JACC Vol. 14, No. 5
November 1, 1989:1139–48

Beat to Beat Variability in Cardiovascular Variables: Noise or Music?

MARVIN L. APPEL, MS, RONALD D. BERGER, MD, PHD, J. PHILIP SAUL, MD, JOSEPH M. SMITH, MD, PHD, RICHARD J. COHEN, MD, PHD

Cambridge, Massachusetts

Cardiovascular variables such as heart rate, arterial blood pressure, stroke volume and the shape of electrocardiographic complexes all fluctuate on a beat to beat basis. These fluctuations have traditionally been ignored or, at best, treated as noise to be averaged out. The variability in cardiovascular signals reflects the *homeodynamic* interplay between perturbations to cardiovascular function and the dynamic response of the cardiovascular regulatory systems. Modern signal processing techniques provide a means of analyzing beat to beat fluctuations in cardiovascular signals, so as to permit a quantitative, noninvasive or minimally invasive method of assessing closed loop hemodynamic regulation and cardiac electrical stability. This method promises to provide a new approach to the clinical diagnosis and management of alterations in cardiovascular regulation and stability.

(J Am Coll Cardiol 1989;14:1139–48)

Cardiovascular variables such as heart rate, arterial blood pressure, stroke volume and the configuration of electrocardiographic (ECG) complexes all fluctuate from beat to beat. The variation in pulse rate synchronous with respiration (respiratory sinus arrhythmia) was noted in ancient times and the respiratory variation in arterial blood pressure was documented by Hales in 1733 (1).

Beat to Beat Variation in Cardiovascular Signals

Despite the long-standing recognition of the presence of beat to beat variation in cardiovascular signals, physicians and physiologists have tended to overlook the possible significance of subtle beat to beat variability. The variability has generally been treated as *noise* that is to be either ignored or averaged out. Thus, one reports the *mean* heart rate averaged over many beats and the *typical* systolic or diastolic blood pressure. Electrocardiograms are similarly interpreted by analyzing the morphology of typical waveforms and identifying those waveforms that are grossly abnormal.

Part of the historical reason that subtle beat to beat variability in cardiovascular variables has received marginal attention is that it was difficult to characterize before digital computers became available. Although analog signal analyzers such as spectrum analyzers predated digital signal processing, their applicability to cardiovascular signals was limited. Analysis of beat to beat variability in cardiovascular signals often requires a flexible combination of feature recognition (e.g., R wave detection, interval measurement, determination of systolic or diastolic arterial blood pressure) with more traditional signal analysis techniques. Such an approach is enormously facilitated by digital processing and is cumbersome to achieve with analog processing.

From the Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts. This work was supported by Grant 1RO1-HL39291-01, from the National Institutes of Health, Bethesda, Maryland, Grant NAGW-988, from the National Aeronautics and Space Administration of Washington, D.C., a grant from the Whitaker Foundation, Mechanicsburg, Pennsylvania; a grant from the Johnson and Johnson HST Research Fund, Cambridge, Massachusetts and a grant from the Colin Medical Instrument Co., South Plainfield, New Jersey. M. Appel is grateful for support from the Fannie and John Hertz Foundation, Livermore, California.

Manuscript received March 31, 1989, accepted June 7, 1989.

Address for reprints: Richard J. Cohen, MD, Massachusetts Institute of Technology, Room E25–330d, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139.

This article is part of a series of articles celebrating the 40th anniversary of the American College of Cardiology. The series attempts to set the stage for the future by describing current state of the art management of selected major cardiovascular problems and the basic knowledge that will provide directions for advances in diagnosis and therapy.

0735-1097/89/$3.50

JACC Vol. 14, No. 5
November 1, 1989:1139–48

Perhaps the area in which the potential clinical significance of beat to beat variability in cardiovascular signals was first recognized is obstetrics (2). With the advent of fetal monitoring, it was noted that the fetal heart rate fluctuated from beat to beat. This variability correlated with fetal viability; a diminution in this beat to beat variability indicated fetal compromise. The postulated mechanism for this observation was that the fetal heart rate is modulated on a beat to beat basis by the parasympathetic and sympathetic nervous systems. Depression of the central nervous system secondary to anoxia leads to a loss of this fine beat to beat modulation of heart rate and, hence, to a more metronome-like heartbeat.

