Influence of Cheyne-Stokes respiration on ventricular response to atrial fibrillation in heart failure

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Submitted 6 January 2005; accepted in final form 27 June 2005

Influence of Cheyne-Stokes respiration on ventricular response to atrial fibrillation in heart failure. J Appl Physiol 99: 1689–1696, 2005. First published June 30, 2005; doi:10.1152/japplphysiol.00027.2005.—In subjects with sinus rhythm, respiration has a profound effect on heart rate variability (HRV) at high frequencies (HF). Because this HF respiratory arrhythmia is lost in atrial fibrillation (AF), it has been assumed that respiration does not influence the ventricular response. However, previous investigations have not considered the possibility that respiration might influence HRV at lower frequencies. We hypothesized that Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) would entrain HRV at very low frequency (VLF) in AF by modulating atrioventricular (AV) nodal refractory period and concealed conduction. Power spectral analysis of R-wave-to-R-wave (R-R) intervals and respiration during sleep were performed in 13 subjects with AF and CSR-CSA. As anticipated, no modulation of HRV was detected at HF during regular breathing. In contrast, VLF HRV was entrained by CSR-CSA (coherence between respiration and HRV of 0.69 (SD 0.22) at VLF during CSR-CSA vs. 0.20 (SD 0.19) at HF during regular breathing, P < 0.001). Comparison of R-R intervals during CSR-CSA demonstrated a shorter AV node refractory period during hyperpnea than apnea [minimum R-R of 684 (SD 126) vs. 735 ms (SD 147), P < 0.001] and a lesser degree of concealed conduction [scatter of 178 (SD 56) vs. 246 ms (SD 72), P = 0.001]. We conclude that CSR-CSA entrains the ventricular response to AF, even in the absence of HF respiratory arrhythmia, by inducing rhythmic oscillations in AV node refractoriness and the degree of concealed conduction that may be a function of autonomic modulation of the AV node.

IN SUBJECTS WITH SINUS rhythm, respiration has a profound effect on heart rate variability (HRV): heart rate accelerates during inspiration and decelerates during expiration. This respiratory sinus arrhythmia is manifest in the frequency domain as a peak in HRV at the high frequency (HF) of respiration (0.15–0.5 Hz). In contrast, among subjects with atrial fibrillation (AF), respiratory modulation of ventricular rate (VR) at HF is either completely absent (14) or markedly diminished (28). These observations, which have given rise to the notion that respiration has little or no influence on HRV in AF, have been based on studies that either have not used frequency domain techniques or have looked for respiratory effects on HRV only at HF. However, the possibility that respiration might be capable of entraining HRV at lower frequencies has not been examined.

The VR in AF is not completely random. For example, the VR displays a circadian variation, being higher during the day and lower at night (13). These nonrandom alterations in rate have been attributed to modulation of the electrophysiological properties of the AV node, mediated by the autonomic nervous system (13, 14).

During AF, the VR is determined mainly by the electrophysiological properties of the atrioventricular (AV) node, chiefly the AV refractory period and the degree of concealed AV conduction. The AV refractory period determines the shortest possible time between successive atrial impulses that can be successfully transmitted to the ventricles (36). Concealed AV conduction is the phenomenon whereby atrial impulses incompletely penetrate the AV junction and do not reach the ventricles but affect the transmission of subsequent impulses (16, 42). In turn, changes in AV node refractory period and concealed conduction are considered reflections of alterations in autonomic input to the AV node (13, 14, 24, 45).

Our laboratory has previously shown, in subjects with systolic left ventricular heart failure and sinus rhythm, that Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) entrained HRV at the very low frequency (VLF, < 0.05 Hz) of periodic breathing (17, 18, 37). Because sinoatrial rate and AV nodal conduction are modulated by the autonomic nervous system in a similar fashion (14, 24, 45), this finding suggested that CSR-CSA might also be capable of organizing the seemingly random ventricular response to AF by entraining corresponding cyclical changes in AV nodal conduction. We, therefore, hypothesized that this breathing pattern would influence VR in AF at VLF by causing cyclical changes in the electrophysiological properties of the AV node. If so, this would be the first demonstration of respiratory modulation of HRV in the frequency domain in AF. To test this hypothesis, we studied patients with systolic left ventricular heart failure who also had AF and CSR-CSA during sleep. We studied patients with systolic heart failure because they have a high prevalence of both CSR-CSA and AF.

