 54 CHF patients (31 men, 23 women; age, 69.4±11.6 years): 24 (44%) had an old myocardial infarction, 10 (19%) had dilated cardiomyopathy and 10 (19%) had valvular heart disease (aortic stenosis in 4, aortic regurgitation in 1, mitral stenosis in 3 and mitral regurgitation in 2). Study patients were treated with β-blockers (54%), angiotensin-converting enzyme inhibitors (69%), Ca-antagonist (35%), diuretics (87%) and digoxin (28%). There were 17 patients (34%) with a history of diabetes mellitus (DM). At hospital discharge, 13 patients were in NYHA functional class I, 14 in class II, 24 in class

III and the remaining were in class IV. The LVEF derived from the resting ECG gated ^{99m}Tc perfusion imaging was 44%.

Follow-up was completed in August 2003. Within a mean follow-up period of 19.7 months (range, 0.6–39.9 months), cardiac events occurred in 18 patients: 3 died suddenly, 4 died of progressive heart disease, and 11 were re-hospitalized for worsening pulmonary congestion. The baseline characteristics for patients with and without cardiac events are listed in Table 1. CHF patients with cardiac events tended to be older and there was a higher incidence of females than in the patients without events, but without statistical significance. The incidence of systolic hypertension, hyperlipidemia, and base-line medications including β-blockers, angiotensin-converting enzyme inhibitors, diuretics and digitalis were similar. CHF patients with cardiac events had a higher incidence of DM than patients without events. In addition, BNP and NYHA functional class were different between the 2 groups.

Relation Between HRV and Cardiac Events

All five 24-h average spectral indices of HRV between the CHF patients with and without cardiac events are shown in Table 2. VLF power, LF power and TP were significantly different between the 2 groups. VLF power was the most powerful risk stratifier in HRV. In multivariate analysis, of VLF power, LF power, TP, DM, NYHA functional class and BNP, VLF power was the independent predictor for cardiac events (chi-square=6.24, p=0.01) (Table 3).

The receiver-operating characteristic analysis indicated that VLF power=6.0 ln (ms^2) was the suitable cutoff point for predicting cardiac events (Fig 1). Among 28 patients with VLF power <6.0 ln (ms^2), 15 (53.6%) had a cardiac event, whereas only 3 (11.5%) of 26 patients with VLF power ≥6.0 ln (ms^2) experienced such an event. Thus, VLF power <6.0 ln (ms^2) predicted cardiac events with 66.7% sensitivity and 63.8% specificity. Fig 2 shows the Kaplan-Meier cumulative event-free curve for VLF power. The 3.3-year event free rate was 45% of CHF patients with VLF power <6.0 ln (ms^2) and was 87% in CHF patients with VLF power ≥6.0 ln (ms^2).

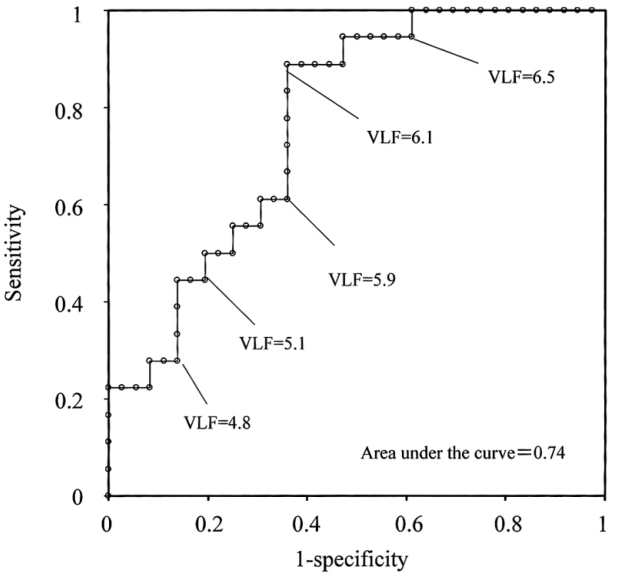

Fig 1. Receiver-operating characteristic curve for determining the optimal cutoff value of the very low frequency (VLF) power for predicting cardiac events. Each actual number denotes the cutoff value for VLF power.

