Heart Rate Turbulence and Heart Rate Variability in Patients with Atrial Synchronous Ventricular Pacing

HARUN KILIC, M.D.,* OZLEM KARAKURT, M.D.,* RAMAZAN AKDEMIR, M.D.,* MEHMET DOGAN, M.D.,* ASUMAN BICER, M.D.,* SADIK ACIKEL, M.D.,* GOKSEL CAGIRCI, M.D.,* and HUSEYIN GUNDUZ, M.D.†

From the *Cardiology Department, Diskapi Yildirim Beyazit Training and Education Hospital, Ankara, Turkey; and †Cardiology Department, Abant Izzet Baysal University, Bolu, Turkey

Background: *Heart rate turbulence (HRT) and heart rate variability (HRV) have been shown to be independent and powerful predictors of mortality in a specific group of cardiac patients. Pacing has unfavorable effects on autonomic function. Our aim is to investigate autonomic responses to atrial synchronous ventricular pacing (VDD) by evaluating HRT and HRV parameters.*

Methods and Results: *The study groups comprised 12 control and 12 patients without organic heart disease and with normal sinus function who were implanted with a permanent VDD pacing system for high-degree atrioventricular block. The HRV and HRT analysis were assessed from a 24-hour Holter recording. There was no statistically significant difference between the two groups for HRV parameters. When HRT parameters were compared, turbulence onset was significantly higher in the cardiac paced group than the controls group (2.729 ± 8.818 vs –1.565 ± 8.301, P = 0.006), but no statistically significant difference was found between the two groups for turbulence slope (11.166 ± 10.034 vs 31.675 ± 28.107, P = 0.68). The number of patients who had abnormal HRT onset was significantly higher in the paced group than controls (9 vs 2, P = 0.004).*

Conclusion: *Atrial synchronous pacing has unfavorable effects on autonomic function. Altered ventricular depolarization sequence may lead to changes in autonomic response. Although we found no difference in HRV parameters between the control and VDD patient groups, the HRT onset and number of patients with abnormal HRT onset was significantly higher in VDD patients. HRT onset can be a better way of noninvasive autonomic response predictor in VDD patients. (PACE 2008; 31:1113–1117)*

atrial synchronous pacing*, *heart rate variability*, *heart rate turbulence

Introduction

Early studies have demonstrated the importance of physiological pacing. Atrioventricular synchronized pacing had better hemodynamic and metabolic results.[1–3] Previous reports have shown that single-chamber ventricular pacing provokes unfavorable sympathetic activation compared with dual-chamber pacing.[4–7] However, no studies have previously compared the autonomic responses in atrial synchronous pacing (VDD) patients with healthy subjects. Alterations (mostly reductions) in heart rate variability (HRV) have been used to assess cardiac autonomic function. Depressed HRV after myocardial infarction (MI) may reflect a decrease in vagal activity directed to the heart, which leads to increase of sympathetic mechanisms and to cardiac electrical instability. A reduction of HRV has been reported in several diseases like cardiac failure, essential hypertension, heart transplantation, myocardial infarction.[8–10]

Heart rate turbulence (HRT) is a measure of autonomic response to perturbations of arterial blood pressure after single ventricular premature complexes (VPCs).[11] Its clinical significance lies in its ability to determine the risk stratification. The disappearance of HRT implies the loss of normal autonomic nervous regulation in favor of sympathetic system.[12] Heart rate turbulence has been shown to be an independent and powerful predictor of mortality, with greater predictive value than HRV.[11]

No studies have previously evaluated HRT in patients with a VDD pacemaker. In this study, we aimed to define the effect of VDD pacing on cardiac autonomic function via assessment of HRT and HRV in these patients.