METHODS

Subjects. We studied 13 patients with AF (Table 1) who had symptomatic heart failure and systolic left ventricular dysfunction (left ventricular ejection fraction < 45% by radionuclide angiography...

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Frequency spectral analysis. Spectral analysis is a form of frequency domain analysis that makes use of the fact that component signals can be described by sinusoidal functions of differing amplitude and frequency. The component signals are extracted from the signal being analyzed and used to generate a plot of power (variability) distributed as a function of frequency, referred to as the power spectrum. In the present study, the heart rate [expressed as its inverse, R-wave to R-wave (R-R) interval] and ventilatory signals were analyzed with frequency spectral analysis by using Fourier transforms. This allowed study of the signals and of their interactions at separate frequencies. Segments 13 min 40 s in length were used to provide acceptable frequency resolution at the periodic breathing frequency. Analyses were confined to periods during which there was a stable pattern of breathing (either regular breathing or CSR-CSA) during stage 2 non-rapid eye movement sleep to maximize stationarity of the R-R interval data.

Once data were acquired, they were analyzed over two stages. The first stage (preprocessing) involved extracting the R-R intervals. The R-R intervals and all other signals were then passed through a low-pass digital filter (5th order, cutoff frequency = 0.8 Hz) and resampled at 10 Hz. In addition to allowing reduction of the data set, the low-pass filter suppressed the spectral power at the heartbeat frequency. The second stage of processing involved subdividing the 13-min 40-s data set, composed of 8,192 points, into overlapping segments of 2,048 points each, with half-overlapping of each segment. A Blackman-Harris window was applied to minimize spectral leakage. The cross-power spectrum and autopower spectrum were then ensemble averaged over the seven segments to reduce spectral variance. Power spectra were obtained over the frequency range of 0.005–0.8 Hz.

With instantaneous lung volume (ILV) derived from the VT signal taken as the input variable, and R-R interval and BP taken as the output variables, we calculated spectral power, coherence, and phase angles at the respiratory (i.e., high) frequency during periods of regular breathing and at the VLF of periodic breathing during CSR-CSA. Coherence is a measure (from 0 to 1) of the linear correlation between input and output signals. A “significant” coherence implies a strong relationship between two signals at the frequency of interest. The value of 0.5 to indicate significant coherence was first proposed by de Boer et al. (7, 8) and has subsequently been adopted by most authors who use spectral analysis techniques. However, the value is somewhat arbitrary and does not constitute a true test of statistical significance. Accordingly, we used a method first described by Manjarrez et al. (19), wherein a coherence value is considered significant if it exceeds the 95% confidence interval of the coherence function across the entire spectrum from 0.005 to 0.8 Hz. As an internal control, we also examined spectral power and coherence of VR and respiration at VLF (measured at the frequency of the previously observed periodic breathing for each patient) during regular breathing.

Electrophysiologic evaluation. The ventricular response to AF is largely determined by the electrophysiologic properties of the AV node: specifically, the AV nodal refractory period and the degree of concealed AV conduction. Both of these parameters can be estimated by using information derived from the R-R interval time series (2, 3, 6, 13). To ensure the robustness of our findings, we employed both the original technique of R-R interval analysis described by Billette et al. (3), as well as a separate technique devised by Chishaki et al. (6) and modified by Hayano et al. (13), which employs Lorenz plots to account for the rate dependency of AV nodal conduction. First, the R-R interval series for each patient was divided into sequences occurring during hyperpneic and apneic phases. Wide complex beats were identified visually and excluded from the analysis by two investigators who were blinded to the respiratory signal. Mean R-R intervals and estimates of AV conduction were then compared between apnea and hyperpnea.

The AV nodal refractory period is easily estimated by the minimum R-R interval (3), whereas the scatter (SD) of R-R intervals estimates the degree of concealed conduction (13). Accordingly, minimum R-R interval and R-R interval scatter (corresponding to AV nodal refractory period and degree of concealed AV conduction, respectively) were compared between hyperpnea and apnea. The minimum R-R interval was taken as the fifth percentile of the R-R interval distribution. The fifth percentile value rather than the absolute minimum R-R interval is considered a more reliable estimate of the AV nodal refractory period because it represents more than a single event and has been validated against direct measurements of minimum AV nodal refractory period obtained by rapid atrial pacing (3).

