Mechanisms of respiratory sinus arrhythmia in patients with mild heart failure

MAGDI EL-OMAR, ATTILA KARDOS, AND BARBARA CASADEI
University Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

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El-Omar, Magdi, Attila Kardos, and Barbara Casadei. Mechanisms of respiratory sinus arrhythmia in patients with mild heart failure. Am J Physiol Heart Circ Physiol 280: H125–H131, 2001.—The high-frequency (HF) component of the heart rate variability (HRV) is regarded as an index of cardiac vagal responsiveness. However, when vagal tone is decreased, nonneural mechanisms could account for a significant proportion of the HF component. To test this hypothesis, we examined the HRV spectral power in 20 patients with mild chronic heart failure (CHF) and 11 controls before and during ganglion blockade with trimethaphan camsylate (3–6 mg/min iv). A small HF component was still present during ganglion blockade, and its amplitude did not differ between CHF patients and controls. The average contribution of nonneural oscillations to the HF component was 15% (range 1–77%) in patients with CHF and 3% (range 0.7–30%) in healthy controls (P < 0.005). During controlled breathing at 0.16 Hz, however, it decreased to 1% (range 0.2–13%) in healthy controls and 5% (range 1–44%) in CHF patients. Our results indicate that the HF component can significantly overestimate cardiac vagal responsiveness in patients with mild CHF. This bias is improved by controlled breathing, since this maneuver increases the vagal contribution to HF without affecting its nonneural component.

autonomic nervous system; vagus nerve; stretch

SPECTRAL ANALYSIS of heart rate (HR) variability (HRV) is a widely accepted method for evaluating the cardiac autonomic modulation in physiological and pathological conditions (27). In particular, it is well established that in the supine position and at a breathing frequency >0.15 Hz the high-frequency (HF) component of the HRV power spectrum (i.e., respiratory sinus arrhythmia) provides a measure of “cardiac parasympathetic responsiveness,” since it reflects the modulation of vagal cardiac efferent activity by breathing and the sinoatrial response to that modulation (23, 24). However, a small HF component has been seen in the transplanted denervated human heart (2, 3, 18, 25) and in healthy subjects after autonomic blockade (7, 23), suggesting that breathing-related changes in atrial transmural pressure (6, 21) or in the direction of the cardiac axis (17) may be responsible for at least part of the HRV in the HF range. In young healthy subjects, the contribution of nonneural mechanisms to the HF power of the HRV increases from 1% at rest to 30% during exercise (7). This implies that, in the presence of vagal withdrawal, the HF component may significantly overestimate cardiac parasympathetic responsiveness, especially when its power is normalized for the R-R interval (RR) variance (16). These findings may be applicable to patients with chronic heart failure (CHF) who are known to have impaired cardiac parasympathetic responsiveness and a reduced HRV (5, 9, 22). Experimental data, however, indicate that right atrial stretch may suppress neural and nonneural components of respiratory sinus arrhythmia (14), suggesting that the relative contribution to the HF power in patients with CHF may remain small, despite a reduction in HRV. To test this hypothesis, we calculated the relative contribution of autonomic and nonneural inputs to the HF power of the HRV in patients with mild CHF and in healthy age-matched controls.

METHODS

Twenty patients with stable heart failure [New York Heart Association (NYHA) Class II, mean age 61 ± 2 yr] and 11 age-matched healthy subjects (mean age 58 ± 2 yr) volunteered for the study. The latter were in good health as indicated by medical history, physical examination, electrocardiogram (EGC), and arterial blood pressure (BP) measurements. None of healthy subjects was taking any medication. All patients had been in stable CHF for ≥3 mo. Fifteen patients had had a documented myocardial infarction, one had chronic ischemic heart disease, and four had dilated cardiomyopathy. All patients were on angiotensin-converting enzyme inhibitors and furosemide, and one was on a β-blocker. None was on digitalis or antiarrhythmic drugs. The average radionuclide left ventricular ejection fraction was 25 ± 6% (mean ± SD).

