EDITORIAL

Heart Rate Variability: Recent Developments

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Without heart beat there would not be human life. Without heart rate variability (HRV) life would be shorter. Throughout the history of medicine, there has been an interest in heart rate. Since Kleiger et al. 1987 published the landmark study showing that HRV is an indicator of long-term prognosis after an acute myocardial infarction,¹ the research in the field has increased exponentially.² Several methods of HRV have been used to describe different components of the complex regulatory system between heart rate and the autonomic nervous system. Time-domain and frequency-domain measures can be considered classic methods for measuring HRV. Recently, there has been growing interest in nonlinear methods of HRV as these methods may reveal more delicate changes in heart rate dynamics than conventional HRV measurements.³

Decreased values of conventional HRV measures have been associated with an increased risk of mortality in postinfarction,^{1,4,5} and heart failure patients.⁶ Previous studies support the concept that decreased HRV is also associated with sudden arrhythmic death in postinfarction patients,⁷ but this issue can reliably be resolved only in large-scale prospective follow-up studies including patients with implantable cardioverter defibrillators (ICDs). Long-term 24-hour electrocardiographic (ECG) recordings usually are used in HRV analysis. However, short-term ECG recordings have been suggested to be sufficient to yield data about conventional HRV measures in predicting mortal-

ity.^{8,9} In recent studies, some of the newer nonlinear measures of HRV have been suggested to be better predictors of mortality than traditional methods.¹⁰⁻¹⁴ The power-law slope β describing long-term fractal-like heart rate behavior has been shown to be more powerful predictor of mortality than conventional markers in the elderly.¹² More negative values of β have been associated with increased mortality,^{10,11,15} and precede the spontaneous onset of ventricular fibrillation in postinfarction patients.¹⁶ Furthermore, postinfarction studies have suggested that reduced short-term scaling exponent α_1 measuring short-term fractal-like scaling properties of heart rate dynamics is a more powerful predictor of mortality than conventional HRV measures^{10,11} and that low α_1 values are associated with vulnerability to ventricular tachycardia,¹⁷ ventricular fibrillation,¹⁶ arrhythmic death, and nonarrhythmic cardiac death.¹¹ Recent observations in a relatively small group of high-risk patients with ICDs show that α_1 obtained from short-term 10-minute ECG recordings yields important prognostic information about the risk of appropriate ICD shocks/death or death alone.¹³ The short-term scaling exponent α_1 has also been suggested to be a specific risk marker of cardiac death, particularly sudden cardiac death, in the elderly.¹⁸ Some of the nonlinear HRV measures, such as the short-term scaling exponent, have some advantages over the conventional HRV measures considering risk stratification purposes. These advantages include: less dependency on heart rate, less inter-

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individual variation,^{19,20} smaller relative changes of individual values over time after an acute myocardial infarction,²⁰ and relatively good comparability of individual values between long-term and short-term ECG recordings.²¹

In this issue of the *Annals of Noninvasive Electrocardiology* three original studies provide important incremental information about HRV. Ridha et al. found that carvedilol, a nonselective beta-blocker with alpha-1 blocking properties, improves the short-term scaling properties of heart rate dynamics and most of the conventional HRV parameters in patients with heart failure. Their observations are in agreement with previous findings that have shown that beta-blocker therapy increases the conventional measures of HRV.²²⁻²⁴ However, this increase in the conventional HRV measures partly has been attributed to the decrease in heart rate. Recent data suggest that the beta-blocker therapy with atenolol (antiadrenergic modulation) increases the short-term scaling exponent in patients with congestive heart failure, indicating the reversal of the deteriorated heart rate scaling behavior.²⁵ The present findings by Ridha et al. extend this observation to carvedilol, a nonselective beta-blocker with alpha-1 blocking properties. Recent findings in healthy men show that noradrenaline (adrenergic modulation) decreases the short-term scaling exponent α_1 (26). These notions are interesting in light of previous data that show that high levels of plasma noradrenaline increases²⁷ and beta-blocker therapy decreases mortality in patients with heart failure.^{27,28}

In another article in the present issue, Tateishi et al. present a novel idea of using power spectrum of HRV at the Cheyne-Stokes breathing (CSB) band in detecting this abnormal respiratory pattern in patients with congestive heart failure. They show that increased HRV at the CSB band adjusted to very low frequency power of power spectrum can predict the risk for readmission to a hospital due to worsening of heart failure. These findings provide a good example of the versatility of possible HRV analysis applications. In addition, these observations remind us how important it is to take into account respiratory patterns in the interpretation of the spectral analysis findings of HRV.³⁰

The analysis of HRV can give insight into various pathophysiological processes including the progression of focal coronary atherosclerosis.³¹ Furthermore, percutaneous transluminal coronary angioplasty (PTCA) has served as a model for

ischemia and reperfusion in many studies using HRV. In the present issue, Kanadasi et al. contribute to this scientific literature by showing that the reduction of HRV after PTCA is associated with restenosis risk score and the degree of revascularization.