Discussion

Measures of HRV as Risk Predictors in CHF

Patients with heart failure have abnormalities of the autonomic nervous system, typified by increased sympathetic activity, decreased vagal tone and depressed baroreceptor responsiveness[23,24] HRV is determined by a complex interaction of sympathetic and parasympathetic influences, which are modulated by central and peripheral nervous system influences on sinus node automaticity. LF power is a measure of the modulation of vagal and sympathetic tone by baroreflex activity[16] whereas HF power is a pure measure of the modulation of vagal tone by respiratory frequency and depth[17,18] and together, they account for only approximately 6% of the total power in the 24-h heart rate power spectrum; however, VLF power constitutes the majority of the TP in HRV. In the present study, we demonstrated that HRV analysis could be useful for predicting

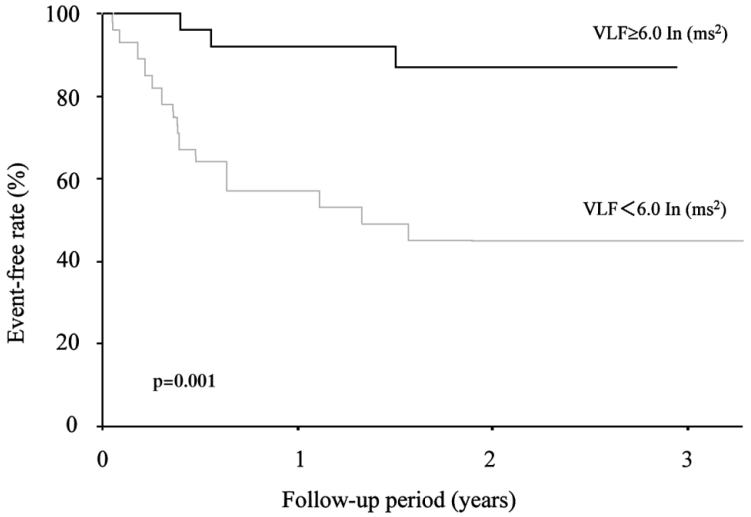

Fig 2. Kaplan-Meier cumulative event-free curve in congestive heart failure (CHF) patients stratified to those with very low frequency (VLF) power <6.0 ln (ms^2) and ≥6.0 ln (ms^2). The 3-year event-free rate was 45% of CHF patients with a VLF power <6.0 ln (ms^2) and was 87% in CHF patients with a VLF power ≥6.0 ln (ms^2).

cardiac events in patients with CHF. We found that depressed HRV measures were associated with a higher risk of cardiac events. Among the spectral measures of HRV, the VLF component was the most powerful and independent predictor of cardiac events in patients with CHF. Because it had been reported that VLF power had an interesting relation with arrhythmic death after myocardial infarction[13] we explored the capability of VLF power to predict cardiac events in patients with CHF, most of which were worsening of CHF. This is a potentially important and surprising finding because it might be expected that the measures of HF and LF, which are more closely associated with autonomic function or baroreflex gain, might be better indexes of prognosis[16–18]

Several drugs are now available that favorably influence HRV in patients with CHF. Recent data indicate that β-blockers and digoxin prevent death from progressive heart failure, and this effect may be mediated in part by the beneficial effect that these agents have on neuroendocrine function[25,26] Patients with a VLF power <6.0 In (ms^2) are at considerable risk of cardiac events and may have the most to gain from the prescription of additional drug therapy.

Comparison With Other Risk Predictors to Identify High-Risk Patients With CHF

In this study, VLF power was a more powerful risk stratifier than other established risk predictors such as NYHA functional class, BNP, LVEF and NE. CHF is a very common clinical disorder; with noninvasive cardiac testing revealing that as many as one-third of these patients have normal left ventricular systolic function, implicating diastolic dysfunction as the primary cause of their symptoms[27,28] Because the present study also involved many CHF patients with normal systolic function, so LVEF and NE tended to be improved after therapy and they might not be significant. On the other hand, BNP is a neurohormone secreted mainly in the cardiac ventricles in response to volume expansion and pressure overload[29,30] Its concentration is elevated in patients with left ventricular dysfunction, which correlates with the severity as well as the prognosis[31,32] Furthermore, Lubien et al found that BNP could reliably detect the presence of diastolic abnormalities[33] BNP sharply reflects cardiac stress, so BNP might be more a powerful risk stratifier than LVEF, NE and NYHA functional class in this study.