Methods

Patients

All examinations were performed in Diskapi Training and Research Hospital from May 2007 to December 2007. A total of 24 cases were investigated. The study groups comprised 12 healthy control (mean age 58 ± 10 years) and 12 patients (mean age 61 ± 13 years) without organic heart disease and with normal sinus function who were implanted with a permanent VDD pacing system for high-degree atrioventricular block. Lower rate

Address for reprints: Harun Kilic, M.D., Oyak 10. Kisim 10/16 06530 Cayyolu, Ankara, Turkey. Fax: 903122414830; e-mail: doctorharun@gmail.com

Received January 23, 2008; revised March 28, 2008; accepted May 7, 2008.

was minimized to preserve intrinsic normal sinus node activation sequences.

Patients who had disorders such as ischemic and rheumatic heart disease, diabetes mellitus, stenotic valvular heart disease, or severe left ventricular dysfunction and patients taking drugs affecting cardiorespiratory responses were excluded. All subjects were asked to avoid smoking and drinking any caffeinated beverages during the study.

Echocardiography

An experienced echocardiographer assessed the echocardiographic studies. In all subjects, transthoracic two-dimensional and Doppler echocardiographic examinations were performed using a Vingmed Vivid 3 echocardiographic system (General Electric Vingmed Ultrasound, Tirat Hacarmel, Israel) and 2.5–3.5 MHz transducers. The measurements were carried out according to the standards of the American Society of Echocardiography, using the parasternal long axis and apical four-chamber windows.

We assessed the left ventricle end-diastolic and end-systolic dimensions, left ventricle ejection fraction, wall motion abnormality existence, left atrium dimension, right atrium and ventricle dimension, valve pathologies (stenosis or regurgitation).

Holter Analysis

All patients and controls underwent 24-hour Holter monitoring. All patients were in sinus rhythm throughout the recording period. Holter electrocardiograms (ECGs) were analyzed using the DMS CardioScan 12 Holter system (DM Software Inc., Stateline, NV, USA).

The HRV analysis was assessed over a 24-hour period and was performed in time domains and power spectral analyses according to the European Society of Cardiology/North American Society of Pacing and Electrophysiology guidelines. The following time-domain and power spectral parameters were calculated:

Mean of all normal RR intervals (mean RR); Standard deviations of all NN intervals (SDNN); mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording (SDNNI); standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN); the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD); the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50); the very low frequency range power (VLF power); and the high-frequency range power (HF power); the low-frequency range power (LF power); and low-frequency/high-frequency power ratio (LF/HF ratio).

Heart rate turbulence parameters were calculated according to the original method reported by Schmidt et al.[11,13] Two numerical descriptors were estimated: turbulence onset reflecting the initial phase of sinus rhythm acceleration and turbulence slope describing deceleration phase. Heart rate turbulence onset was defined as the difference between the mean of the first two sinus-rhythm RR intervals following the compensatory pause after a premature ventricular complex (PVC) and the mean of the last two sinus-rhythm RR intervals preceding the PVC, expressed as a percentage of the former. The HRT slope was defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after PVC, expressed as millsecond per beat. The HRT onset or slope was defined as abnormal if the onset was $\geq 0\%$ or the slope was ≤ 2.5 ms/beat. Patients with atrial fibrillation or without PVCs, or PVCs preceded by noise or artifacts were excluded from HRV and HRT analysis. Figure 1 shows an example of heart rate turbulence. Nominal atrioventricular (AV) interval was 120 ms. AV interval was optimized by using the Ritter method.[14] Holter analysis was repeated after optimization.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 11.0 software for Windows. Descriptive statistics were made and all data were expressed as mean $\pm$ standard deviation and % ratio. The quantitative values between two groups were compared using Student's *t*-test, and the qualitative values were compared using the χ^2 test. P value of < 0.05 was considered as statistically significant in all cases.