Indeed, beat to beat variability in cardiovascular variables often reflects an interplay between various perturbations to cardiovascular function and the response of the cardiovascular regulatory systems to these perturbations. The perturbations may be either exogenous or endogenous. For example, perturbations may result from environmental stress, changes in posture and the mechanical effects of respiratory variation in intrathoracic pressure on the filling and emptying of cardiovascular structures. Similarly, autoregulatory adjustments in local vascular resistance in different tissue beds lead to fluctuations in total vascular resistance, thus perturbing global cardiovascular function. Perturbation to cardiac electrical function may emanate from the variability inherent in such arrhythmias as atrial fibrillation or from subtle beat to beat variation in conduction times through regions of myocardial tissue. The response of the cardiovascular regulatory system may include, for example, the arterial baroreceptor reflex impinging on heart rate and peripheral vascular resistance, as well as the autonomic modulation of cardiac conduction processes.

Thus, by studying beat to beat variability one has the opportunity to study *homeodynamics*, the dynamic processes involved in the maintenance of *homeostasis*. One can glean information about the nature of the perturbations to which the cardiovascular system is exposed as well as the regulatory responses to these perturbations.

Heart Rate and Blood Pressure Variability

Heart rate power spectrum. Heart rate is perhaps the most easily accessible cardiovascular signal for analysis of variability. Spectral analysis involves decomposing a signal into a sum of sine waves of different amplitudes and frequencies. The power spectrum presents the squared amplitude of the sine waves as a function of frequency. Power spectra are familiar to us in the spectrometric analysis of the frequency content of light. Spectral analysis of heart rate variability is similar except that, in the case of visible light, the typical frequencies of interest are on the order of 10^{14} to 10^{15} Hz, whereas for heart rate variability analysis the frequencies of interest are <1 Hz.

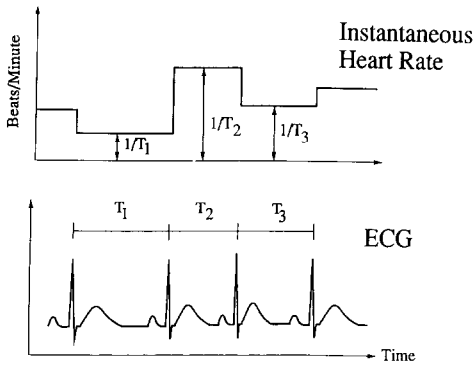
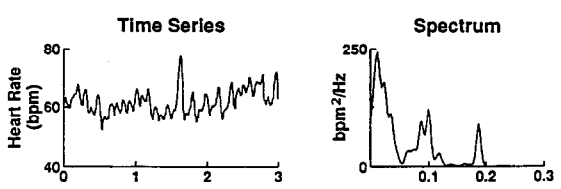


Figure 1. Derivation of instantaneous heart rate signal (heart rate tachogram) from the electrocardiographic (ECG) signal.

Computation of the heart rate power spectrum involves detection of the QRS complexes of the ECG, defining an instantaneous heart rate signal (Fig. 1) and then applying filtering and spectral estimation techniques to the heart rate signal (Fig. 2) (3). From a 5-min epoch of heart rate one can compute a power spectrum for frequencies above roughly 0.01 Hz. Early investigators (4) identified peaks in the heart rate power spectrum located at approximately 0.04 and 0.10 Hz and the respiratory frequency, although in any given spectrum one or more of these peaks may not be present. Our laboratory (5,6) used pharmacologic blockade in the conscious dog to demonstrate the physiologic mechanisms involved in mediating heart rate fluctuations at these frequencies. Parasympathetic blockade, using the peripheral muscarinic blocking agent glycopyrrolate, abolished all heart rate fluctuations above 0.15 Hz and substantially reduced lower frequency heart rate fluctuations. Adding beta-sympathetic blockade with propranolol removed the residual low frequency fluctuations, leading to a metronome-like heartbeat. Thus, fluctuations above 0.15 Hz are purely parasympathetically mediated, whereas lower frequency fluctuations are jointly mediated by the sympathetic and parasympathetic nervous systems. Similar results have been observed in humans (7,8). The mechanism for this effect is revealed in the 1934 work of Rosenblueth and Simeone (9). They showed that the heart rate response to a change in parasympathetic efferent activity is extremely rapid, occur-

Figure 2. Human heart rate signal and corresponding heart rate power spectrum. Notice the three peaks, one at the respiratory frequency near 0.2 Hz and two at lower frequencies centered near 0.1 and 0.04 Hz.



