Relation of Heart Rate and Blood Pressure Turbulence Following Premature Ventricular Complexes to Baroreflex Sensitivity in Chronic Congestive Heart Failure

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Reduced heart rate variability (HRV) and attenuated baroreflex sensitivity (BS) after myocardial infarction and in patients with chronic congestive heart failure (CHF) are associated with poor prognosis. Recent studies have shown that a large proportion of the prognostic power from HRV measurements is localized in heart rate turbulence immediately after ventricular premature complexes. The mechanism of heart rate turbulence remains unknown. In the present study, we explore its relation to BS. In 45 patients with CHF and ≥3 ectopic beats in a 30-minute period, measurements of RR interval and continuous, noninvasive blood pressure (BP) were studied at rest. In response to an ectopic beat, average heart rate turbulence was 9.4 ms/beat (SD 6.1). Mean BP turbulence was 0.72 mm Hg/beat (SD 0.56). Using the ratio of heart rate and BP turbulence slopes to estimate BS showed good agreement ($r = 0.67, p < 0.0001$) with the $\alpha$-index method ($BS_\alpha$). This relation was attributable to a marked correlation between heart rate turbulence and $BS_\alpha$ ($r = 0.70, p < 0.0001$); there was no correlation between BP turbulence and the $BS_\alpha$ ($r = 0.1, p = NS$). Twenty-nine percent of patients had postectopic pulsus alternans, with a mean decay time of 1.4 beats (SD 0.5). The presence of pulsus alternans was associated with a significantly lower heart rate turbulence slope (6.3 [SEM 1.0] vs 10.7 [SEM 1.2] ms/beat, $p = 0.03$). Thus, heart rate turbulence is an effective measure of the baroreflex, correlating strongly with a standard measure. This is because it is the heart rate, rather than the BP, response to an ectopic beat that conveys the information relevant to BS measurement.

A ttenuation of autonomic reflex modulation of heart rate predicts poor outcome after myocardial infarction and in patients with chronic congestive heart failure (CHF). One method of measuring this modulation of heart rate is the examination of spontaneous heart rate variability (HRV) from a standard 24-hour ambulatory electrocardiographic Holter recording. Alternatively, if specialized equipment is available that can measure blood pressure (BP) continuously, a short recording can measure both BP stimuli (natural or pharmacologic) and the heart rate response to them. The ratio of the heart rate response to the BP stimulus (baroreflex sensitivity, BS) can be calculated in a few minutes and is a useful prognostic marker. A recent detailed reevaluation of the data obtained from the more widely available 24-hour electrocardiographic data has identified that almost all its discriminant prognostic power can be extracted by considering only the few beats that follow a ventricular premature complex (VPC) — heart rate turbulence. Despite the potential clinical value of this simple test in noninvasive risk stratification of patients with myocardial infarction, there has been no formal evaluation of the mechanism of heart rate turbulence, which would be important in understanding why it predicts prognosis. If postectopic heart rate turbulence is a manifestation of BS, its use in risk stratification could be supported by a number of baroreflex-based prognostic studies. We examined the dynamics of the integrated physiologic heart rate and BP response to ectopic beats in patients with CHF to clarify the mechanism of postectopic heart rate turbulence.

METHODS

Subjects and measurements: Forty-five patients with CHF were recruited from a specialist clinic. They were diagnosed on the basis of clinical assessment (a history of dyspnea and symptomatic exercise intolerance with previous signs of pulmonary congestion or peripheral edema) and/or evidence of left ventricular dysfunction from radionuclide ventriculography or echocardiography. Patients with atrial fibrillation, permanent pacemakers, <3 ectopic beats in a 30-minute recording, or clinical instability within the preceding 3 months were not eligible. Average age was 62 years (SD 11). Thirty patients had heart failure due to coronary artery disease, 13 had idiopathic dilated cardio-

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myopathy, and 2 had heart failure due to mitral regurgitation. The mean ejection fraction assessed by radionuclide ventriculography was 33% (SD 14%; n = 33). Six patients were in New York Heart Association class I, 26 in class II, and 13 in class III. Forty-two of the patients were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, 39 were on diuretics, and none were receiving a β blocker, digoxin, or other antiarrhythmic drug. Thirty-six of the patients were men and 9 were women. All subjects gave informed consent and the study was approved by the local ethical committee. The subjects were studied between 1 P.M. and 5 P.M. hours under standardized conditions, in a quiet room at a comfortable temperature. All patients fasted for ≥2 hours before testing and were not allowed to smoke or drink alcohol- or caffeine-containing beverages for 24 hours before the study. On arrival at the investigation unit, the subjects rested supine for 30 minutes and then underwent a 30-minute recording of heart rate and noninvasive BP.