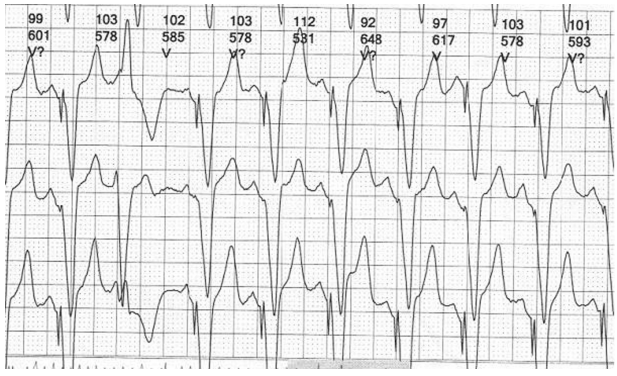

Figure 1. *An example of heart rate turbulence.*

Table I.

Comparison of Clinical, Echocardiographic, and Electrocardiographic Characteristics in Patients with Atrial Synchronous Ventricular Pacing and Control Group

	Paced Group n = 12	Control Group n = 12	P Values
Age (years)	61 ± 13	58 ± 10	0,345
Gender (M/F)	7/5	8/4	0,143
Hypertension	7	5	0,454
Smokers (%)	5	6	0,234
PVC count per day	543 ± 236	408 ± 198	0,389
Mean heart rate (min)	68 ± 13	75 ± 8	0,560
Left ventricle ejection fraction (%)	58 ± 5	63 ± 4	0,067
Left ventricle end diastolic dimension (mm)	56 ± 7	53 ± 6	0,078
Left ventricle end systolic dimension (mm)	39 ± 5	37 ± 3	0,098
Left atrium dimension (mm)	37 ± 4	35 ± 4	0,365
Fractional shortening (%)	31 ± 2	34 ± 3	0,435

Results

Twelve patients with permanent VDD pacing (seven men and five women, mean age 61 ± 13 years) and twelve healthy controls without cardiac pacemaker (eight men and four women, mean age 58 ± 10 years), a total of 24 cases, were included in this study. Age, sex, smoking, presence of hypertension, prevalence of PVCs, mean heart rate, left ventricular ejection fraction, and left atrium dimension were not significantly different between two groups (Table I). Mean atrial sense wave was 3.9 ± 0.96 mV. Ventricular pacing incidence was 99,8 ± 0,96%. Nominal AV delay was 120 ms. Mean optimal AV delay was found as 136 ± 13.3 ms. When HRT parameters were compared, TO was significantly greater in paced group than the controls group (2.7292 ± 8.8187 vs −1.5650 ± 8.3013, P = 0.006), but no statistically significant difference was found between the two groups for TS (11.1667 ± 10.0348 vs 31.6750 28.1070 vs, P = 0.680). The number of patients who had abnormal HRT onset was significantly higher in the paced group than the controls (9 vs 2, P = 0.004). But the number of patients who had abnormal HRT slope was not significantly different between the two groups. Also, HRV parameters were not significantly different between the two groups. Table II summarizes the HRT and HRV parameters in the VDD patients with nominal AV delay and controls. Optimization of AV delay makes no statistically significant effect on HRT and HRV parameters (Table III).

Discussion

Cardiac pacing may be associated with a variety of hemodynamic and neurohumoral responses. There are substantial data providing evidence that asynchronous ventricular-inhibited pacing (VVI) pacing leads to exaggerated sympathetic activation. In contrast, there are controversial reports of whether AV sequential synchrony has any autonomic advantages over fixed-rate pacing.[5,7] Andersen et al.[15] had a randomization to atrial-inhibited pacing (AAI) or VVI pacing in patients with sinus node dysfunction. They showed improved survival and less heart failure in analysis at 5.5 years. With AAI pacing, the patient maintains intrinsic AV conduction and avoids the abnormal depolarization pattern of right ventricular pacing. Investigators from the Mode Selection Trial[16] demonstrated that in patients with normal baseline QRS duration, the cumulative percentage of ventricular pacing is a strong predictor of hospitalization for heart failure and the risk of atrial fibrillation also increases linearly with the cumulative percentage of ventricular pacing. This occurs even when AV synchrony is preserved. Chiladakis et al.[17] investigated the autonomic effects of short-term single- and dual-chamber pacing by HRV. They found that AAI pacing appears to have lesser effect on sympathovagal balance. Synchronous VDD and DDD stimulation favor a shift in autonomic balance toward sympathetic predominance. Asynchronous VVI pacing triggers both sympathetic overactivity and vagal withdrawal.

