Beat-to-Beat Variations of Heart Rate Reflect Modulation of Cardiac Autonomic Outflow

J. Philip Saul

What is most intriguing about heart rate (HR) variability is that there is so much of it. HR is constantly responding both rapidly and slowly to various physiological perturbations. We now understand that the frequency and amplitude of these HR fluctuations are indicative of the autonomic control systems underlying the response.

Introduction

Since the 1930s, the control of physiological systems has been understood in terms of homeostasis, a process by which system variables are maintained within a relatively narrow range by the system control elements. For the intact cardiovascular system, feedback and control mechanisms are particularly efficient at maintaining the mean values of arterial blood pressure (ABP) and central venous volume within a narrow range by constant regulation of heart rate (HR) and vascular tone. Thus quantifying changes in the mean value of ABP or HR may not unveil substantial responses in the underlying control systems during periods of hemodynamic stress.

Alternatively, spontaneous fluctuations of HR and ABP reflect the interaction between ongoing perturbations to the cardiovascular system and the response of its regulatory mechanisms. Analysis of beat-to-beat variability of HR and ABP can provide specific quantitative information about modulation of cardiac vagal, cardiac sympathetic, and peripheral sympathetic nervous activity (1, 8, 9, 13). Although HR and ABP fluctuations at the respiratory frequency and at lower frequencies (<0.15 Hz, period >6 s) were recognized well before the 20th century, quantitative assessment of the characteristics and significance of these fluctuations has been much more recent. The critical importance of normal HR variability was first elucidated in observations of fetal HR, where it became clear that absence of the normal beat-to-beat variability of HR is indicative of abnormal central nervous modulation of HR and in indication for emergency Caeserian section.

In the early 1970s power spectral analysis was first employed to quantify spontaneous HR variability in normal humans (5). These investigators described three typical peaks in the HR power spectrum (Fig. 1): *1*) a peak at the respiratory frequency corresponding to respiratory sinus arrhythmia (RSA), *2*) a peak centered near 0.1 Hz considered important in ABP control, and *3*) a peak at 0.04 Hz thought to be related to peripheral vasomotor regulation. Further work has shown that although there is a tendency for HR fluctuations to occur in the three described frequency ranges, the frequency as well as the amplitude of the spectral peaks is constantly changing in response to various hemodynamic perturbations, such that over the course of an entire day, few preferential frequencies stand out in normal individuals (12).

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Mediators of the fluctuations

Experiments using pharmacologic blockade of the sympathetic and parasympathetic inputs to the sinoatrial (SA) node have demonstrated that virtually all HR fluctuations >0.03 Hz are caused by changing levels of the efferent activity of these inputs and have shown that each of the autonomic branches mediate HR fluctuations in different frequency bands (1, 8, 9). Specifically, HR fluctuations at frequencies >0.15 Hz are mediated solely by changing levels of vagal activity, whereas fluctuations <0.15 Hz can be mediated by changing levels of both cardiac vagal and sympathetic activity. HR fluctuations <0.03 Hz (period of 50 s) may be also mediated by changing plasma levels of neurohormones. Recently, Berger et al. (2), using a contemporary systems analysis technique to study the canine atrial rate response to induced broad-band fluctuations of vagal and sympathetic firing frequency, directly confirmed the differential response of HR to fluctuations of the activity of the two autonomic branches. In addition, their findings allowed for a complete and precise description of the response characteristics of HR to modulation of these inputs as a function of frequency (i.e., the frequency response or transfer function) and led to formulation of a model for neural control of HR (Fig. 2*B*).

In this model, the HR response to modulation of sympathetic neural activity is characterized by a fixed time delay and a marked roll-off in gain at frequencies >0.1 Hz (only low frequencies are fully transmitted), whereas parasympathetic HR control is characterized by a rapid broad-band response that is inverted, since increasing vagal activity leads to a decrease in HR (180° phase shift). In engineering terms, the responses have the gain and phase characteristics of low-pass filters such that the sympathetic filter has a much lower cutoff frequency than that of the parasympathetic filter. Although poorly understood, the slower response of HR to modulation of sympathetic activity seems to lie at the level of neurotransmitter ki-

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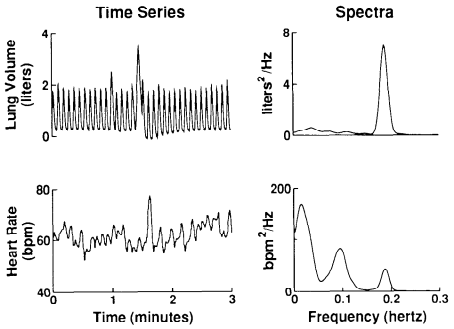