Despite many advancements, the analysis of HRV is still mainly a researcher's tool. Before it can be a useful tool for clinicians, at least the following questions have to be answered: What method(s) of HRV analysis should be used in clinical settings? What would be a recommendable length of ECG recording? Under what kind of conditions should the ECG recordings be done? What are the recommended cut-points of selected HRV measures for risk stratification purposes in different cardiac conditions, in similar cardiac conditions with different degrees of left ventricular dysfunction and heart failure, and in different age and gender groups? What is the accuracy of selected HRV measures in predicting different adverse events in different cardiac conditions? What would be the expected benefits of HRV analysis to patients' further evaluation and treatment? Could the HRV analysis be used in the patients' follow-up, etc.? The treatments of cardiac patients are continuously developing. It would be important to identify good noninvasive methods for risk stratification. Hopefully, after further developments and standardization, the analysis of HRV will, in the near future, serve as a useful aid for preselection of cardiac patients for more focused evaluation and treatment.

REFERENCES

1. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256-262.
2. Huikuri HV, Mäkikallio T, Airaksinen KEJ, et al. Measurement of heart rate variability: A clinical tool or a research toy? *J Am Coll Cardiol* 1999;34:1878-1883.
3. Perkiömäki JS, Mäkikallio TH, Huikuri HV. Nonlinear analysis of heart rate variability: fractal and complexity measures of heart rate behavior. *Ann Noninvas Electrocardiol* 2000;5:179-187.
4. Zuanetti G, Neilson JM, Latini R, et al. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. *Circulation* 1996;94:432-436.
5. Bigger JT, Fleiss J, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164-171.
6. Nolan J, Batin PD, Andrews R, 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.

7. Lombardi F, Mäkikallio TH, Myerburg RJ, et al. Sudden cardiac death: role of heart rate variability to identify patients at risk. *Cardiovasc Res* 2001;50:210-217.
8. Bigger JT, Fleiss JL, Rolnitzky LM, et al. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation* 1993;88:927-934.
9. Fei L, Copie X, Malik M, Camm AJ. Short- and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. *Am J Cardiol* 1996;77:681-684.
10. Mäkikallio TH, Høiber S, Køber L, et al. the TRACE Investigators. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am J Cardiol* 1999;83:836-839.
11. Huikuri HV, Mäkikallio TH, Peng CK, et al., for the DIAMOND Study Group. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;101:47-53.
12. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, et al. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation* 1998;97:2031-2036.
13. Perkiömäki JS, Zareba W, Daubert JP, et al. Fractal correlation properties of heart rate dynamics and adverse events in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 2001;88:17-22.
14. Mäkikallio TH, Huikuri HV, Hintze U, et al., for the DIAMOND Study Group. Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *Am J Cardiol* 2001;87:178-182.
15. Bigger JT Jr, Steinman RC, Rolnitzky LM, et al. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation* 1996;93:2142-2151.
16. Mäkikallio TH, Koistinen J, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarction. *Am J Cardiol* 1999;83:880-884.
17. Mäkikallio TH, Seppänen T, Airaksinen KEJ, et al. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. *Am J Cardiol* 1997;80:779-783.
18. Mäkikallio TH, Huikuri HV, Mäkikallio A, et al. Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J Am Coll Cardiol* 2001;37:1395-1402.
19. Pikkujämsä SM, Airaksinen KEJ, Mäkikallio TH, et al. Determinants and interindividual variation of R-R interval dynamics in middle-aged subjects. *Am J Physiol (Heart Circ Physiol)* 2001;280:H1400-H1406.
20. Perkiömäki JS, Zareba W, Ruta J, et al., for the IDEAL Investigators. Fractal and complexity measures of heart rate dynamics after acute myocardial infarction. *Am J Cardiol* 2001;88:777-781.
21. Perkiömäki JS, Zareba W, Kalaria VG, et al. Comparability of nonlinear measures of heart rate variability between long- and short-term electrocardiographic recordings. *Am J Cardiol* 2001;87:905-908.
22. Niemelä MJ, Airaksinen KEJ, Huikuri HV. Effect of beta-blockade on heart rate variability in patients with coronary artery disease. *J Am Coll Cardiol* 1994;23:1370-1377.
23. Sandrone G, Mortara A, Torzillo D, et al. Effects of beta-blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. *Am J Cardiol* 1994;74:340-345.
24. Keeley EC, Page RL, Lange RA, et al. Influence of metoprolol on heart rate variability in survivors of remote myocardial infarction. *Am J Cardiol* 1996;77:557-560.
25. Lin LY, Lin JL, Du CC, et al. Reversal of deteriorated fractal behavior of heart rate variability by beta-blocker therapy in patients with advanced congestive heart failure. *J Cardiovasc Electrophysiol* 2001;12:26-32.
26. Tulppo MP, Mäkikallio TH, Seppänen T, et al. Effects of pharmacological adrenergic and vagal modulation on fractal heart rate dynamics. *Clin Physiol* 2001;21:515-523.
27. Swedberg K, Eneroth P, Kjekshus J, et al., for the Consensus Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* 1990;82:1730-1736.
28. Kennedy HL. Current utilization trends for beta-blockers in cardiovascular disease. *Am J Med* 2001;110(Suppl. 5A):2S-6S.
29. Packer M, Bristow MR, Cohn J, et al., for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-1355.
30. Penttilä J, Helminen A, Jartti T, et al. Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: effects of various respiratory patterns. *Clin Physiol* 2001;21:365-376.
31. Huikuri HV, Jokinen V, Syväne M, et al., for the Lipid Coronary Angioplasty Trial (LOCAT) Study Group. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;19:1979-1985.