In our study, we found no statistically significant difference between the VDD patients and healthy subjects for HRV parameters. When HRT parameters were compared, HRT onset was significantly higher in the cardiac-paced group than the controls group. Intraventricular conduction delay results in ventricular mechanical discoordination and decreases the overall cardiac

Table II.

Comparison of HRT and HRV Parameters in Patients with Atrial Synchronous Ventricular Pacing at Nominal AV Delay and Control Group

	Paced Group Nominal AV Delay	Control Group	P Values
HRT onset (%)	2,729 ± 8,818	−1,565 ± 8,301	0,006
HRT slope (ms/beat)	11,166 ± 10,034	31,675 ± 28,107	0,680
Abnormal HRT onset, n (%)	9 (75)	2 (16)	0,004
Abnormal HRT slope, n (%)	3 (25)	3 (25)	1,0
SDNN (ms)	164,75 ± 41,88	153,38 ± 66,11	0,616
SDNNI (ms)	61,33 ± 13,78	72,53 ± 67,65	0,579
SDANN (ms)	151,33 ± 41,65	125,23 ± 37,85	0,114
rMSSD (ms)	44,33 ± 36,97	80,38 ± 116,34	0,316
sNN50 (%)	11,16 ± 7,90	21,00 ± 22,61	0,167
Mean RR (ms)	807 ± 107	820 ± 70	0,747
Total power	2511 ± 1805	3852 ± 1636	0,070
VLF power	1789 ± 1339	2481 ± 1070	0176
LF power	443 ± 316	953 ± 458	0,004
HF power	231 ± 186	385 ± 280	0,128
LF/HF ratio	2,2 ± 1,7	2,0 ± 2,0	0,816

Abbreviations: HRT = heart rate turbulence; HRV = heart rate variability; AV = atrioventricular.

efficiency. The abnormal spread of excitation induced by right ventricular stimulation appears to have adverse effects on autonomic nervous regulation.

Schmidt et al.[11] introduced into electrocardiology a new noninvasive sudden death risk factor called heart rate turbulence, which is a physiological, biphasic reaction with early acceleration

Table III.

Comparison of HRT and HRV Parameters in Patients with Atrial Synchronous Ventricular Pacing at Optimal AV Delay and Control Group

	Paced Group Optimal AV Delay	Control Group	P Values
HRT onset (%)	0,84 ± 3,27	−1,565 ± 8,301	0,004
HRT slope (ms/beat)	7,24 ± 4,28	31,675 ± 28,107	0,859
Abnormal HRT onset, n (%)	8 (66,7)	2 (16)	0,006
Abnormal HRT slope, n (%)	2 (16,6)	3 (25)	0,8
SDNN (ms)	132,81 ± 17,46	153,38 ± 66,11	0,281
SDNNI (ms)	50,00 ± 10,71	72,53 ± 67,65	0,432
SDANN (ms)	116,36 ± 16,72	125,23 ± 37,85	0,051
rMSSD (ms)	42,72 ± 16,58	80,38 ± 116,34	0,316
sNN50 (%)	17,09 ± 7,73	21,00 ± 22,61	0,272
Mean RR (ms)	876 ± 45	820 ± 70	0,782
Total power	2908 ± 901	3852 ± 1636	0,294
VLF power	1921 ± 750	2481 ± 1070	0,384
LF power	493 ± 198	953 ± 458	0,004
HF power	263 ± 189	385 ± 280	0,312
LF/HF ratio	1,9 ± 0,9	2,0 ± 2,0	0,921

Abbreviations: HRT = heart rate turbulence; HRV = heart rate variability; AV = atrioventricular.

and subsequent deceleration of sinus rhythm in response to a premature ventricular complex. Heart rate turbulence is believed to reflect baroreflex sensitivity. It was shown in retrospective and prospective studies that HRT is an independent and powerful predictor of mortality after myocardial infarction with greater predictive power than HRV.