FIGURE 1. Instantaneous respiratory and heart rate (HR) time series and power spectra from 1 normal individual who is standing. Respiratory rate is voluntarily controlled with a metronome at 12 breaths/min or 0.2 Hz. Thus respiratory signal has virtually all its energy near 0.2 Hz, as displayed in the power spectrum. Conversely, HR signal is more complicated. HR spectrum clearly divides energy or variance in signal into the 3 typical frequency bands: *1*) respiratory frequency of 0.2 Hz (RSA), *2*) near 0.1 Hz (so-called 10-s rhythm), and *3*) at a very low frequency centered about 0.02 Hz (period of ~50 s). Three peaks are not always seen, and in fact, the frequency and amplitude of these peaks may vary dramatically within an individual depending on autonomic state and activity level. Peaks >0.15 Hz are due only to modulation of vagal activity, while peaks <0.15 Hz may be result of modulation of both cardiac sympathetic and vagal activity.

netics and receptor activation, as indicated in Fig. 2*B*. The model also suggests that the rate responses to the two autonomic inputs add linearly to produce the final HR, a situation known to be unrealistic for large fluctuations but which may apply when only small perturbations about the mean operating point are considered.

The differential frequency response of HR to modulation of cardiac sympathetic and parasympathetic efferent activity is the critical link for using spectral measures of HR variability to probe autonomic control of the heart. The idea is that by understanding the transfer characteristics of the neural control system and measuring the system output HR, one can estimate the characteristics of the autonomic inputs. This notion is certainly true at frequencies >0.15 Hz where only vagal modulation affects HR, but it is obviously more suspect at lower frequencies where both autonomic branches have an effect. Of course, if the effects of one or the other autonomic inputs are absent, then the short-term HR fluctuations that remain are caused primarily by the other autonomic branch.

Origin of the fluctuations

Factors that modulate the cardiac autonomic inputs (Fig. 2*A*) obviously play a dominant role in HR control, but it must be remembered that the final common pathway for their effect on HR is primarily the cardiac vagal and sympathetic efferents. Consequently, their effect may be ultimately determined by the autonomic response characteristics discussed above (i.e., the vagal and sympathetic filters). Figure 2*A* shows diagrammatically how central command, respiration, arterial baroreflexes, and cardiopulmonary reflexes may all modulate cardiac autonomic activity and subsequently HR. Central command can obviously be modulated at virtually any frequency and seems to play an important role in many situations, including emotional responses and the initial responses to exercise; however, because central command is difficult both to measure and control, little emphasis will be placed on it in this discussion.

Respiratory frequencies (>0.15 Hz). In practice respiratory activity seems to be the only significant physiological noise source >0.15 Hz. In addition, respiratory activity only rarely occurs at frequencies <0.15 Hz (9 breaths/min). If one combines these observations with the knowledge that the vagus is the only autonomic input capable of modulating HR at frequencies >0.15 Hz, it quickly becomes obvious that higher frequency fluctuations of HR specifically reflect respiratory modulation of cardiac vagal activity. Of course, as multiple investigators have shown, respiration mediates its effect on vagal activity and HR through a number of mechanisms, which include a direct central action on vagal efferents and mechanical influences on the arterial and cardiopulmonary baroreflexes. It is important to note that respiration also modulates sympathetic efferent activity, but at typical respiratory frequencies (>0.15 Hz) the SA node response to that activity is simply too slow to significantly modulate HR. However, if respiratory activity does occur at lower frequencies, HR will be modulated through the effects of respiration on both sympathetic and vagal activity.

Midfrequencies (0.03–0.15 Hz). HR and ABP fluctuations at and below this frequency range are referred to variably as Mayer waves. In contrast to the situation at higher frequencies, at lower frequencies <0.15 Hz, the situation is much more complex. Not only are both sympathetic and vagal activity capable of modulating HR, but spontaneous feedback rhythms seem to occur, centered at frequencies between 0.05 and 0.1 Hz (periods 10–20 s). Both experimental and computer modeling results support the notion that baroreflex feedback is necessary for these rhythms. Based on these studies one might speculate that the frequency and amplitude of the HR oscillations depend on the relative gains of the elements that modulate cardiac vagal, cardiac sympathetic, and peripheral sympathetic efferent activity. For instance, a relatively larger vagal influence should increase the oscillatory frequency toward 0.1 Hz because of the rapid rate response to vagal stimuli and, conversely, a larger sympathetic influence should reduce the frequency toward 0.05 Hz because of the slower sympathetic response.