Subjects with a history of atopic allergy, glaucoma, diabetes mellitus, atrial fibrillation, angina pectoris, or ECG evidence of ischemia-limiting exercise, chronic obstructive pulmonary disease, and liver or renal failure were excluded.

Written consent was obtained after the subjects were informed of the procedures and risks involved in the study. The protocol was approved by the Central Oxford Research Ethics Committee.

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breathing at 0.16 Hz. Minute averages of tidal volume (V
, ml) were obtained by dividing V
 by the breathing frequency.

The pulse interval response to baroreceptor stimulation
was then tested (26). Briefly, three to five rapid intravenous
injections of phenylephrine hydrochloride (Boots Pharma-
ceuticals) were given at ~3-min intervals. The initial dose of
0.05 mg was adjusted to obtain an increase in systolic BP
between 10 and 20 mmHg. Beat-by-beat BP recordings from
the finger were obtained noninvasively by an infrared photo-
plethysmograph (Finapres 2300 BP monitor, Ohmeda) while
the RR was measured from the ECG. The reflex lengthening
of the RR in response to the phenylephrine-induced increase
in systolic BP [i.e., the “baroreflex sensitivity,” in ms/mmHg
(26)] was taken as an index of reflex vagal activity.

A 0.1% NaCl solution of the ganglion blocker tri-
methaphan camsylate (Arfonad, Roche) was then infused
through an indwelling cannula in an antecubital vein. Beat-
by-beat BP and ECG were monitored continuously during the
infusion. The initial infusion rate of 3 mg/min was slowly
increased until the RR response to phenylephrine was abol-
ished. During ganglion blockade (GB), the dose of phenyleph-
rine was adjusted to achieve a peak systolic BP similar to
that obtained at baseline. The use of GB to inhibit the neural
inputs to the heart was preferred to the more conventional
α-adrenergic and muscarinic receptor antagonism for two
reasons: (1) Unlike propranolol or atropine, trimethaphan
camsylate has a very short half-life. This meant that we
could reverse possible adverse reactions very rapidly and
shorten considerably the period of observation after the ex-
periment. (2) In our hands, high doses of atropine (i.e., 0.04
mg/kg) do not block the cardiac baroreceptor reflex in all
subjects.

When GB was reached, recordings of ECG, breathing fre-
frequency, and V
 during spontaneous and controlled breathing
were repeated.

Power spectral analysis of HRV. The ECG and breathing
traces were digitized on-line by a 12-bit analog-to-digital
converter (AT-Codas, Dataq Instruments) at a sampling rate
of 600 Hz. The QRS complex was detected by identifying the
points of the low-pass-filtered first derivative of the ECG
signal, which exceeded an adaptive threshold. Each QRS
complex and its triggering were verified by visual inspection.
The breathing signal was sampled once every cardiac cycle.
Time series of 256 consecutive RR intervals were used for spectral
analysis. The autoregressive method, which was used to
evaluate the power spectral density of the RR series, has
been described in detail previously (7). Briefly, a computer
program first calculated the autoregressive coefficients using
the Levinson-Durbin algorithm, and the model order was
chosen by the Akaike information criterion starting from a

Table 1. HRV before and during GB in patients with mild heart failure and age-matched controls

<table>
<thead>
<tr>
<th></th>
<th>RR, ms</th>
<th>SDRR, ms</th>
<th>LE, ms</th>
<th>HE, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHF</td>
<td>Controls</td>
<td>CHF</td>
<td>Controls</td>
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<tr>
<td><strong>Spontaneous breathing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>745.5 ± 49.3</td>
<td>867.9 ± 50.4</td>
<td>25.63 ± 4.03</td>
<td>35.53 ± 2.82‡</td>
</tr>
<tr>
<td>GB</td>
<td>635.1 ± 37.3*</td>
<td>648.0 ± 48.0*</td>
<td>6.55 ± 0.47*</td>
<td>5.80 ± 0.48*</td>
</tr>
<tr>
<td><strong>Controlled breathing at 0.16 Hz</strong></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>740.0 ± 51.0</td>
<td>866.3 ± 51.0</td>
<td>27.91 ± 4.12</td>
<td>45.66 ± 4.61‡</td>
</tr>
<tr>
<td>GB</td>
<td>643.0 ± 37.1*</td>
<td>636.6 ± 51.5*</td>
<td>7.07 ± 0.73*</td>
<td>6.24 ± 0.70*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 15 patients with chronic heart failure (CHF) and 9 controls. HRV, heart rate variability; GB, ganglion blockade; RR, R-R interval; SDRR, RR standard deviation; LF, amplitude of the low-frequency component; HF, amplitude of the high-frequency component. *P < 0.005, GB vs. baseline; †P < 0.05, controlled breathing vs. spontaneous breathing; ‡P < 0.05, CHF vs. controls.
minimum order of 12. A spectral decomposition method was then applied to evaluate the power and the central frequency of the low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.50 Hz) components. The relative contribution of nonneural mechanisms to the HF power was calculated as follows:

\[
\text{HF power after GB (ms²)} \times 100
\]

\[
\text{HF power before GB (ms²)}
\]

The very-low-frequency component (<0.04 Hz) was examined to assess the presence of narrow peaks indicating periodic breathing (19).

**Cross-spectral analysis.** To assess the relationship between respiration and HF oscillations, the cross spectrum and squared coherence function of the HRV and the breathing signal were calculated as described by Pagani et al. (20). Briefly, cross spectra were computed by fast Fourier transformation, using a triangular window, on successive 50% overlapping series of 64 RRs each. The squared coherence function was used to evaluate the correlation between breathing and RR oscillations at the same frequency. The value of this function is regarded as an analog of the squared correlation coefficient \(r^2\) and ranges from 0 to 1.

**Statistical analysis.** Values are means ± SE. ANOVA (SuperANOVA, Abacus Concepts) was used to compare the data within the protocol stages and between patients with CHF and healthy subjects. To achieve a normal distribution and to normalize the variance of the data between stages, comparisons were made using the square root of the power of the spectral components (i.e., their amplitude, in ms). Nonparametric statistic was employed to compare the contribution of nonneural mechanisms to the HF power in CHF patients and controls. For this variable, data are given as geometric means. Statistical significance was accepted at \(P < 0.05\).

**RESULTS**

Two CHF patients and one control subject could not complete the study, since they developed a vasovagal reaction (bradycardia, nausea, sweating, and hypotension) shortly after the start of the infusion of trimethaphan camsylate. In two CHF patients and one control subject, the infusion of trimethaphan camsylate was not attempted, since the presence of frequent ectopic beats did not permit a satisfactory analysis of the baseline ECG recordings.

GB was usually obtained with an infusion rate of trimethaphan camsylate between 5 and 6 mg/min. At these doses, the increase in BP induced by the intra-

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**Table 2. \(V_t\) and \(V_T\) before and during GB**

<table>
<thead>
<tr>
<th>CHF</th>
<th>Controls</th>
<th>CHF</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td><strong>Spontaneous breathing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.9 ± 0.5</td>
<td>7.7 ± 0.7</td>
<td>517.3 ± 30.3</td>
</tr>
<tr>
<td>GB</td>
<td>6.9 ± 0.5</td>
<td>7.6 ± 0.8</td>
<td>500.9 ± 34.0</td>
</tr>
<tr>
<td><strong>Controlled breathing at 0.16 Hz</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.4 ± 0.4</td>
<td>8.7 ± 1.0</td>
<td>768.3 ± 44.3*</td>
</tr>
<tr>
<td>GB</td>
<td>7.3 ± 0.5</td>
<td>8.8 ± 1.1</td>
<td>756.3 ± 54.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(V_t\), ventilation; \(V_T\), tidal volume. * \(P < 0.05\) compared with spontaneous breathing.