**Data collection:** BP was measured noninvasively by a Finapres device (model 2300; Ohmeda, California), with the cuffed finger resting comfortably at the level of the heart. The Finapres cuff was wrapped around the index finger of the left hand. The subjects were allowed to be accustomed to the Finapres device for several minutes; the servo-adjust mechanism was turned off before recording. This device has been widely used for the beat-to-beat measurement of BP and has been validated against intra-arterial recordings.9 The electrocardiogram was acquired from the limb lead with the largest R wave (usually lead II). All data were sampled at 1,000 Hz on a computer using an analog-to-digital converter (National Instruments, Austin, Texas). The readings were saved onto floppy disk and analyzed off-line with custom software, which measured RR intervals and beat-to-beat BP.

**Heart rate turbulence:** Heart rate turbulence was calculated as previously described.7 In brief, all VPCs that occurred in isolation (preceded and followed by ≥20 normal sinus beats) were selected by a computer algorithm and confirmed manually. For each of these VPCs, a heart rate turbulence value was calculated as the maximum positive slope of the regression line over any sequence of 5 sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after a VPC (Figure 1). The value of the turbulence slope is expressed in millisecond per beat. The turbulence slope was calculated for each VPC and averaged to give the patients' heart rate turbulence. Figure 2(A) shows the classic response in a patient with a normal pattern of heart rate turbulence, which is characterized by an initial acceleration (decrease in RR interval) followed by a deceleration (increase in RR interval) and a return to the resting state after 15 to 20 beats. This is the pattern of heart rate response found by Schmidt et al7 to predict good prognosis in patients after myocardial infarction. In contrast, Figure 2(B) shows a different pattern of heart rate turbulence, in which the deceleration is delayed in onset and weak in slope. This pattern has been identified by Schmidt et al7 as predicting poor prognosis. The heart rate turbulence value gives a quantitative measure of this pattern. In the examples shown above, the heart rate turbulence slopes are 6.7 and 2.7 ms/beat, respectively.

**Blood pressure turbulence:** BP turbulence was defined as the slope of the regression line over the 5 pulses corresponding to the RR intervals used for heart rate turbulence (Figure 1), with the BP data series shifted 1 beat to account for the delay of the baroreflex.10 The value for the patient’s BP turbulence is taken as the average BP turbulence slope for all the patient’s VPCs, and was expressed in mm Hg/beat.

**Baroreflex sensitivity:** The first 10 minutes of data taken at rest were used to calculate BS by the spectral analysis method as previously described.11 Briefly, after removal of ectopic beats by linear interpolation, power spectral analysis was performed on the RR interval and systolic BP data through the use of an autoregressive algorithm, with the model order selected according to the Akaike information criterion. A model order between 12 and 18 was found to be appropriate in all cases. The component in the low frequency (0.04 to 0.15 Hz) band was considered. The α-index was computed as the square root of the ratio

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**FIGURE 1.** Heart rate and BP response to a premature ventricular beat (VPC). Lower panels, thick lines indicate the region selected by the algorithm for measurement of heart rate and BP turbulence slopes. ECG = electrocardiogram.
between RR and systolic BP spectral powers in the low-frequency (αLF) band, in the presence of an adequate coherence (>0.5) between the RR interval and systolic BP as assessed by cross-spectral analysis. For each isolated VPC episode, a turbulence-derived BS was defined as the regression slope of RR interval against systolic BP (during the same 5-beat interval used for the measurement of the heart rate and BP turbulence slopes). For each patient, the slopes from the individual VPC episodes were averaged to obtain the turbulence-derived BS, expressed in ms/mm Hg.

**Statistical analysis:** Numerical distributions are described by their mean and SD. Estimates of subgroup means are quoted with SEM. Comparisons between group means were carried out with Student’s t test. Comparison between the 2 measures of BS was performed by the method of Bland and Altman, which involves plotting the signed difference between 2 measures against the mean of the 2 measures.