Very low frequencies (<0.03 Hz). HR and ABP fluctuations centered at lower frequencies <0.05 Hz have been observed and studied in a variety of circumstances. It is clear that multiple variables have a physiological influence on these very-low-frequency fluctuations, including blood volume status, carotid artery occlusion, cardiac pump competence, and low-frequency oscillations of respiratory tidal volume (periodic or Cheyne-Stokes-like breathing) (15). In some studies very-low-frequency HR fluctuations have been found to be critically dependent on ABP fluctuations at the same frequency, suggesting a role for arterial baroreflexes, whereas in others HR and sympathetic nerve oscillations have continued despite elimination of the ABP fluctuation, suggesting the arterial baroreflex is not always necessary to sustain these oscillations (10).

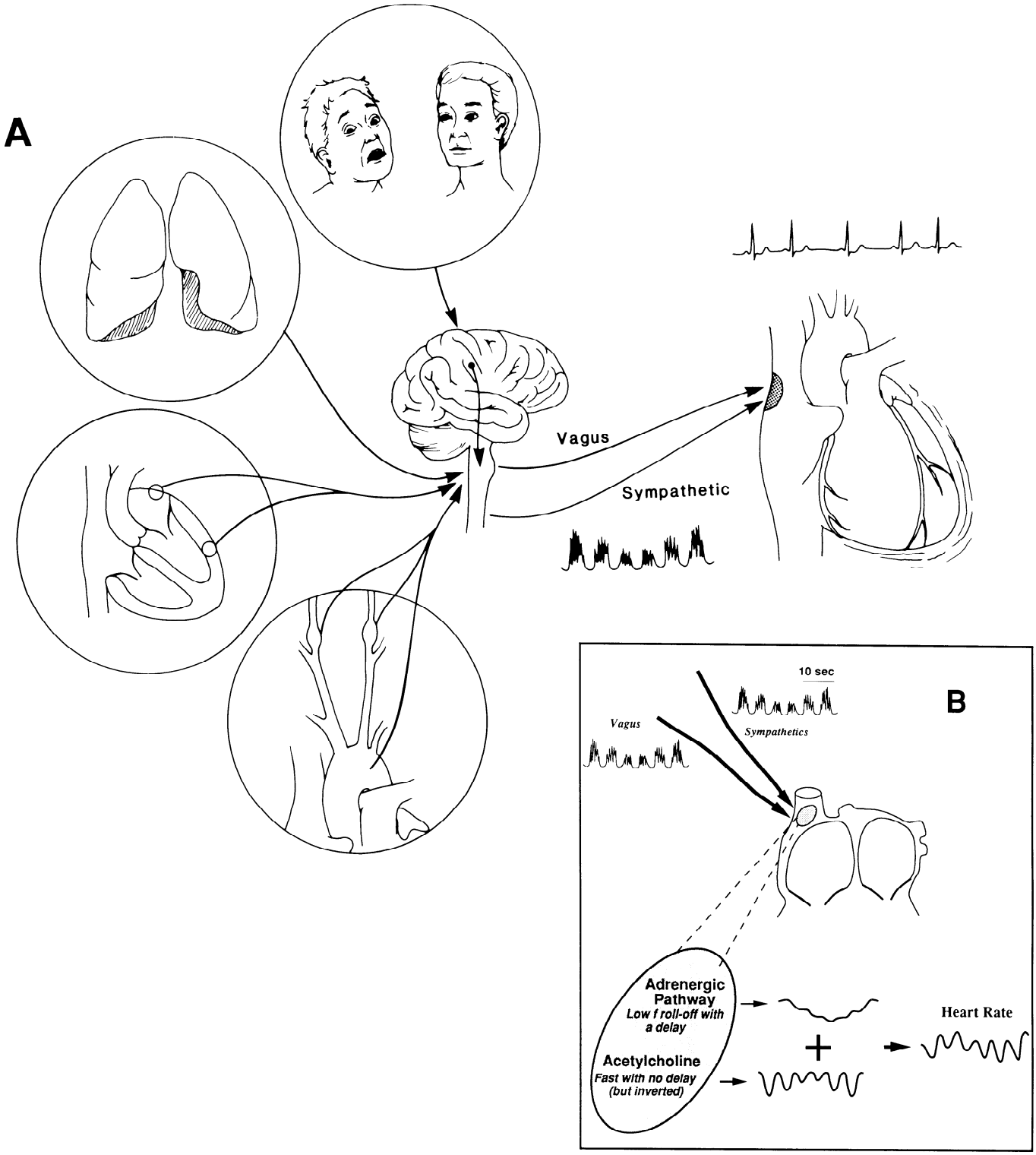

FIGURE 2. Model of short-term HR control. Central command, respiration, and feedback from arterial and cardiopulmonary baroreceptors modulate cardiac vagal and sympathetic efferent activity (*A*). HR response (i.e., HR variability) is then determined by response characteristics of sinoatrial node to modulation of activity of each of the autonomic branches (*inset B*). See text for full details.

Interpretation of HR spectra

It is important to realize that short-term HR fluctuations are the direct result of the heart's response to changing levels or modulation of cardiac autonomic activity and are not necessarily related to the mean firing rates of the vagal and sympathetic fibers. Although, in general, modulation of these inputs by factors such as respiration and the heart's response to that modulation will be larger when the mean levels are higher, it is certainly possible for