Table 1. Baseline and demographic data of study subjects

<table>
<thead>
<tr>
<th>n</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>68.4 (SD 9.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4 (SD 4.9)</td>
</tr>
<tr>
<td>Central AHI, events/h</td>
<td>27.1 (SD 12.1)</td>
</tr>
<tr>
<td>Obstructive AHI, events/h</td>
<td>3.7 (SD 4.0)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27.5 (SD 15.1)</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Idiopathic-dilated cardiomyopathy</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Nondihydropyridine</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>9 (69.2)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>4 (30.8)</td>
</tr>
</tbody>
</table>

Values are means (SD); n, no. of subjects. BMI, body mass index; AHI, apnea-hypopnea index; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Because both AV nodal refractory period and concealed conduction vary with heart rate, the rate-dependent refractory period and degree of concealed conduction were estimated according to the Lorenz plot technique described by Hayano and coworkers (13). Separate Lorenz plots were generated for R-R interval sequences (2, 6) occurring in the hyperpneic and apneic phases, wherein each R-R interval was plotted on the vertical axis against the immediately preceding R-R interval on the horizontal axis. For each Lorenz plot, the R-R intervals occurring after a particular length of preceding R-R interval have a distribution with a distinct lower limit, corresponding to the rate-dependent AV nodal refractory period. The set of lower limits associated with each length of preceding R-R interval defines a straight line (the lower envelope), above which longer R-R intervals are scattered (Fig. 1).

The regression line of the lower envelope was generated as follows. First, the horizontal axis was divided into eight consecutive bins so that each bin included an equal number of data points. Then, within each bin, the minimum value of the subsequent R-R interval was determined. These eight minimum values were then subjected to linear regression analysis to define the lower envelope. The estimated rate-dependent refractory period was then defined as the intercept of the lower envelope on the horizontal axis. The estimated rate-dependent degree of concealed conduction was quantified as the degree of scatter above the lower envelope calculated as the root-mean-square difference of R-R intervals from the regression line of the lower envelope (scattering index).

**Statistical analysis.** Results are reported as means (SD). In a given subject, respiration (ILV) was considered to exert a significant influence on VR (R-R intervals) and BP when the coherence between the two signals exceeded the 95% confidence interval (19) across the frequency range from 0.005 to 0.8 Hz. The prevalences of significant coherences between ILV and HRV at HF during regular breathing and at VLF during both CSR-CSA and regular breathing were compared by Fisher’s exact tests, and average values of coherence and peak power spectral densities at HF and VLF during each breathing condition were compared within subjects using repeated-measures analysis of variance with post hoc Tukey’s test. Mean R-R intervals and estimates of AV conduction were compared between apnea and hypopnea using paired t-tests. The statistical software used was SigmaStat 2.03 (SPSS). Results were considered significant at $P < 0.05$.

**RESULTS**

**Subjects.** Characteristics of the 13 study subjects are shown in Table 1. They were all men who were generally elderly and mildly overweight, with markedly depressed left ventricular systolic function due mainly to ischemic cardiomyopathy. They had a moderate degree of CSR-CSA as indicated by their apnea-hypopnea indexes.

