A noninvasive measure of baroreflex sensitivity without blood pressure measurement

L. Ceri Davies, BSc, MRCP,a Helen Colhoun, MFPHM,b Andrew J. S. Coats, DM, FRCP,a Massimo Piepoli, MD, PhD,a and Darrel P. Francis, MA, MRCPa
London, United Kingdom

Background Baroreflex sensitivity (BRS) and heart rate variability (HRV) are attenuated in cardiovascular disease and can give important prognostic information. Conventional measures of BRS require expensive or invasive equipment for the beat-to-beat measure of blood pressure (BP). We examined the possibility of developing a protocol that would provide a relatively standardized BP stimulus, which might obviate the need to measure BP beat-by-beat.

Methods and Results Fifty-five patients with chronic heart failure (mean age 59 [SD 11] years) and 20 healthy control subjects (mean age 53 [SD 14] years, P not significant) underwent 5-minute recordings of BP (by photoplethysmograph) and R-R interval during 0.1-Hz controlled breathing. The size of the oscillations in BP was the same in the 2 groups (3.6 mm Hg vs 4.1 mm Hg, P = .5). There was, however, a significant difference in the amplitude of the R-R interval oscillations (77 ms vs 31 ms, P < .0001). The amplitude of the R-R interval oscillations correlated strongly with BRS (r = 0.81, P < .0001) with controlled breathing BRS, and r = 0.51, P < .0001 with α index). There was no correlation with the size of BP oscillations (r = –0.13, P not significant with controlled breathing BRS, and r = –0.15, P not significant with α index).

In a separate study, a group of 22 young patients (mean age 36 years) with type I diabetes mellitus and 28 healthy control subjects (mean age 39 years) underwent measurement of resting HRV and amplitude of R-R interval oscillations during 0.1-Hz breathing. There was no significant difference in triangular index or low-frequency R-R interval power between the 2 groups. There was, however, a significant difference in the amplitude of R-R interval oscillations during controlled breathing between patients with diabetes and healthy control subjects. Total and high-frequency RR interval variability was also significantly different between the 2 groups.

Conclusion During 0.1-Hz breathing, the marked difference in BRS between patients with CHF and age-matched control subjects is the result of smaller R-R interval oscillations. In young patients with diabetes, these R-R interval oscillations are significantly smaller than age-matched control subjects, even when some measures of spontaneous HRV are not different between groups. Breathing at 0.1 Hz provides a standard BP stimulus and concentrates spectral power of heart rate at one frequency, enabling simple evaluation of BRS even when BP measurement is not available. (Am Heart J 2002;143:441-7.)

Attenuation of baroreflex sensitivity (BRS) and heart rate variability (HRV) predicts poor outcome after myocardial infarction (MI) and in patients with chronic heart failure (CHF).1-3 Conventional measures of BRS require the beat-to-beat measurement of blood pressure (BP), either invasively or noninvasively, with expensive equipment. This limits the widespread use of BRS measurement in routine clinical practice, despite its powerful prognostic value.4 Although assessment of HRV is available from 24-hour Holter monitoring, accurate analysis is time consuming, dependence on multiple uncontrolled physiologic stimuli mars interpretation,5 and its prognostic value may not be as strong as that of BRS.2,6

We recently studied assessment of BRS by asking subjects to breathe gently at 0.1 Hz.7 This entrains oscillations in BP, which act by means of the baroreflex to cause oscillations in heart rate. BRS measurement by this technique was found to be highly reproducible (in comparison with conventional techniques) and to agree well with conventional measures.7

The purpose of the present study was 2-fold. First, we explored the relative contribution of R-R and BP oscillations to BRS in a group of patients with heart failure. Second, we assessed the utility of R-R interval oscillations during controlled breathing in patients with diabetes.