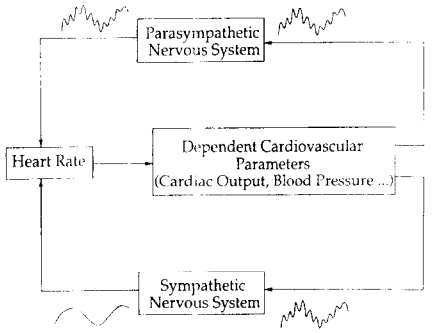


Figure 3. Simple model of heart rate control. Fluctuations in heart rate affect dependent cardiovascular variables (e.g. arterial blood pressure). Fluctuations in these variables are detected by sensors (e.g., baroreceptor), and reflex adjustments in heart rate are mediated by the parasympathetic and sympathetic nervous systems. The figure indicates the low-pass character of the sympathetic system relative to the parasympathetic system.

ring usually within a single beat. The change in heart rate in response to changes in efferent sympathetic activity is much slower, occurring on a time scale up to 20 s. Thus, the sympathetic system is simply too sluggish to mediate fluctuations in heart rate at normal respiratory frequencies. The sympathetic system acts like a low-pass filter, whereas the parasympathetic system acts like a broad band-pass filter (Fig. 3). More recently, we have shown (10) that this filtering effect occurs at the sinoatrial node.

Blood pressure power spectrum. In addition to studying fluctuations in heart rate, one can similarly compute the power spectrum of fluctuations in arterial blood pressure. The power spectrum of blood pressure fluctuations is similar to that of heart rate at frequencies below the mean heart rate itself. One notes respiratory frequency fluctuations and lower frequency (Mayer wave) fluctuations in arterial blood pressure. Evidence from a number of sources suggests that the lower frequency (0.02 to 0.12 Hz) fluctuations in heart rate and blood pressure may result from a resonance in the baroreflex control of peripheral resistance at these frequencies, and that heart rate fluctuations at these frequencies represent a compensatory heart rate baroreflex response (6,11,12).

Clinical factors related to variability in heart rate and blood pressure spectral peaks. A number of studies have been conducted relating the size of spectral peaks to various