**Frequency spectral analysis.** Figure 2 shows tracings from a representative subject demonstrating no significant respiratory arrhythmia during regular breathing. The power spectrum shows only a “white noise” pattern characteristic of AF (14, 44). Figure 3 illustrates periodic respiratory-related oscillations in VR R-R intervals at the VLF of CSR-CSA in the same subject. The R-R intervals increase (i.e., VR falls) during apnea, and the R-R intervals decrease (i.e., VR rises) during hypopnea. Evidence of respiratory arrhythmia at HF was absent in all but one subject, and no subject had evidence of respiratory-related HRV at VLF during regular breathing (Table 2). In contrast, during CSR-CSA, significant respiratory-related HRV at VLF was observed in 12 subjects (92%). The group-average coherence between respiration and R-R interval at VLF during CSR-CSA was significantly greater than that between respiration and R-R interval at either VLF or HF during regular breathing ($P < 0.001$ for both). Peak power spectral densities of both respiration (input power) and R-R intervals (output power) were approximately sevenfold higher at VLF during CSR-CSA [$11.1 \text{ I}^2/\text{Hz (SD 9.5)}$ and 764 $\text{ms}^2/\text{Hz (SD 674)}$, respectively] than at HF during regular breathing [$1.71 \text{ I}^2/\text{Hz (SD 2.62)}$ and 103 $\text{ms}^2/\text{Hz (SD 95)}$, respectively, $P < 0.05$ for both]. The phase angle between VLF oscillations and the R-R intervals have a distribution with a distinct lower limit, corresponding to the rate-dependent AV nodal refractory period. The set of lower limits associated with each length of preceding R-R interval defines a straight line (the lower envelope), above which longer R-R intervals are scattered (Fig. 1).

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![Fig. 1. Lorenz plot of R-wave-to-R-wave (R-R) intervals in atrial fibrillation (AF) from a representative subject with AF. Each R-R interval is plotted on the vertical axis against the immediately preceding R-R interval on the horizontal axis. Dotted vertical lines indicate the separation of values into 8 bins. The solid line indicates the lower envelope, obtained by linear regression of the minimum value within each bin. RR$_n$, $n$th R-R interval; RR$_{n+1}$, $(n + 1)$th R-R interval; LE$_{1.0}$, intercept of the lower envelope at 1.0 s.](image-url)

![Fig. 2. Time (left) and frequency (right) domain data from a representative subject during regular breathing. There is no respiratory variation in R-R interval. The power spectrum (which shows variability of the parameter plotted against frequency) displays only a “white noise” pattern, which is characteristic of AF and lacks the distinct high frequency peak in R-R interval variability, which denotes respiratory arrhythmia. Coherence between respiratory and R-R interval variability at the breathing frequency is low (0.29).](image-url)
in respiration and HRV was 33° (SD 27), indicating that peak VR followed peak respiration by 7.7 s (SD 3.8).

In three subjects, BP was monitored and also observed to oscillate at VLF during CSR-CSA, such that BP peaks occurred during hyperpnea and troughs during apnea (Fig. 4). VLF oscillations in respiration and BP were highly coherent [0.74 (SD 0.22), >95% confidence interval in all subjects]. The phase angle between VLF oscillations in respiration and BP was 30° (SD 28), almost identical to that between respiration and VR. Thus BP and VR oscillated synchronously, indicating that changes in VR did not arise from a baroreflex mechanism.

VR, AV node refractoriness, and concealed conduction. Figure 5 shows a Lorenz plot illustrating rate-dependent changes in estimated AV nodal refractoriness and concealed conduction in the same subject as depicted in Figs. 2 and 3. During hyperpnea, there is a downward shift of the lower envelope and a decrease in the scatter above the envelope (Fig. 6), a comparison of the distribution of R-R intervals during CSR-CSA for all 13 subjects is displayed. During hyperpnea, the mean R-R interval was lower than during apnea [989 (SD 207) ms vs. 735 ms (SD 147), P < 0.001], and 595 (SD 113) ms vs. 668 ms (SD 114), P = 0.018, respectively]. Similarly, both estimates of concealed conduction, R-R interval scatter (non-rate dependent), and scattering index (rate dependent) were lower during hyperpnea than during apnea [178 (SD 56) ms vs. 246 ms (SD 72), P = 0.001, and 431 (SD 120) ms vs. 494 ms (SD 158), P = 0.029, respectively].