Methods

Subjects and measurements

CHF patients and age-matched control subjects. Fifty-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 ventriculogram or echocardiogram. Patients with atrial fibrillation, permanent pacemakers, more than 2 ectopic beats per minute, or clinical instability within the preceding 3 months were not eligible. All were receiving diuretics and either angiotensin-converting enzyme inhibitors or angiotensin II antagonists. No patients were receiving digoxin or β-blockers. Six were in New York Heart Association (NYHA) class I, 25 in class II, 19 in class III, and 5 in class IV. Twenty age-matched healthy control subjects were also studied who had no significant medical history, no abnormalities on examination, and were not taking regular medication.

Young patients with diabetes and age-matched control subjects. The subjects in this study formed a subgroup of those from a larger study, the full recruitment of which is described elsewhere. Briefly, patients with insulin-dependent (ie, type I) diabetes were randomly taken from the diabetes registers of 5 London hospitals. A random age- and sex-matched healthy population was obtained from the lists of 2 London general practices. Of the total population of 199 patients with diabetes and 201 nondiabetic subjects, 50 were randomly included in this substudy. Exclusion criteria included pregnancy and renal replacement therapy. Two patients (a diabetic male patient and a nondiabetic female subject) were on β-blockers. The mean BP was 115/71 mm Hg in both groups.

Data collection in the CHF study

The subjects were studied between 1 PM and 5 PM under standardized conditions in a quiet room at a comfortable temperature. All had fasted for at least 2 hours before testing and were not allowed to smoke or drink beverages containing alcohol or caffeine for 24 hours before the study. All subjects gave informed consent, and the study was approved by the local ethics committee.

On arrival at the investigation unit, the subjects rested supine for 30 minutes and then underwent a 10-minute recording of heart rate and noninvasive BP. BP was measured noninvasively by a Finapres device (model 2300, Ohmeda, Calif), with the cuff fastened around the index finger of the left hand. The subjects underwent several minutes of acclimation to the Finapres, and the servoadjust mechanism was turned off before recording. The electrocardiogram (ECG) was acquired from the limb lead with the largest R wave (usually lead II). Respiratory excursion was measured with a mercury-in-Silastic silicone rubber (Dow Corning Corp, Midland, Mich) strain gauge. All data were sampled at 1000 Hz on a computer with an analog-to-digital converter (National Instruments). The readings were saved to floppy disk and analyzed offline with custom software, which measured R-R intervals and beat-to-beat BP.

BRS

Controlled breathing protocol. Subjects were guided to breathe at 0.1 Hz for 5 minutes by following a sinusoidal visual and auditory signal. Heart rate, BP, and respiration were measured as described previously. Each subject was initially observed by an investigator for 30 seconds to ensure that the breathing pattern was being followed adequately before recording began. The resultant R-R interval and systolic BP (SBP) signals were processed with a simple time-domain digital filter to extract the signal component at the frequency of interest (0.1 Hz [Figure 1]), and the size of the oscillations in SBP and R-R interval were calculated. BRS_Br is the ratio of the average amplitude of oscillations in the R-R interval to the average amplitude of oscillations in SBP.

BRS by the spectral analysis method. Power spectral analysis was performed on 10 minutes of resting R-R interval and SBP 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 (LF, 0.04 to 0.15 Hz) band was considered. The α index was computed as the square root of the ratio between R-R interval and SBP spectral powers in the LF band (BRSC_LF), in the presence of an adequate coherence (>0.5) between the R-R interval and SBP as assessed by cross-spectral analysis.

HRV. In the diabetic substudy, 10-minute recordings of heart rate were made with the subjects resting in a supine position. All data were sampled at 1000 Hz on a computer with an analog-to-digital converter (National Instruments). The readings were saved to floppy disk and analyzed offline with custom software, which measured R-R intervals. Ectopic beats were removed by interpolation. Measures of HRV included triangular index and R-R interval power (total power, LF [0.04-0.15 Hz] power, and high-frequency [HF, 0.15-0.4 Hz] power). The subjects also underwent a 5-minute recording of breathing at 0.1 Hz. The amplitude of the R-R interval oscillations was calculated as described previously.

Statistical analysis

Numeric distributions are described by mean and SD. Comparisons between group means were made with the Student t test, and each mean was qualified by its SE. The Pearson product-moment correlation coefficient was used to quantify the relationship between the size of oscillations in BP and R-R interval and BRS. A P value <.05 was taken as significant.