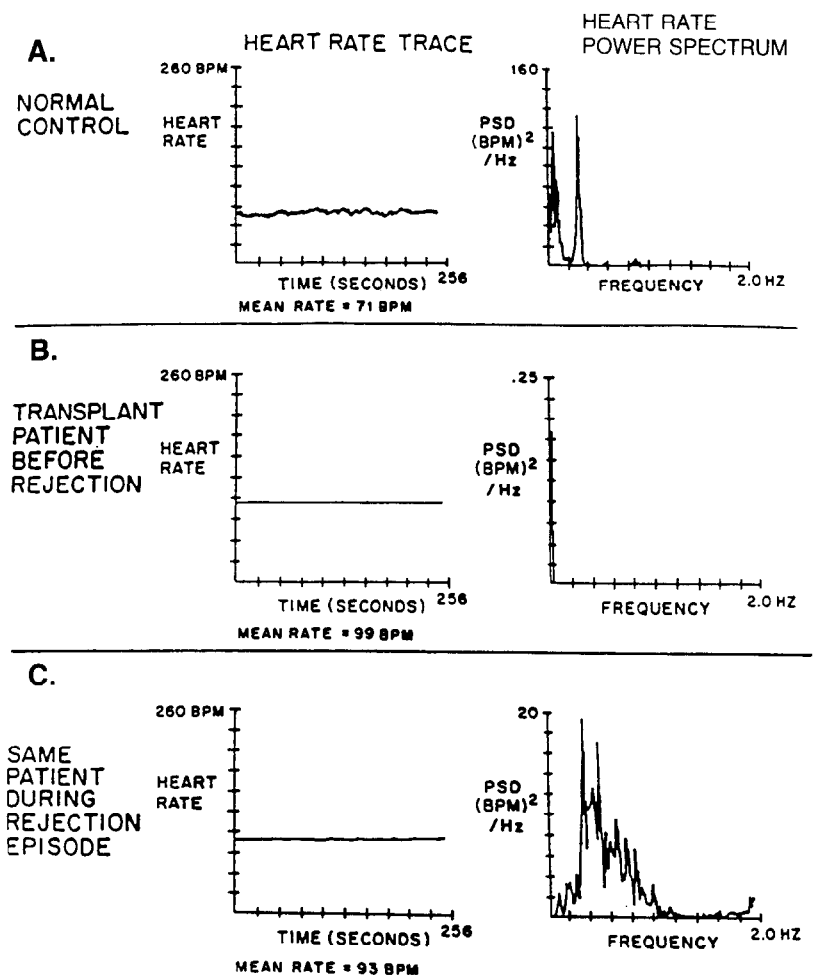


Figure 4. Heart rate traces and power spectra from a healthy control subject (**A**), a cardiac transplant recipient without rejection (**B**) and the same patient during a subsequent rejection episode (**C**). Note the different y axis scales for power spectral density (**PSD**) in each frame (reproduced from reference 18 with permission).

JACC Vol. 14, No. 5
November 1, 1989:1139–48

physiologic and pathophysiologic states. Low frequency fluctuations are greatly enhanced by standing, hemorrhage, aortic constriction and hypotension (7,8,13,14). Respiratory frequency fluctuations are decreased by standing and exercise. The area of low and high frequency peaks decreases with aging (15). In a retrospective study, Gordon et al. (16) showed a decreased ratio of low frequency to respiratory frequency power in the heart rate power spectrum of pediatric patients after cardiac surgery, who subsequently died. Patients with heart failure have diminished power at all frequencies >0.02 Hz (17). Cardiac transplant patients have greatly diminished heart rate variability compared with control subjects, but during rejection may demonstrate a broad-band pattern of variability indicative of variable beat to beat supraventricular conduction (18) (Fig. 4).

Kleiger et al. (19) demonstrated that diminished heart rate variability (using nonspectral measures) in postmyocardial infarction patients is an extremely strong predictor of mortality. Myers et al. (20) found that decreased power in the heart rate power spectrum was also predictive of mortality.

Clinical interpretation. Although the areas of spectral peaks in heart rate and blood pressure do vary widely under varying pharmacologic and physiologic conditions, the significance of a change in a spectral peak area may be difficult to interpret diagnostically. For example, the area of the respiratory frequency peak in heart rate is often interpreted as a measure of vagal tone. However, the area of the respiratory peak in heart rate reflects the intensity of respiratory effort (the input) as well as the strength of the coupling between respiration and heart rate variation. This coupling largely reflects the incremental gain of the parasympathetic nervous system at this frequency. This frequency-dependent incremental gain may or may not be directly related to the mean level of vagal tone. Similarly, the amplitude of the low frequency peak in heart rate may reflect the amplitude of (peripheral, central or both) blood pressure oscillations at these frequencies, as well as the strength of the parasympathetically and sympathetically mediated coupling of blood pressure to heart rate fluctuations. Thus, a multitude of factors might be expected to alter low frequency heart rate fluctuations, including interventions that alter the control of blood pressure fluctuations and those that alter coupling between blood pressure and heart rate fluctuations.

Figure 5. Transfer function H transforms input x(t) into output y(t).

Transfer Function Analysis

To characterize directly the coupling between different physiologic variables, our laboratory has been developing methods for transfer function analysis. The transfer function is the incremental gain as a function of frequency between an input x and output y (Fig. 5). Thus, the transfer function evaluated at frequency f yields the amplitude of an output sine wave of frequency f divided by the amplitude of an input sine wave at the same frequency. Transfer function analysis is applicable to linear systems.

The transfer function can be measured by applying pure sinusoidal inputs to linear systems. This is time consuming and laborious, especially in a physiologic system whose state may change in time. Therefore, we have employed "white noise" stimulation techniques in which a known broad-band signal is applied to a system and the output is measured. The white noise technique enables one to measure the transfer function at many different frequencies simultaneously. We (10) used this approach to demonstrate directly the low-pass character of sympathetic synaptic transmission and the more broad-band parasympathetic transfer function relation in the canine sinoatrial node.