either mean vagal or sympathetic activity to be elevated without the presence of significant modulation, or for modulation to occur without a significant response from the heart (e.g., saturation). Thus it is most appropriate to interpret HR spectral peaks as quantifiers of autonomic responsiveness rather than autonomic "tone." This issue is extremely important in the interpretation of low-frequency fluctuations.

Clinical observations

Analyses of spontaneous fluctuations of HR and ABP have proven useful in understanding cardiovascular regulation in normal adults (8, 9) and adults with congestive heart failure (CHF) (13), diabetes (3), hypertension (7), and cardiac transplants (11). In fact, changes in HR variability patterns have been indicative of graft rejection in the transplanted heart (11), may be predictive of sudden cardiac death after myocardial infarction (6), and seem to predict impending cardiovascular collapse in hospitalized infants who have otherwise appeared stable (4).

Congestive heart failure. As exemplified in Fig. 3*B*, heart rate spectral power is reduced at all frequencies in patients with chronic CHF but is virtually absent at frequencies >0.04 Hz. Power at frequencies <0.04 Hz seems to be relatively preserved due to a discrete 60- to 80-s (~0.15 Hz) oscillation of HR (Fig. 3*B*) that is associated with a similar pattern in respiratory activity. The low-frequency respiratory activity resembles Cheyne-Stokes respiration in some patients but in most patients falls within the range of normal. Thus, in normal subjects, HR responds to low- and high-frequency physiological perturbations, whereas in patients with CHF, HR responds only to very-low-frequency perturbations (<0.04 Hz). The findings first demonstrate a marked derangement of HR modulation in patients with severe CHF. In addition, the model proposed in Fig. 2 can be used to suggest that the frequency characteristics of HR fluctuations in these patients are consistent with abnormal baroreflex responsiveness to physiological stimuli and that there is diminished vagal, but preserved sympathetic modulation of HR (13).