Oxyhemoglobin desaturation during CSR-CSA was minimal but significant [mean nadir SaO2 per CSR-CSA cycle was 90% (SD 4) during the hyperpnea vs. 93% (SD 5) during the apnea, P = 0.038]. Note that minimum SaO2 occurs during the hyperpnea, rather than the apnea, due to delays in circulation time between the pulmonary circulation and the ear, as well as inherent delays in the response time of the oximeter itself. These inherent delays preclude accurate calculation of the true phase delay between SaO2 changes and VR changes. Therefore, coherence between SaO2 and VR was not calculated, since it would be high (given that SaO2 fluctuates in concert with changes in respiration, which are themselves coherent with

Table 2. Coherences between respiration and R-R intervals

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>EF</th>
<th>AHI</th>
<th>VLF Coherence During CSR-CSA</th>
<th>VLF Coherence During Regular Breathing</th>
<th>HF Coherence During Regular Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>17.7</td>
<td>0.66*</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>21.2</td>
<td>0.85*</td>
<td>0.41</td>
<td>0.18</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>26.0</td>
<td>0.58*</td>
<td>0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>29.2</td>
<td>0.86*</td>
<td>0.38</td>
<td>0.29</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>47.3</td>
<td>0.52*</td>
<td>0.10</td>
<td>0.65*</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>18.8</td>
<td>0.18</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>30.1</td>
<td>0.88*</td>
<td>0.25</td>
<td>0.29</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>23.4</td>
<td>0.96*</td>
<td>0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>29.6</td>
<td>0.43*</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>53.5</td>
<td>0.86*</td>
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<tr>
<td>11</td>
<td>31</td>
<td>34.0</td>
<td>0.85*</td>
<td>0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>12</td>
<td>22</td>
<td>38.5</td>
<td>0.58*</td>
<td>0.04</td>
<td>0.35</td>
</tr>
<tr>
<td>13</td>
<td>20</td>
<td>46.6</td>
<td>0.70*</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.5(15)</td>
<td>31.5 (11.5)</td>
<td>0.64 (0.29)†</td>
<td>0.17 (0.15)</td>
<td>0.19 (0.18)</td>
</tr>
</tbody>
</table>

EF, ejection fraction; AHI, apnea-hypopnea index; VLF, very low frequency; CSR-CSA, Cheyne-Stokes respiration with central sleep apnea; HF, high frequency. *Coherence exceeds 95% confidence interval in the range 0.005–0.8 Hz. †P < 0.001 compared with VLF and HF coherence during regular breathing.
changes in VR) but difficult to interpret physiologically without information about phase delay between these two signals.

DISCUSSION

A number of studies have shown that respiratory variation in VR in AF is either absent or markedly attenuated. However, these studies examined respiratory influences only in the normal breath-to-breath HF range (14, 28, 44). The present study demonstrates that respiratory oscillations during CSR-CSA have important effects on VR at VLF in heart failure patients with AF, even though HF respiratory arrhythmia during regular breathing was, as expected, absent or negligible. Over three decades ago, Urbach et al. (38) described slowing of the VR during apneas and speeding during hyperpneas in patients with AF. Our data are consistent with those observations and indicate that the immediate mechanism responsible for oscillations in VR during CSR-CSA is a respiratory-related cyclical alteration in the electrophysiological properties of the AV node.

**Frequency spectral analysis.** In the frequency domain, the respiratory variations of CSR-CSA differ from those of regular breathing in two ways: they are of higher magnitude and of lower frequency. It is possible that respiratory variation must exceed a certain level to influence AV nodal conduction. Indeed, the transformation from regular breathing to CSR-CSA resulted in an approximately sevenfold increase in the input power of respiration (ILV), in association with a sevenfold increase in output power of R-R intervals.

The lower frequency of CSR-CSA compared with regular breathing may also be important. Recently, some groups have applied spectral analysis to AF and reported that the ventricular response to AF is not completely random, particularly at lower frequencies. While the power spectrum of AF resembles random “white noise” at HF, it is indistinguishable from the power spectrum associated with sinus rhythm at lower frequencies, with the same 1/frequency fractal component (14). Given the similarity of the power spectrum of HRV in AF to that of sinus rhythm at lower frequencies, VR in AF may also be subject to the same low-frequency influences. Our findings reinforce this concept. VR in AF is chaotic at HF, but it is, nonetheless, strongly influenced by respiration at lower frequencies, responding in much the same way as sinus rhythm (18, 37). In this regard, the AV node in AF may act as a physiological low-pass filter for VR, because it responds only to those influences below a certain frequency threshold.