Clinical application. The white noise technique can be used clinically by utilizing respiration as a controlled broad-band input (21). Subjects are instructed to inspire in synchrony with randomly spaced audio "beeps" (Fig. 6). Depth

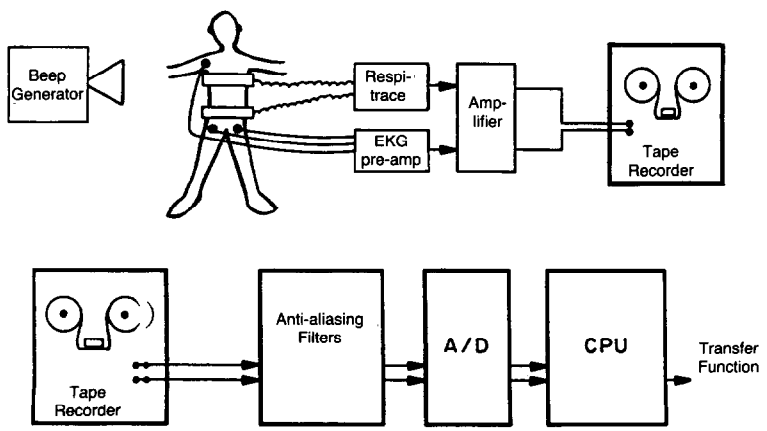


Figure 6. Assessment of respiration to heart rate transfer function in humans. Electrocardiogram and respiration are monitored during random interval breathing cued by a 'beep' generator. Recorded signals are filtered, undergo analog to digital (A/D) conversion and are analyzed by a computer program (reproduced from reference 37 with permission).

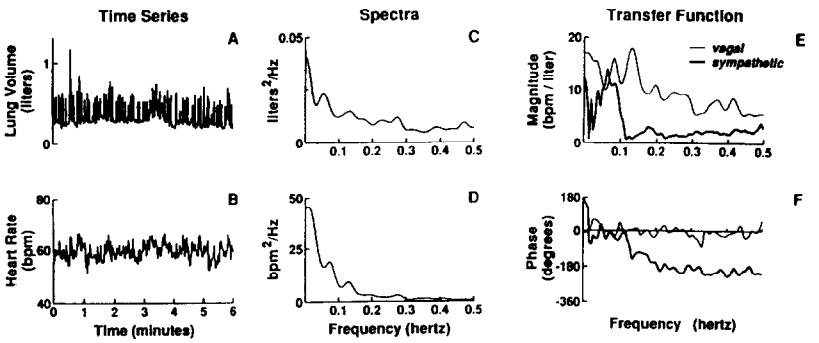
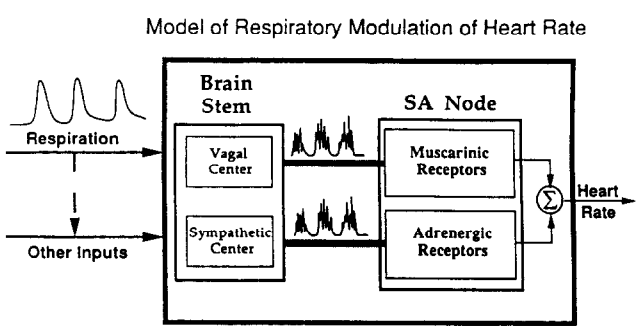


Figure 7. Respiration to heart rate transfer function analysis during white noise breathing in man. The time series (**A and B**) and spectra (**C and D**) reveal the broad-band nature of the signals. The transfer function magnitude (**E**) during "vagal" conditions (β-sympathetic blockade with propranolol, position supine) rolls off gradually with frequency. The transfer function during "sympathetic" conditions (parasympathetic blockade with atropine, position standing) rolls off more abruptly, indicative of the low-pass nature of the β-sympathetic filter. The phase (**F**) remains near zero during "vagal conditions" and rolls off linearly under "sympathetic conditions," suggestive of a fixed time delay.

of respiration is not controlled, thus leaving total ventilation unperturbed. Respiration is measured with a noninvasive volumetric transducer (Respitrace) and heart rate is determined from the ECG. The transfer function between the measured lung volume signal and the heart rate is determined (Fig. 7). In a pure sympathetic state, the transfer function is "low-pass," whereas in a parasympathetic state the transfer function is more broad-band. Although this coupling involves more than just the autonomic nervous system, the autonomic nervous system is the critical component (Fig. 8).