For the diabetic study, the difference in HRV and R-R interval oscillations between patients with diabetes and subjects who were nondiabetic was assessed with multiple linear regression to adjust for age and sex. Because these variables had a skewed distribution, they were log transformed before analysis.

Results

Study in patients with CHF and age-matched control subjects

Patient characteristics. The average age of the 55 patients with CHF was 59 (SD 11) years. Forty-four had heart failure from coronary artery disease, 9 had idiopathic dilated cardiomyopathy, and 2 had heart failure from mitral regurgitation. The mean ejection fraction was 30% (SD 15%, n = 33). Eight patients were in NYHA class I, 41 in class II, and 6 in class III. Fifty-two of the patients were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist,
and none were receiving a β-blocker. Forty-three of the patients were men and 12 were women. The average age of the 20 healthy control subjects was 53 (SD 14) years, \( P = .1 \). Fifteen were men and 5 were women.

**BRS.** BRS was significantly lower in the patient group than in the healthy volunteer group. BRSC\(_{\text{br}}\) was 10.0 (SE 1.3) ms/mm Hg in patients versus 19.0 (SE 2.0) ms/mm Hg in control subjects \( (P < .001) \). BRS\(_{\alpha}\) was 8.0 (SE 0.7) ms/mm Hg in patients versus 15.8 (SE 1.5) ms/mm Hg in control subjects \( (P < .0001) \).

**Amplitude of BP and RR interval oscillations during 0.1-Hz controlled breathing.** There was no difference in the amplitude of the BP oscillations between patients (3.6 [SE 0.3] mm Hg) and control subjects (4.1 [SE 0.4] mm Hg, \( P \) not significant [NS]).

There was, however, a significant difference in the amplitude of R-R interval oscillations. The amplitude was 31 (SE 4) ms in patients versus 77 (SE 12) ms in controls \( (P < .0001) \) [Figure 2]. In the example shown, both the control subject and the patient with CHF have SBP oscillations of amplitude 5 mm Hg. However, the amplitude of the R-R interval oscillation is much smaller in the patients (~50 ms vs ~100 ms). As a result, the BRS is also lower (10.8 ms/mm Hg vs 24.3 ms/mm Hg).

**Agreement between cardiovascular oscillations and BRS.** There was a strong correlation between the amplitude of R-R interval oscillations and BRSC\(_{\text{br}}\) \( (r = 0.81 \text{ for the whole group}; \ r = 0.82 \text{ for patients with CHF}; \ r = 0.77 \text{ for control subjects} \ [P < .0001 \text{ for all comparisons})]. There was no correlation between the size of SBP oscillations and BRSC\(_{\text{hr}}\) in either group \( (r = -0.13 \text{ for the whole group}; \ r = -0.22 \text{ for patients with CHF}; \ r = -0.05 \text{ for control subjects} \ [P = \text{NS for all comparisons}]) \). There was a significant correlation between the amplitude of oscillations in SBP and R-R interval in the control subjects \( (r = 0.54, P = .01) \), but this was not seen in the patients with CHF \( (r = 0.15, P = .3) \).

There was relatively good agreement between the 2 measures of BRS with a mean difference of 2.4 ms/mm Hg (BRSC\(_{\alpha}\) yielded the higher of the 2 results). The SD of the difference was 7.5 ms/mm Hg.

In the whole group, there was a significant correlation between the amplitude of R-R interval oscillations and BRSC\(_{\alpha}\) \( (r = 0.51, P < .0001) \). The agreement was seen in patients with CHF \( (r = 0.48, P = .0002) \), but not in the healthy control subjects \( (r = 0.18, P = .5) \). There was no correlation between the amplitude of oscillations in SBP and BRSC\(_{\alpha}\) \( (r = -0.15 \text{ for the whole group}; \ r = -0.24 \text{ in patients with CHF}; \ r = -0.26 \text{ in healthy control subjects}) \).