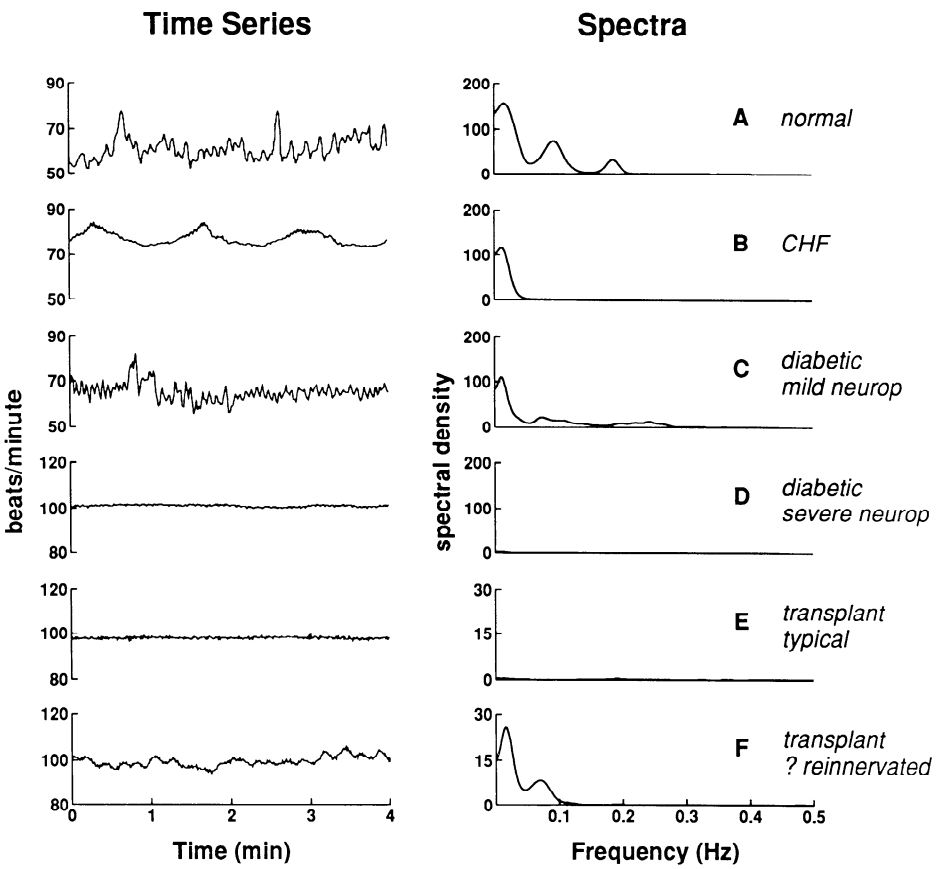

FIGURE 3. Examples of 4-min segments of HR and corresponding spectra from a normal subject (*A*) and patients with CHF (*B*), diabetes (*C* and *D*), and cardiac transplants (*E* and *F*). Although range of heart rates in beats/min (bpm) on *y*-axis is different for *subjects A–C* than for *subjects D–F*, scale of 40 bpm is the same for all tracings. Note that spectral density scale is the same in tracings *A–D* (0–200 bpm^2/Hz) for comparison with data from the normal subject but is changed to 0 to 30 bpm^2/Hz for the 2 transplant subjects to better demonstrate the unusual finding of low amplitude but frequency-specific HR fluctuations in trace (*F*). Also note similarities between data for the diabetic subject with severe neuropathy and the "typical" transplant subject.

Diabetes. In diabetic subjects, an association has been found between the presence and degree of peripheral neuropathy, as judged by standard neurologic testing, and cardiac autonomic neuropathy, as judged by HR spectral power (Fig. 3, *C* and *D*). Previous investigators using both HR variability and other autonomic tests have debated over the time course of sympathetic vs. parasympathetic neuropathy (3). In agreement with both schools of thought, recent unpublished data from our laboratory suggest that some diabetics have a predominant vagal neuropathy, whereas in others the defect is primarily sympathetic.

Transplantation. As expected, denervation of the donor heart after cardiac transplantation usually leads to virtual absence of all short-term (Fig. 3*E*) but not long-term heart rate variability. Two possible exceptions to this situation have been found. Sands et al. (11) recently reported a broad-band (in frequency) increase in HR spectral power that tracked biopsy-proven rejection in some transplant recipients. They suggested that the findings were due to involvement of the SA node or supraventricular conduction system in the rejection process, which then led to erratic beat-to-beat variation in R-wave position. They also speculated that HR spectral analysis may serve as a noninvasive indicator of rejection in selected patients. Prospective studies were proposed. The second exception is shown in Fig. 3*F*, which demonstrates recurrence of discrete spectral peaks in a patient who is ~36 mo posttransplantation. Although the peaks are of low amplitude, their frequency characteristics strongly suggest the presence of sym-

pathetic neural control of HR in this patient. Because the patient had both donor and recipient P waves that were uncoupled from each other on the surface electrocardiogram, the findings further suggest sympathetic reinnervation of the donor sinus node, a previously undescribed result in humans.

These analyses of HR and ABP variability have already provided both clinically useful information and important insights into the mechanisms involved in hemodynamic regulation; however, the approach has substantial limitations. Interpretations of these data have been restricted both by an inability to characterize the underlying autonomic control mechanisms when only system outputs such as HR are measured and by the limited number of oscillatory frequencies that occur spontaneously. The situation is analogous to trying to characterize the human ear by only knowing what an individual heard without a priori information about the frequency and amplitude of the actual auditory stimuli and also without auditory stimuli at a broad range of frequencies. The characterization would be incomplete at best. To solve these problems, one would like to stimulate the system's inputs (e.g., respiration, baroreceptors) at a broad range of frequencies and gauge the system's frequency response [just as is done for hearing with an audiogram and as Berger et al. (2) did for the SA node]. This determination can be realized by either stimulating at a large number of frequencies individually or by attempting to input a broad band or "whitened" signal that contains all frequencies simultaneously. The first of these approaches is somewhat bulky and time consuming but has been used in evaluating a number of physiological systems in past studies. The second approach is used commonly to assess physical systems but has been employed only rarely in the evaluation of physiological systems.