Linearity hypothesis. Transfer function analysis is applicable to linear systems. In linear systems a sinusoidal input will lead to a sinusoidal output at the same frequency. The cardiovascular system may demonstrate nonlinear behavior over large changes in state. We hypothesize, however, that for relatively small fluctuations of cardiovascular signals about their mean, the signals are linearly coupled—the system is thus linear about a given operating point. The white noise stimulation technique provides a direct means for testing this linearity hypothesis. Two different sequences of broad-stimulation will lead to the estimation of the same transfer function only if the system is indeed linear. Repeated measurements of the transfer functions do, in fact, lead to highly reproducible results, thus substantiating the linearity hypothesis. Although linear systems analysis applies here, nonlinear interactions may nonetheless play an important role in other aspects of cardiovascular signal variability.

Figure 8. Model of respiratory modulation of heart rate. The "respiratory" center is centrally coupled with "vagal" and "sympathetic" centers. In addition, mechanical effects of respiration on hemodynamics lead to feedback input to autonomic centers by way of ("other inputs"). SA = sinoatrial.



System Identification Techniques

Analysis of multiple interacting cardiovascular signals. The use of controlled exogenous broad-band inputs enables one to directly measure coupling between signals. However, the coupling may not always be simple to interpret, particularly when feedback loops are involved. For example, consider the coupling between heart rate and arterial blood pressure. As a result of the pumping action of the heart and the impedance properties of the vasculature, fluctuations in heart rate are mechanically coupled to fluctuations in arterial blood pressure. In turn, fluctuations in arterial blood pressure are coupled to heart rate fluctuations through the baroreceptor reflex. A single transfer function measurement would intertangle these two physiologically distinct feedforward and feedback features. However, autoregressive moving average algorithms (22) are available that impose *causality* conditions on the measured transfer functions, allowing one to separately identify the feedforward and feedback transfer functions.

One can generalize this approach to analyze a multiplicity of interacting cardiovascular signals. In particular, if one measures n signals, one can construct as many as $n(n-1)$ possible causal couplings between them, each of which might represent a distinct physiologic mechanism. In such a system model there may also be associated with each signal a noise source representing endogenous or exogenous perturbations. Efforts to estimate the transfer relations and power spectra of the noise sources by analyzing spontaneous fluctuations have been reported (11,23). Our laboratory has introduced the idea of using broad-band exogenous stimulation to achieve this system identification in a reliable way (24). Provided that the signals are sufficiently broad-band, it

JACC Vol. 14, No. 5
November 1, 1989:1139–48

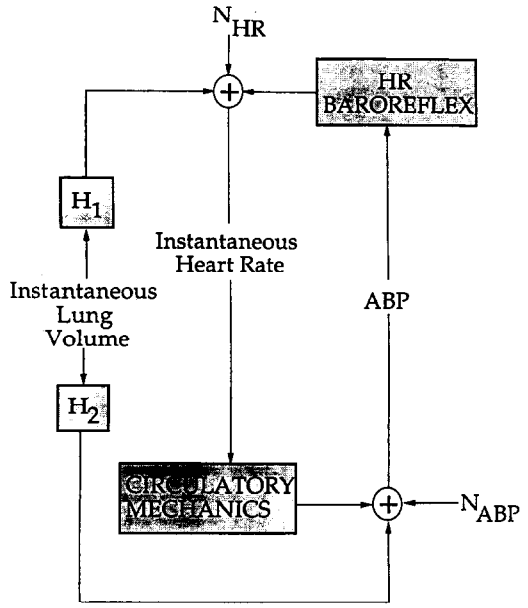


Figure 9. Identifiable closed loop model of short-term cardiovascular control. (See text for discussion.) ABP = arterial blood pressure; CIRCULATORY MECHANICS = transfer function representing blood pressure response to a single heartbeat; H_1 and H_2, respectively, are the neurally mediated coupling between respiratory activity and heart rate, and the mechanically mediated coupling between variations in lung volume and blood pressure. NABP and NHR = noise sources (arterial blood pressure and heart rate, respectively).

is possible to estimate each of the transfer relations and the power spectra of the noise sources.