![Fig. 4. Time domain panel from a representative subject depicting synchronous oscillations in blood pressure (BP) and R-R interval accompanying Cheyne-Stokes respiration. Maximum ventricular rate (i.e., trough in R-R interval) coincides with maximum BP, indicating that rises in ventricular rate are not the result of a baroreflex mechanism. Both ventricular rate and BP peak during the hyperpnea.](image)

![Fig. 5. Lorenz plots of R-R intervals during hyperpnea and apnea from the same subject shown in Figs. 2 and 3. The solid line indicates the regression line on the lower envelope of each scattergram. During hyperpnea, there is a downward shift of the lower envelope and a decrease in the scatter above the envelope compared with apnea, indicating a reduction in AV nodal refractory period and degree of concealed conduction.](image)
AV node refractoriness and concealed conduction. AV node refractoriness determines the lower limit of the R-R intervals (which are manifestations of successive impulses successfully conducted by the AV node) during AF and is the most important determinant of mean VR (2, 3). However, the characteristic “irregular irregularity” of VR in AF cannot be explained by AV node refractoriness. Because an atrial impulse is always immediately available at the end of the AV node refractory period, a relatively regular ventricular response might be expected, with each R-R interval being close to the length of the refractory period. The chaotic rhythm characteristic of AF arises not from AV node refractoriness but mainly from concealed AV conduction. This is the phenomenon whereby atrial impulses penetrating incompletely into the AV junction do not reach the ventricles but affect the transmission of subsequent impulses (16, 42). Concealed conduction, by creating a high level of variation in the number and frequency of penetrating impulses, results in the classic chaotic rhythm of AF. The greater the degree of concealed conduction, the greater the scatter of the R-R intervals.

We obtained estimates of AV nodal refractory period and concealed conduction during hyperpnea and apnea using both rate-independent and rate-dependent techniques. Using either technique, the findings were consistent: hyperpnea results in shorter R-R intervals, a shorter AV node refractory period, and a lesser degree of concealed conduction than apnea.

These cyclical variations in AV conduction most likely result from changes in the autonomic neural modulation of the electrophysiological properties of the atria and AV node (13, 14, 24, 45), since it has been demonstrated under a variety of conditions that AV refractory period is shortened by sympathetic activity and lengthened by parasympathetic activity (20, 24, 36, 45). Similarly, parasympathetic stimulation of the atria has been shown to increase the degree of concealed conduction (23). AV conduction has been shown to be altered by hypoxia but only at levels of hypoxia much more extreme than we observed in our subjects (31, 47). Although AV conduction has not been reported to be influenced by direct effects of hypercapnia or cardiac stretch, it is remotely possible that these factors may influence AV conduction.

Oscillations in ventricular response were present, despite almost all of the subjects being on medications that can influence conduction through the AV node and slow VR in AF (26). Mean VR was higher during hyperpnea than during apnea, regardless of whether or not patients were taking β-blockers or digoxin. The lack of effect of these AV nodal blocking agents on our findings may be due to our inability to detect small changes due to the small number of subjects in our study, which precluded assessment of overlapping subgroups.

Nor does the failure of our findings to be influenced by medications shed light on the physiological mechanisms, since β-blockers act on the sympathetic nervous system, whereas digoxin acts largely through the parasympathetic nervous system.

Oscillations in autonomic outflow during CSR-CSA might be the direct result of oscillations in central respiratory drive (12, 41). Indeed, sympathetic nervous system activity has been shown to be elevated and to oscillate during CSR-CSA (22, 40). There is evidence for direct connections between respiratory and cardiovascular sympathetic neurons in the brain stem. Activation of the respiratory neurons can coactivate these sympathetic neurons (12) in animal preparations. In intact humans, there is evidence both for and against respiration directly causing sympathoexcitation. Isocapnic hyperventilation has been shown by one group to diminish baroreflex suppression of muscle sympathetic nerve activity (MSNA) (39), but another did not detect any increase in MSNA with increasing levels of respiratory motor output (33). However, we have previously reported, in a heart failure patient with AF and CSR-CSA, that MSNA rose during hyperpnea and fell during apnea in concert with rises and falls in VR and BP, respectively, (5), and that these changes in VR and BP are not eliminated by correction of hypoxia (17).