We have recently shown that the accuracy and sensitivity of variability measurements in assessing autonomic modulation of HR can be enhanced by accounting for the amplitude of an input to HR control, respiration, and by standardizing the frequency content of that input between individuals. The HR response

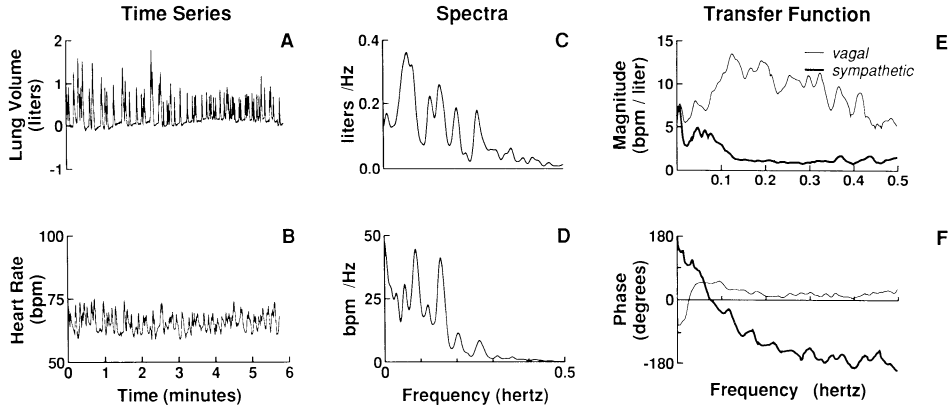

FIGURE 4. Use of broad-band calibrated respiratory activity to probe autonomic HR control. Although mean respiratory rate is 12 breaths/min, interval between breaths varies randomly between 1 and 15 s, as shown for 1 subject in *A*. HR response is similarly erratic (*B*) so that variance of both HR and respiratory signals is spread out over a range of frequencies from 0 to 0.5 Hz (*C* and *D*). This allows for sufficient excitation energy to determine the frequency response of HR to respiratory activity over entire frequency range. Transfer function magnitudes and phases are averages from 14 subjects, 7 in supine position after propranolol (pure vagal HR control) and 7 in upright position after atropine (pure sympathetic HR control). Transfer functions have gain and phase characteristics determined primarily by SA node responses to modulation of autonomic activity (i.e., vagal response is broad band with minimal phase delay; sympathetic response has significant magnitude at only lower frequencies and has a phase delay). Above 0.25 Hz, sympathetic data are unreliable because of low coherence.

to calibrated respiratory activity was determined during 6-min periods in which the respiratory rate was voluntarily controlled in a predetermined but erratic fashion (Fig. 4, *A–D*). Thus respiration served as a frequency probe of autonomic control. Selective autonomic blockade, with either atropine or propranolol, and changes in posture were used to dissect the sympathetic and parasympathetic contributions. The gain and phase of the frequency-response functions describe how the autonomic nervous system responds to a stimulus, in this case respiration, as a function of frequency. We found that the sympathetic (standing + atropine) response is characterized by markedly reduced gain >0.1 Hz and a phase delay, whereas vagal (supine + propranolol) modulation of HR is characterized by higher gain at all frequencies and no phase delay (Fig. 4, *E* and *F*). Because modulation of both cardiac sympathetic and parasympathetic activity occurs with respiration, the data provide the basis for noninvasively "fingerprinting" the sympathetic and vagal components of cardiac control in individual patients (14).

Conclusion

The differential frequency response of the sinus node to modulation of sympathetic and parasympathetic activity underlies the value of quantitative HR analysis. Although power spectral analysis of HR has proven to be a useful noninvasive technique for understanding both normal and abnormal cardiovascular regulation in humans, analysis of cardiorespiratory fluctuations is probably most informative when system outputs such as HR can be quantitatively related to inputs such as respiration. Future work should be directed toward similar analyses of the more complicated closed-loop interactions between HR and ABP.

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