**Study of patients with diabetes and age-matched control subjects**

**Patient characteristics.** The characteristics of the subjects in this study are shown in Table I.

**HRV.** The controlled breathing data was analyzable in all 50 patients. In 6 patients, the resting R-R interval data was of poor quality and could not be analyzed. The HRV results are shown in Table II.

After correction for age and sex, there was a signifi-
cant difference between the amplitude of R-R interval oscillations in patients with diabetes compared with non-diabetic control subjects ($P = .04$). When this analysis was restricted to those subjects who had analyzable resting data, the difference was more significant ($P = .03$). Total and HF R-R interval power was significantly different between the 2 groups ($P = .04$ and $P = .01$, respectively). There was no difference in triangular index or LF R-R interval power between the diabetic and nondiabetic groups ($P = .05$ and $P = .09$, respectively).

**Figure 2**

Measurement of BRS by the controlled breathing method in A, a healthy control subject and B, a patient with CHF. The amplitude of oscillations in SBP are similar in the 2 patients, although there is a large difference in the amplitude of R-R interval oscillations. Dotted lines, Measured signal; continuous lines, filtered signal.

A  
BRS = 24.35 ms/mm Hg

B  
BRS = 10.79 ms/mm Hg
Discussion

This study has shown that when measuring BRS by monitoring beat-by-beat R-R interval and BP during slow breathing at 0.1 Hz, almost all the information relevant to determining the BRS is carried within the R-R interval signal. This is true for patients with CHF and in age-matched healthy control subjects. In patients with autonomic dysfunction as a result of diabetes mellitus, there is depression of the amplitude of oscillation in the R-R interval. This measure is as good at distinguishing between patients with and without diabetes as standard techniques of resting HRV assessment. The size of R-R interval oscillations during 0.1-Hz controlled breathing can be detected easily and noninvasively without expensive equipment for beat-to-beat BP and can be analyzed with a relatively simple and transparent method, which together make the technique a potentially useful test of BRS function.

BRS in cardiovascular disease

Sensitivity of the arterial baroreflex has long been recognized to be attenuated in patients with cardiovascular disease, and the degree of this attenuation has been confirmed as an important risk stratifier, independent of conventional clinical markers, in patients after acute MI. BRS is also attenuated in patients with diabetes with autonomic neuropathy and contributes to the increased risk of sudden death seen in this group. The widespread use of simple, cheap, and easy methods of identifying patients at high risk of adverse cardiovascular events would therefore allow the correct allocation of limited resources and of potentially dangerous interventions. All current methods of assessing BRS require either expensive equipment or invasive procedures for the beat-to-beat measurement of SBP, thus limiting its use in clinical practice. However, because randomized controlled trials have focused on therapies, they have used widely available risk stratification measures, effectively excluding BRS.

In addition, standard techniques have relatively poor reproducibility and a high failure rate in subjects where BRS is attenuated. One of the contributory factors to this poor reproducibility is the effect of respiration on BP and R-R interval. We have recently described a method of measuring BRS involving controlled 0.1-Hz breathing. This technique has a low failure rate and good reproducibility in healthy control subjects and patients with CHF. Although BRS estimation with this

| Table I. Subject characteristics of diabetic substudy |
|------------------------------------------|----------------|----------------|----------------|----------------|
|                  | Men          | Women         |                  |                  |                  |
|                  | Nondiabetic (n = 12) | Diabetic (n = 5) | Nondiabetic (n = 16) | Diabetic (n = 17) |
|                  | Mean        | SD            | Mean            | SD            |
| Age (y)        | 38          | 3             | 40              | 4             |
| Diabetes duration (y) | —             | 27            | 7              |
| Body mass index | 24.4        | 4.4           | 26.6            | 2.9           |
| Systolic BP (mm Hg) | 124         | 14            | 124             | 14            |
| Diastolic BP (mm Hg) | 75           | 10            | 74              | 7             |