**RESULTS**

**Heart rate turbulence after premature beats:** The mean heart rate turbulence in our patient group was 9.4 ms/beat (SD 6.1). There was no significant difference in heart rate turbulence between men and women (9.8 [SEM 1.1] vs 7.9 [SEM 1.1] ms/beat, respectively, p = 0.4). Patients in New York Heart Association classes I and II had a significantly higher heart rate turbulence slope than patients in New York Heart Association class III (10.7 [SEM 1.2] vs 6.2 [SEM 0.9] ms/beat; p = 0.02). The etiology of heart failure had no effect on the heart rate turbulence slope (ischemic heart disease, 8.9 ms/beat [SEM 1.0]; nonischemic heart disease, 10.4 ms/beat [SEM 1.8], p = 0.4).

**Blood pressure turbulence after premature beats:** We have extended the definition of heart rate turbulence to the BP data, as described in Methods. Figure 1 shows a typical BP response: an initial decrease in BP, followed by an increase, and a return to the resting state after several beats. Mean BP turbulence was 0.72 mm Hg/beat (SD 0.56). There was no significant difference in BP turbulence slope between men or women (0.68 [SEM 0.09] vs 0.89 [SEM 0.22] mm Hg/beat, respectively, p = 0.3). Patients in New York Heart Association classes I and II had a significantly higher BP turbulence slope than patients in New York Heart Association class III (0.84 [SEM 0.11] vs 0.43 [SEM 0.08] mm Hg/beat, p = 0.02). There was no difference in BP slope between the different etiologies of CHF (ischemic heart disease, 0.64 mm Hg/beat [SEM 0.10]; nonischemic heart disease, 0.88 mm Hg/beat [SEM 0.10], p = 0.2).

**Baroreflex sensitivity:** Using the turbulence method, the mean BS was 4.5 ms/mm Hg (SD 7.0). Using the a-index method, the mean BS was 6.8 ms/mm Hg (SD 3.7) (mean BS in a group of 17 age-matched normal controls was 16.4 ms/mm Hg [SD 6.9], p <0.0001). There was a strong correlation between the heart rate turbulence slope and BS (α (r = 0.70, p <0.0001), whereas there was no correlation between the BP turbulence slope and BS (α (r = 0.08, p = NS). A strong correlation (r = 0.67, p <0.0001) was found between the turbulence-derived BS and BS (α. The Bland and Altman plot showing the agreement between the turbulence-derived BS and BS (α is shown in Figure 3. The mean difference was 2.3 ms/mm Hg, with BS (α yielding the slightly higher results. The SD of the difference was 5.2 ms/mm Hg.

**Pulsus alternans after ectopic beats:** Postectopic pulsus alternans occurred in 13 of the patients (29%) (Figure 4), using a definition of a beat-to-beat alternation exceeding 1 mm Hg in beats 3 to 5 following the ectopic (Figure 5A). The patients with postectopic pulsus alternans had a significantly lower HR turbulence slope than those without postectopic alternans (6.3 [SEM 1.0] vs 10.7 [SEM 1.2], p = 0.03). The BS
was also lower in the patients with pulsus alternans. This did not reach statistical significance for BS (6.3 [SEM 0.7] vs 7.0 [SEM 0.7] ms/mm Hg, p = 0.6), but did with the turbulence-derived BS (1.4 [SEM 0.5] vs 5.8 [SEM 1.4] ms/mm Hg, p = 0.05). The patients with postectopic pulsus alternans had significantly lower left ventricular ejection fractions (24% [SEM 3.6%] vs 38% [SEM 2.7%], p = 0.004). In each of the patients with postectopic pulsus alternans, the half-life of decay of the alternation in systolic BP was measured by fitting an exponential decay to the beat-by-beat alternations over the period from the first to the sixth beat after the ectopic beat (Figure 5B). The average half-life was 1.4 beats (SD 0.5).

DISCUSSION
This study has shown that heart rate turbulence can be used to assess BS in patients with chronic heart failure. First, the gradual increase in BP back to normal after an ectopic beat is a stimulus for slowing of the heart rate: the regression slope of this relation gives a good estimate of the BS as defined by a standard method. Second, it is the variation in the postectopic heart rate slope rather than that in the BP slope that conveys the information relevant to measurement of BS; no correlation was found between BP turbulence and BS. The third finding of the study is that there is a high prevalence of pulsus alternans in the postectopic period in patients with CHF, and that patients with this finding have a lower heart rate turbulence slope and BS, and a lower left ventricular ejection fraction.