Clinical application. A clinically applicable approach to system identification is shown in Figure 9. In this example, a subject performs "white noise" breathing while lung volume, arterial blood pressure and the ECG are recorded. The transfer function representing the arterial blood pressure response to a single heartbeat (circulatory mechanics) and the baroreceptor coupling between changes in arterial blood pressure and heart rate (HR baroreflex) are shown as well as the neurally mediated coupling between respiratory activity and heart rate (H_1) and the mechanical coupling between variations in lung volume and arterial blood pressure (H_2). The noise source (N_{ABP}) represents all fluctuations in arterial blood pressure not attributable to fluctuations in heart rate or respiratory activity. The noise source (N_{HR}) represents all fluctuations in heart rate not attributable to fluctuations in arterial blood pressure or respiratory activity. Thus, the noise sources represent the input of all physiologic mechanisms not expressly considered in the model.

In Figure 10 we show an example of the computed values of these transfer relations and the spectra of the noise sources obtained during white noise breathing. (Here the transfer relations are shown in the time domain as impulse response functions. The impulse response function is the output y that results from an arbitrarily narrow impulse of unit area applied to the input x. The impulse response is the inverse Fourier transform of the transfer function.) Figure 10a demonstrates the heart rate response that would be

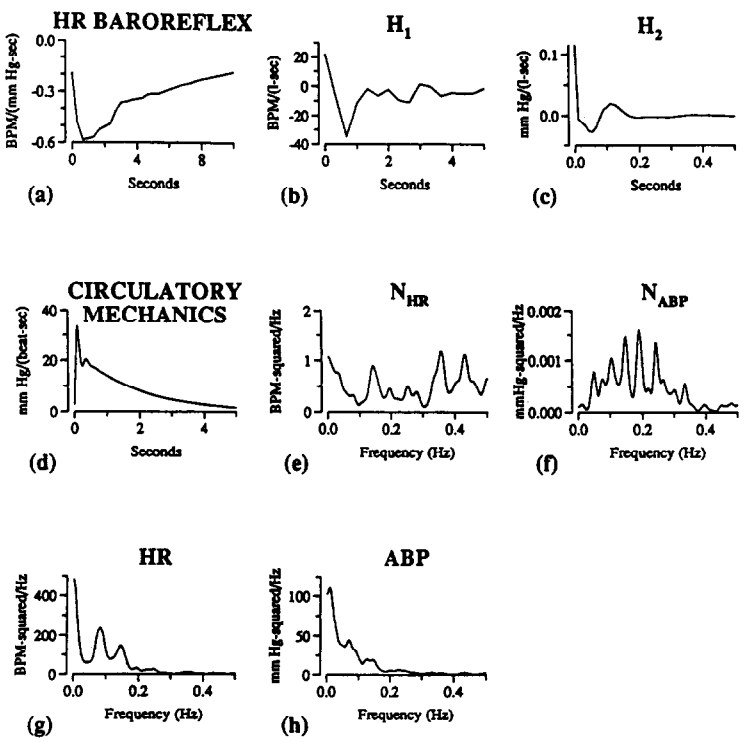


Figure 10. Impulse response functions and power spectra of noise sources, heart rate and arterial blood pressure of Figure 9 identified from a human subject during white noise breathing. (See text for discussion.) Abbreviations as in Figure 9.

obtained if one could deliver an impulse in arterial blood pressure; it shows that, after an initial rapid drop, the heart rate gradually returns to baseline. The heart rate and arterial blood pressure responses to an impulse in lung volume (Fig. 10b and c) are biphasic. The blood pressure response, however, is very short and very low in amplitude. Figure 10d shows the arterial blood pressure response to a single heartbeat (note the presence of a dicrotic notch). The noise spectra in Figures 10e and f constitute <1% of the energy in the raw heart rate and arterial blood spectra shown in Figures 10g and h. Thus, nearly all the heart rate and arterial pressure variability in this study can be ascribed to respiratory variation and the couplings between the signals.