While changes in both sympathetic and parasympathetic tone can influence AV conduction, our findings are more compatible with sympathetic influences. Our subjects had heart failure, which is associated with greatly diminished parasympathetic modulation of heart rate (11). Indeed, the loss of the normal parasympathetic modulation of heart rate was the earliest autonomic abnormality described in both experimental and human heart failure (1, 4, 9, 30). Considering that respiratory modulation of both sympathetic and parasympathetic outflow has been shown to be dependent on the level of preexisting tone (10), the observed changes in AV properties that correspond with oscillations in BP are more likely to be the result of sympathetic than of parasympathetic modulation. However, the larger VR values accompanying CSR-CSA might...
conceivably engage parasympathetic reflexes (35) not active during regular breathing in these patients.

Because hyperpnea-induced increases in BP following apnea have been shown to be due to increases in sympathetic outflow (15), our observation of synchronous BP oscillations in three patients lends further support for a sympathetic mechanism being responsible for our findings.

Another way in which we might distinguish between the sympathetic and parasympathetic nervous systems is to examine the latency of the responses. The oscillations in mean VR and BP lagged changes in respiration by ~8 s. Thus there appears to be a relatively long time constant between generation of central respiratory drive, ventilation, and the subsequent VR and vasomotor responses. This 8-s delay is again more in keeping with the behavior of the sympathetic than the parasympathetic nervous system, which has a shorter time constant (27). On the other hand, the observed differences in concealed conduction have been linked more closely to the effects of parasympathetic (25, 42) than sympathetic (43) stimulation, implying that both arms of the autonomic nervous system might be influenced by CSR-CSA.

Alterations in blood gases might be a necessary intermediate step by which CSR-CSA exerts its cyclical effects on the autonomic nervous system. The sympathoexcitatory effects of CO2 are likely to be particularly relevant in patients with CHF and CSR-CSA, in whom there is evidence of an enhanced muscle sympathetic nerve response to CO2 (21). Dips in oxygen saturation also accompany CSR-CSA, and, because of the circulatory delay, such dips are maximal in the middle of the hyperpnea and should cause stimulation of sympathetic activity at that time. Thus, although the hypoxia we observed was relatively mild [nadir SaO2 90% (SD 4)], we cannot exclude its role in causing the observed oscillations in VR, particularly since the peripheral chemoreceptors are sensitized in CHF (32, 34). Nevertheless, our laboratory has previously shown that oscillations in heart rate and BP occur during periodic breathing even in the absence of hypoxia (17).

Limitations. Our study is limited by the lack of direct measurements of sympathetic and parasympathetic activity. Instead, the activity of the autonomic nervous system has been surmised by analyzing its putative effect on AV nodal electrophysiology. Moreover, we cannot exclude the role of intermediate steps between the generation of central respiratory drive and the observed electrophysiological changes, such as alterations in blood gases, lung stretch reflexes, or direct effects on cardiac stretch.

It is remotely possible that CSR-CSA influences the electrophysiology of the AV node by a completely nonautonomic mechanism, such as a direct effect of local hypoxia or cardiac stretch. However, no such direct effects of these factors on AV nodal conduction have been reported, with the exception of much more extreme levels of hypoxia (31, 47).

In conclusion, in subjects with heart failure and AF, VLF oscillations in VR occur in time with periodic oscillations in ventilation during CSR-CSA, such that mean VR is higher during hyperpnea than during apnea. In addition, we have demonstrated that the electrophysiological mechanism mediating these oscillations in VR is cyclical alterations in AV nodal refractory period and concealed conduction that occur in time with oscillations in ventilation. The precise means by which CSR-CSA influences these properties of the AV node remain to be determined, but changes in sympathetic or parasympathetic activity are the most likely candidates. To determine whether these effects are mediated centrally, or peripherally through alterations in blood gases, or engagement of lung stretch reflexes will require further investigation.

GRANTS

This work was supported by the Canadian Institutes of Health Research (Grants MOP 11607 and UI 149909). R. S. T. Leung is supported by a Canadian Institutes of Health Research Clinician Scientist Phase I Award, J. S. Floras by a Heart and Stroke Foundation of Ontario Career Scientist Award, and T. D. Bradley by a Canadian Institutes of Health Research Senior Scientist Award.

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