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**Fig. 2.** Tachogram (top) and power spectra of the HRV (middle) and breathing signal (bottom) before and during GB in a healthy subject. Whereas the low-frequency (LF) component (centered at ~0.1 Hz) is completely abolished by GB, the high-frequency (HF) component (0.15–0.50 Hz) is still present, albeit greatly reduced in amplitude (note the different scale in the y-axis).
venous injection of phenylephrine was associated with a modest shortening of the RR in four subjects (Fig. 1) and no change in the others, with the exception of one CHF patient, in whom a trimethaphan camsylate infusion of 6 mg/min did not completely abolish the RR lengthening associated with phenylephrine. Since high doses of trimethaphan camsylate can cause respiratory depression, it was considered unsafe to increase the rate of infusion further, and the data from this patient were not included in the final analysis. During GB, all subjects experienced dry mouth and cycloplegia.

**Baseline measurements.** The mean RR did not differ between CHF patients (n = 15) and age-matched control subjects (n = 9); however, the standard deviation of the RR was lower in CHF patients during spontaneous (P < 0.05) and controlled (P < 0.001) breathing (Table 1). Likewise, patients had lower baroreflex sensitivity (4.34 ± 0.81 vs. 10.85 ± 2.31 ms/mmHg, P < 0.05) and a reduced HF component (Table 1). There were no significant differences in VTV, VT (Table 2), or spontaneous breathing frequency between control subjects and CHF patients (0.24 ± 0.02 and 0.28 ± 0.03 Hz, respectively). Controlled breathing at 0.16 Hz increased VT (Table 2) and the amplitude of the HF component (Table 1) in both groups.

The amplitude of LF oscillations was significantly greater in healthy controls than in CHF patients during spontaneous breathing; this difference, however, was no longer present during controlled breathing (Table 1). The center frequency of the LF component did not differ between the two groups (0.09 ± 0.01 vs. 0.10 ± 0.01 Hz during spontaneous breathing and 0.09 ± 0.01 vs. 0.09 ± 0.01 Hz during controlled breathing).

During spontaneous breathing, narrow peaks in the very-low-frequency range (centered at ~0.02 Hz) of the HRV power spectrum were found in two CHF patients. Analysis of the respiration signal showed that they were due to periodic breathing. This abnormal breathing pattern was not seen during controlled breathing or GB (data not shown).

**GB.** GB caused a significant reduction in the mean RR and its standard deviation (Table 1) in both groups. The RR fluctuations in the LF range were completely abolished by GB, but some degree of respiratory sinus arrhythmia persisted in all subjects and did not differ in magnitude between CHF patients and healthy controls (Table 1, Figs. 2 and 3). The correlation between RR fluctuations in the HF range and the breathing signal was not affected by GB (coherence values of 0.82 ± 0.03 and 0.89 ± 0.02, respectively), indicating that a close relationship between these signals persisted after neural control of sinoatrial node activity was abolished.

There was no significant change in VTV or VT in either group with GB (Table 2). Breathing frequency was not affected by GB and did not differ between controls and CHF patients (0.24 ± 0.03 and 0.27 ± 0.02 Hz, respectively). Controlled breathing significantly increased VT (Table 2) but did not affect the amplitude of the HF component after GB (Table 1).
Nonneural contribution to the HF power in CHF patients and in healthy controls. During spontaneous breathing, the relative contribution of nonneural mechanisms to the HF power was 3% in healthy controls (range 0.7–30%) and 15% in patients with CHF (range 1–76%, \( P < 0.005 \) vs. controls). During controlled breathing, nonneural mechanisms accounted for 1% of the HF power in healthy controls (range 0.2–13%) and 5% in CHF patients (range 1–44%, \( P < 0.005 \) vs. controls and \( P < 0.01 \) for the effect of controlled breathing at 0.16 Hz in both groups; Fig. 4).

In all subjects, the natural logarithm of the nonneural contribution to HF was inversely related to the RR standard deviation (Fig. 5; adjusted \( r^2 = 0.53 \) during spontaneous breathing and 0.50 during controlled breathing, \( P < 0.0001 \) for both).