Conclusion

Atrial synchronous pacing has unfavorable effects on autonomic function. Altered ventricular depolarization sequence may lead to changes in autonomic response. Although we found no difference in HRV parameters between controls and VDD patients, HRT onset was significantly higher in VDD patients. HRT can be a better noninvasive autonomic response predictor in VDD patients.

Limitations of the Study

This study is a single-center, observational, and nonrandomized comparative study; the number of cases included in the study is low and the authors suggest confirmation of the findings and evaluation of the usefulness of HRT in risk stratification of patients in a larger number of VDD patients.

References

1. Kruse I, Arnman K, Conradson TB, Rydén L. A comparison of the acute and long-term hemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. Circulation 1982; 65:846–855.
2. Leclercq C, Gras D, Le Helloco A, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995; 129:1133–1141.
3. Baller D, Wolpers HG, Zipfel J, Bretschneider HJ, Hellige G. Comparison of the effects of right atrial, right ventricular apex, and atrioventricular sequential pacing on myocardial oxygen consumption and cardiac efficiency: A laboratory investigation. Pacing Clin Electrophysiol 1988; 11:394–403.
4. Ellenbogen KA, Kapadia K, Walsh M, Mohanty PK. Increase in plasma atrial natriuretic factor during ventriculoatrial pacing. Am J Cardiol 1989; 64:236–237.
5. Linde-Edelstam C, Hjemdahl P, Phersson SK, Astrom H, Nordlander R. Is DDD pacing superior to VVIR? A study on cardiac sympathetic nerve activity and myocardial oxygen consumption at rest and during exercise. Pacing Clin Electrophysiol 1992; 15:425–434.
6. Taylor JA, Morillo CA, Eckberg DL, Ellenbogen KA. Higher sympathetic nerve activity during ventricular (VVI) than during dual-chamber (DDD) pacing. J Am Coll Cardiol 1996; 28:1753–1758.
7. Phersson SK, Hjemdahl P, Nordlander R, Astrom H. A comparison of sympathoadrenal activity and cardiac performance at rest and during exercise in patients with ventricular demand or atrial synchronous pacing. Br Heart J 1988; 60:212–220.
8. Malik M, Camm J. Heart rate variability and clinical cardiology. Br Heart J 1994; 71:3–6.
9. Gündüz H, Arinc H, Kayardi M, Akdemir R, Ozyildirim S, Uyan C. Heart rate turbulence and heart rate variability in patients with mitral valve prolapse. Europace 2006; 8:515–520.
10. Yılmaz F, Gündüz H, Karaaslan K, Arinc H, Cosgun M, Sessiz N, Uyan C. Holter analysis in children with adenotonsiller hypertrophy. Int J Pediatr Otorhinolaryngol 2006; 70:1443–1447.
11. Schmidt G, Malik M, Barthel P, Scheider R, Ulm K, Rolnitzky L, Camm AJ. Heart rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999; 353:1390–1396.
12. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93:1043–1065.
13. Francis J, Watanabe MA, Schmidt G. Heart rate turbulence: A new predictor for risk of sudden cardiac death. Ann Noninvasive Electrocardiol 2005; 10:102–109.
14. Ritter P, Dib JC, Mahaux V. New method for determining the optimal atrioventricular delay in paced in DDD mode for complete atrio-ventricular block (abstract). Pacing Clin Electrophysiol 1995; 18:855.
15. Andersen HR, Nielsen JC, Thomsen PE. Long term follow of patients from a randomized trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997; 350:1210–1216.
16. Lamas GA, Lee KL, Sweeney MO. Mode selection trial in sinus-node dysfunction: Ventricular pacing or dual chamber for sinus-node dysfunction. N Eng J Med 2002; 346:1854–1862.
17. Chiladakis JA, Kalogeropoulos A, Manolis AS. Autonomic responses to single- and dual-chamber pacing. Am J Cardiol 2004; 93:985–989.