| Table II. Measures of HRV in diabetic substudy |
|------------------------------------------|----------------|----------------|----------------|----------------|
|                  | Men          | Women         |                  |                  |                  |
|                  | Nondiabetic (n = 12) | Diabetic (n = 5) | Nondiabetic (n = 16) | Diabetic (n = 17) |
|                  | Median        | IQR           | Median          | IQR           |
| Amplitude of R-R interval oscillations [ms] | 99.5         | 52.3          | 69.5            | 36.4          |
| Triangular index [n = 44] | 37.8        | 12.6          | 37.1            | 2.0           |
| Total R-R interval power [m^2] [n = 44] | 1064        | 1698          | 974             | 1038          |
| LF R-R interval power [m^2] [n = 44] | 501          | 594           | 636             | 776           |
| HF R-R interval power [m^2] [n = 44] | 223          | 514           | 126             | 140           |
| Heart rate [beats/min] | 67           | 7             | 63              | 2             |

IQR, Interquartile range.
technique requires beat-to-beat measurement of BP, the present study has shown that the size of BP oscillations is independent of clinical state. Differences in R-R interval amplitude during controlled breathing can therefore be attributed largely to differences in BRS.

HRV
Holter ECG 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 MI and in those with CHF, this has not been confirmed in all studies. In one recent study, although resting measures of HRV failed to differentiate between healthy control subjects and those with asymptomatic left ventricular dysfunction, measures of HRV under physiologic stress (head-up-tilt) were able to do so. In addition, the reproducibility of HRV in patients with CHF is poor. One of the reasons for this is that the prognostic power of ostensibly “spontaneous” HRV may in fact arise from the baroreflex responses to fluctuations in BP occurring immediately after ectopic beats—a phenomenon that has been described as heart rate turbulence. As the clinical state of a patient deteriorates, although intrinsic HRV will fall, standard measures of HRV do not reflect this because of the rise in ectopic frequency, which increases the degree of variability. Measures of HRV that are closely linked to BRS may therefore be stronger predictors of prognosis.

The role of standard measures of HRV in patients with diabetes mellitus is even less clear. Reduced heart rate variation during a single deep breath or 1 to 2 minutes of repeated maximal, slow (0.1 Hz) breathing has been used as a measure of cardiac autonomic dysfunction for many years. This technique has been used as a prognostic marker in a population of patients after MI. One hundred eighty-five patients undertook this test 5 days after MI (87 inferior, 98 anterior). Patients with a heart rate variation of <10 beats/min had an increased risk of death of 1.38 (95% CI 1.13-1.63) compared with patients with a relatively normal heart rate response. One difficulty with the widespread use of this technique is that it requires deep, maximal breathing. The technique described in the present study involves relaxed, slow breathing and has a high success rate in patients with CHF. In the present study, total and HF R-R interval power were also able to differentiate between patients with diabetes and nondiabetic subjects. Spectral analysis of R-R interval data is complex and opaque to the clinical observer, unlike analysis of data from the controlled-breathing technique. Intrinsic statistical uncertainties of autoregressive spectral analysis and issues regarding model order selection can have large effects on power spectral density. In addition, respiration can have a profound effect on R-R interval spectral power. If a subject’s respiratory pattern changes between repeated test episodes, the reproducibility of the test will be compromised, further reducing its effectiveness in routine clinical practice.

Study limitations
Although respiratory frequency is controlled in this technique, tidal volume is not. Altering tidal volume does have an effect on BP and R-R interval variability. However, subjects tend to control their tidal volume automatically when the respiratory rate is also controlled. To make this technique simple for subjects to perform, we have therefore only controlled respiratory rate.

Conclusion
This study has shown that during 0.1-Hz controlled breathing, the marked difference in BRS between patients with CHF and age-matched control subjects is the result of smaller R-R interval oscillations. There is no difference in the amplitude of BP oscillations between the 2 groups. In young patients with diabetes, these R-R interval oscillations are significantly smaller than in age-matched control subjects, even when some measures of spontaneous HRV (LF power and triangular index) are not different between groups. Breathing at 0.1 Hz provides a standard BP stimulus and concentrates spectral power of heart rate at one frequency, enabling simple evaluation of BRS even when BP measurement is not available.

References