**DISCUSSION**

Heart failure is associated with neurohumoral activation and a reduction in cardiac vagal responsiveness (10). Spectral analysis of the HRV in these patients has shown that the absolute power in the LF range decreases with the worsening of the disease and is often absent in NYHA Class IV patients (18). Likewise, the absolute power of the HF component has been found to be significantly decreased from the early stages of the disease (8, 11). However, HR fluctuations in the HF range are present even in the most advanced stages of CHF, where they can account for most of the short-term HRV (11, 18). To explain this finding, it has been suggested that respiratory sinus arrhythmia in severe CHF might be entirely mediated by nonneural mechanisms (11, 18). Experiments in anesthetized pigs, however, have shown a reduction in neural and nonneural HR oscillations in the HF range with atrial stretch (14), suggesting that nonneural modulation of HR may also be suppressed in patients with CHF.

The present study shows that small HR fluctuations synchronous with breathing persist after GB, and their magnitude is similar in healthy subjects and in patients with mild CHF. These residual HF fluctuations are unlikely to be vagally mediated, since, in the dose range employed in this study, trimethaphan camsylate completely abolished the reflex bradycardia in response to the phenylephrine-induced increase in BP (Fig. 1). Moreover, the LF component was abolished by GB in all subjects (Table 1). Since sympathetic and vagal activities have been shown to contribute to the HRV in this frequency range (23), its disappearance with high doses of trimethaphan camsylate provides further evidence for the adequacy of GB. We also show that, during spontaneous breathing, nonneural mechanisms contribute significantly (i.e., 15%) to the HF power in patients with mild CHF but not in healthy age-matched controls (3%). Since nonneural modulation of HR was preserved in CHF patients, its contribution to the HF component was inversely related to HRV (as assessed by the RR standard deviation, Fig. 5). Taken together, our results indicate that the HF power of the HRV can overestimate cardiac parasympathetic responsiveness in patients with mild CHF and, indeed, whenever the HRV is significantly reduced. This is especially the case when HF is expressed in “normalized” units (i.e., as a percentage of the RR variance) or as LF-to-HF ratio (1). Our findings would have been more dramatic if we had included patients with severe CHF. Indeed, we found that the contribution of nonneural oscillation to the HF component of the HRV was ~50% in four NYHA Class III patients...
(data not shown). However, high doses of tri-methaphan camsylate are poorly tolerated in this group; thus we decided to limit our study to less symptomatic patients. Nevertheless, the strong inverse relationship between contribution of nonneural mechanisms to the HF power and HRV provides proof of a basic principle that can be applied to virtually all pathophysiological conditions associated with a reduction in vagal activity or responsiveness (7). Predictably, maneuvers that are known to increase the vagally mediated respiratory sinus arrhythmia, such as slow deep breathing (13), significantly decreased the relative importance of nonneural mechanisms (Fig. 4). Since controlling the breathing rhythm also reduces the incidence of periodic or Cheyne-Stokes respiration in patients with CHF (19), this procedure, as well as the use of absolute units for expressing HF power, appears to be strongly advisable when one attempts to assess cardiac autonomic control or prognosis by using spectral analysis of HRV in patients with CHF.

Mechanisms responsible for the nonneural HF oscillations. HR fluctuations in the HF range result from periodic stretching of the sinoatrial node secondary to changes in atrial transmural pressure with breathing (6, 21). Pacemaking activity is known to be enhanced by mechanical stretch (15), and stimulation of mechanosensitive Cl– channels has been shown to be at least in part responsible for this phenomenon (1, 12). The degree of atrial stretch is dependent on the breathing pattern, and large increases in Vt and Vr have been shown to enhance nonneural respiratory sinus arrhythmia in heart transplant patients (2, 3, 25). Similarly, Perlini et al. (21) found that the HF power of the HRV in anesthetized rabbits after vagotomy and β-adrenergic blockade was positively correlated with Vt and, to a smaller extent, breathing frequency. The main determinant of nonneural HR oscillations, however, was respiratory flow, and combinations of Vt and breathing frequencies that gave the same V˙I also reduced the level of cardiac vagal responsiveness. However, the accuracy of respiratory sinus arrhythmia as a vagal index can be improved by controlled breathing, since this maneuver appears to increase the vagal contribution to respiratory sinus arrhythmia without affecting its nonneural component.

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