The arterial baroreflex has long been recognized to be attenuated in patients after myocardial infarction and with CHF; the degree of this attenuation has been confirmed as an important risk stratifier, independent of conventional clinical markers in patients with acute myocardial infarction.8 One difficulty in
developing reliable noninvasive measures of BS is that the gold standard techniques have poor reproducibility in patient groups. In a study of 31 patients with CHF,13 we showed that the correlation coefficient between BS, and the phenylephrine-derived BS was 0.71, similar to the correlation coefficient of 0.70 between BS, and the heart rate turbulence slope in the present study. A major difficulty preventing widespread adoption of BS as a routine clinical assessment is the requirement of equipment that is able to measure BP continuously and noninvasively. This equipment is expensive and not widely available.

Holter electrocardiographic monitoring, either for 24 hours or for shorter periods, is ubiquitous in hospitals, making the assessment of HRV alone much more practical. Although assessment of HRV from 24-hour Holter recordings has sometimes shown prognostic value in patients after myocardial infarction14 and with chronic heart failure,15 this has not been confirmed in all studies. Kruger et al16 assessed BS (pharmacologic method) and HRV (by statistical and spectral methods) in rats with experimental myocardial infarctions. BS at days 3 and 28 after myocardial infarction were reduced compared with sham-operated rats. There was no difference in HRV, measured at days 28 and 56 after myocardial infarction between the 2 groups, suggesting that BS was a better marker of autonomic imbalance after myocardial infarction. In a study of humans after myocardial infarction,5 BS was a better predictor of arrhythmic events than either HRV or left ventricular ejection fraction.

We suggest that the reason for the disappointing results from prognostic evaluation of HRV lies in the crucial confounding effects of ventricular ectopy. When clinical state worsens, heart rate reflexes become attenuated, giving a lower intrinsic HRV (in regions of recording free of ectopy). However, the frequency of ectopy increases, with each ectopic beat generating a turbulence region in its wake. This constitutes an increment to total HRV, because conventional measures of HRV delete, or correct, only 2 RR intervals when an ectopic beat occurs: the short and the long ones involving the ectopic beat itself. Thus, conventional measures of HRV are assessing the sum of 2 components, 1 which declines with worsening clinical state, and 1 which increases—this hampers its prognostic value. Assessment of heart rate turbulence, by concentrating on ectopy, effectively corrects for the number of ectopic beats. This may explain its considerable prognostic advantage over conventional HRV measures.

Pulsus alternans, the alternation between a strong and weak heart beat during a regular rhythm, was first reported by Traube in 1872.17 This phenomenon, better described as mechanical pulsus alternans, usually occurs in patients with severely impaired ventricular function,18,19 and may or may not be associated with electrocardiographic alternans.20 Mechanical pulsus alternans is caused by a combination of alteration in hemodynamic variables (pressure and volume) and inotropic state.20 Work by McGaughey et al21 in isolated cardiac preparations showed that pulsus alternans was related to the end-diastolic pressure. At the end of 1 beat, end-diastolic volume is elevated. By the Frank-Starling mechanism, stroke volume is enhanced, ejection more complete, and diastolic filling more limited in duration, so that the next end-diastolic volume is lower. On the following beat, stroke volume is smaller and filling more prolonged so that the next end-diastolic volume is higher again, completing the 2-beat alternans cycle. The critical features are sensitivity of contractile force to end-diastolic volume and sensitivity of end-diastolic volume to contractile force: if both are steep enough, alternans will occur, otherwise, any disturbance will decay away without showing alternans. Ectopic beats may trigger the alternans phenomenon by allowing increased diastolic filling after the ectopic beat. The resultant forceful contraction can then develop into the alternans cycle, as described previously, in predisposed subjects. In addition, studies in isolated specimens have shown that mechanical alternans can also occur in the absence of differences in diastolic duration22 and papillary muscle end-diastolic tension,23 and that an index of contractility, independent of end-diastolic diameter, was nearly twice as strong in the “strong” beat than in the “weak” beat.24 The cause of this alternation in contractility is related to alternations in intracellular calcium transit or utilization.25 In our study, patients who exhibited pulsus alternans had significantly lower heart rate turbulence slopes and left ventricular ejection fraction and a trend toward lower BS. It is possible that their cardiovascular control physiology was more impaired and thus prone to respond to the stimulus in this unstable manner.