Abnormal Respiration Pattern in CHF

Nocturnal Cheyne-Stokes respiration (CSR) occurs frequently in patients with CHF and may be associated with sympathetic activation[34] Recently, it have been shown that CSR has a negative effect on survival in patients with CHF[35] On the other hand, Mortara et al have reported that CSR is related to the VLF power in patients with CHF and that CSR lead to a marked increase in HRV, particularly by giving rise to a dominant oscillation in the VLF power[36] That is, it is possible that HRV will be increased in patients with CSR. We have to take into consideration that unexpected abnormalities of respiration may distort HRV and mask prognostic information in patients with CHF.

Mechanistic Implications of the Association Between VLF Power and Prognosis in CHF

VLF power accounts for more than 90% of the total power in the 24-h heart rate power spectrum, but the physiological mechanisms for VLF power have not been identified. VLF power in part reflect thermoregulatory mechanisms, fluctuation in activity of the renin–angiotensin system, and the function of peripheral chemoreceptors[37,38] Recently, Mortara et al[36] and Bernardi et al[39] both reported that respiratory pattern and physical activity are important modulators of VLF power. Abnormal breathing patterns and physical inactivity are common in CHF patients and concerns have been raised as to whether this will limit the prognostic utility of VLF power. It is possible that reduced VLF power will reflect the reduction of the cardiac defensive response toward external stress and will correlate with cardiac events in CHF patients. In addition, VLF power may reflect not only cardiac stress but also general systemic stress. We believe that it will be exciting and important to determine the source of the VLF power spectrum because the VLF power is such a powerful predictor in CHF and the better understanding of the origin of VLF may lead to hypotheses of interventions aimed at improved survival.

Study Limitations

First is the influence of drugs on the HRV parameters. Many of drugs prescribed to the present patients may have influenced the activity of the autonomic nervous system; however, baseline medications were not different between the cardiac and non-cardiac groups, so the influence of drugs is thought to be trivial in this study. Second, diabetic patients were included. Decreased HRV has been shown to be a sign of autonomic nervous system dysfunction in the diabetic patients, which might have a bearing on the result that VLF power and DM were significantly different between the patients with cardiac events and those without cardiac events in this study. However, as VLF power predicted cardiac events independently of DM in multivariate analysis, it is thought that the VLF power has a close relation to the severity of CHF independently of DM. Finally, the study population in this study was small and therefore larger numbers are necessary to confirm whether VLF power can predict cardiac events in the patients with CHF.

In conclusion, the result of this study indicate that VLF power is a powerful and independent risk predictor in patients with CHF.

Acknowledgments

The authors gratefully acknowledge the expert technical assistance of E Hiramatsu, J Murase, C Ueki, and K Higashiyama.

References

1. Akselrod S, Gordon D, Ubel FA, Shanno DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; **213:** 220–222.
2. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; **59:** 178–193.
3. Abe Y, Tamura A, Nasu M. Relationship between heart rate variability and left ventricular remodeling after reperfused first anterior wall acute myocardial infarction. *Circ J* 2003; **67:** 225–228.
4. Abe Y, Tamura A, Nasu M. Effect of preinfarction angina on heart rate variability in the early phase of the first anterior wall acute myocardial infarction. *Circ J* 2002; **66:** 431–434.
5. Nakazawa K, Sakurai T, Takagi A, Kishi R, Osada K, Nanke T, et al. Autonomic imbalance as a property of symptomatic Brugada syndrome. *Circ J* 2003; **67:** 511–514.
6. Li A, Kuga K, Suzuki A, Endo M, Niho B, Enomoto M, et al. Effects of linear ablation at the isthmus between the tricuspid annulus and inferior vena cava for atrial flutter on autonomic nervous activity:

Analysis of heart rate variability. *Circ J* 2002; **66:** 53–57.
7. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; **311:** 819–823.
8. Packer M. Modulation of functional capacity and survival in congestive heart failure: Effects of activation of the sympathetic nervous system. *Postgrad Med* 1988; **83:** 96–103.
9. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, et al. Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998; **98:** 1510–1516.
10. Woo MA, Stevenson WG, Moser DK, Middlekauff HR. Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. *J Am Coll Cardiol* 1994; **23:** 565–569.
11. Bigger JT Jr, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. *J Am Coll Cardiol* 1993; **21:** 729–736.
12. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; **85:** 164–171.
13. Huikuri HV, Koistinen MJ, Yli-Mayry S, Airaksinen KE, Seppanen T, Ikaheimo MJ, et al. Impaired low-frequency oscillations of heart rate in patients with prior acute myocardial infarction and life-threatening arrhythmias. *Am J Cardiol* 1995; **76:** 56–60.
14. Albrecht P, Cohen RJ. Estimation of heart rate power spectrum bands from real-world data: Dealing with ectopic beats and noisy data. *Comput Cardiol* 1988; **15:** 311–314.
15. Rottman JN, Steinman RC, Albrecht P, Bigger JT Jr, Rolnitzky LM, Fleiss JL. Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. *Am J Cardiol* 1990; **66:** 1522–1524.
16. Koizumi K, Terui N, Kollai M. Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmic regulations. *J Auton Nerv Syst* 1985; **12:** 251–259.
17. Katona PG, Jih F. Respiratory sinus arrhythmia: Measure of the parasympathetic cardiac control. *J Appl Physiol* 1975; **39:** 801–805.
18. Fouad FM, Tarazzi RC, Ferrario CM, Fighaly S, Alicandri C. Assessment of parasympathetic control of heart rate by a noninvasive method. *Am J Physiol* 1984; **246:** H838–H842.
19. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation* 1981; **64:** 1227–1234.
20. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; **36:** 2138–2147.
21. Yandle TG, Richards AM, Gilbert A, Fisher S, Holmes S, Espiner EA. Assay of brain natriuretic peptide (BNP) in human plasma: Evidence for high molecular weight bnp as a major plasma component in heart failure. *J Clin Endocrinol Metab* 1993; **76:** 832–838.
22. Goldstein DS, Feuerstein G, Izzo JL Jr, Kopin IJ, Keiser HR. Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. *Life Sci* 1981; **28:** 467–475.
23. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990; **82:** 1724–1729.
24. Ferguson DW, Berg WJ, Roach PJ, Oren RM, Mark AL. Effects of heart failure on baroreflex control of sympathetic neural activity. *Am J Cardiol* 1992; **69:** 523–531.
25. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity in patients with chronic heart failure. *N Engl J Med* 1996; **3334:** 1349–1355.
26. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336:** 525–533.
27. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. *Am J Cardiol* 1984; **54:** 778–782.
28. Soufer R, Wohlgelernter D, Vita NA, Amuchestegui M, Sostman HD, Berger HJ, et al. Intact systolic left ventricular function in clinical congestive heart failure. *Am J Cardiol* 1985; **55:** 1032–1036.
29. Grantham JA, Borgeson DD, Burnett JC Jr. BNP: Pathophysiological and potential therapeutic roles in acute congestive heart failure. *Am J Physiol* 1997; **272:** R1077–R1083.
30. Yandle TG. Biochemistry of natriuretic peptides. *J Intern Med* 1994; **235:** 561–576.
31. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; **96:** 509–516.
32. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; **105:** 2392–2397.
33. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of b-natriuretic peptide in detecting diastolic dysfunction: Comparison with doppler velocity recordings. *Circulation* 2002; **105:** 595–601.
34. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Rrespir Crit Care Med* 1995; **152:** 473–479.
35. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999; **99:** 1435–1440.
36. Mortara A, Sleight P, Pinna GD, Maestri R, Prpa A, La Rouvere MT, et al. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. *Circulation* 1997; **96:** 246–252.
37. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; **84:** 482–492.
38. Parati G, Saul JP, Di Rieuzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: A critical appraisal. *Hypertension* 1995; **25:** 1276–1286.
39. Bernadi L, Valle F, Coco M, Calciati A, Sleight P. Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. *Cardiovasc Res* 1996; **32:** 234–237.