The transfer relations shown here are all linear. However, this type of linear system identification scheme can incorporate nonlinearities. The signals whose interactions are analyzed can be derived from physiologic signals by means of nonlinear transformations. For example, the heart rate signal (Fig. 1) is a nonlinear transformation of the electrocardiogram signal. Thus, one can often incorporate the necessary nonlinearities into the definition of the signals themselves, leaving only linear relations to be analyzed.

The system identification approach shown here can be realized from 5 min of data collection. Using a noninvasive arterial blood pressure recording device (e.g., Colin noninvasive radial artery blood pressure monitor), these measurements can be achieved in a totally noninvasive fashion. This approach enables one to describe the principal mechanisms involved in short-term cardiovascular control with the rigorous mathematical techniques that an electrical engineer uses to describe feedback in an electronic circuit.

Long-Term Heart Rate Fluctuations

Heart rate and blood pressure fluctuations over longer times. Up to now we have been discussing heart rate fluctuations on a time scale of seconds to minutes. However, the heart rate fluctuates with much longer periodicities as well. One can compute the heart rate power spectrum from a 24 h data record down to frequencies of 10^{-5} Hz (25). Kobayashi and Musha (26) first noted that over many decades of frequency the power spectrum decays as $1/f^{\alpha}$ where α is very close to unity. On a log-log scale (see Fig. 11) the heart rate power spectrum appears as a line with a slope close to −1 in value. The peaks in the range of 0.04 to 0.5 Hz are smeared out and appear diminutive on the larger landscape of heart rate variability on the 10^{-5} to 1 Hz range.

The fact that the heart rate spectrum follows this 1/f decay must reflect some fundamental principles of intermediate-term cardiovascular control. Goldberger and West (27) speculated that the 1/f decay could reflect the fractal nature of hemodynamic regulation. However, at this point the origin of the remarkably reproducible 1/f behavior must be considered as unexplained. Arterial blood pressure fluctuations have also been observed to follow a 1/f decay (Donald Marsh, personal communication). The interaction of long-term variability in heart rate, blood pressure and other cardiovascular signals remains an important area of investigation from a physiologic, pharmacologic and pathophysiologic perspective.

Estimates of heart rate variance. An important corollary to the observation that the heart rate power spectrum decays as 1/f over a 24 h time period is that the variance of heart rate variability is not defined, at least on time scales of less than 24 h.

The variance (square of the standard deviation) is just equal to the area under the power spectrum. However, the integral for this area diverges for small f for a 1/f decay. From a practical point of view, this means that estimates of the heart rate variance (or standard deviation) will depend on the record length. The longer the record, the greater the estimated variance as more low frequency power is included. For example, Kleiger et al. (19) estimated RR interval standard deviation over a 24 h period as a predictor of mortality in postmyocardial infarction patients. This 24 h estimate reflects primarily the very low frequency power in heart rate variability, not the peaks above 0.01 Hz.

Variability in the Morphology of ECG Complexes

The morphologies of ECG complexes fluctuate from beat to beat. Some of this variability may reflect the mechanical rotation and translation of the heart in the thorax and the changes in transthoracic impedance, for example that result from respiratory movement. However, variability in ECG configuration may also result from intrinsic beat to beat variability in cardiac conduction processes.

Relation of beat to beat variability in ECG complex morphology to ventricular arrhythmias. Our laboratory was intrigued by the question whether a ventricle in a state of enhanced susceptibility to fibrillation might by marked by an altered pattern of beat to beat variability in QRS and T wave morphology. Does an unstable state, which may give rise to a microscopically disorganized pattern of electrical activity, first manifest itself in terms of subtle beat to beat variability in excitation and repolarization processes? We approached this problem in two ways. One approach involved finite element model computer simulation of cardiac conduction incorporating the dispersion of refractoriness hypothesis (28,29). The second approach involved animal studies in which susceptibility to ventricular fibrillation was augmented by tachycardia, coronary artery ligation, or hypothermia, or combinations thereof (30).

The computer model was found to simulate a wide range of arrhythmias including reentrant premature depolarizations, tachycardia and fibrillation. When analyzing the computer simulation we observed a pattern of "electrical alter-

JACC Vol. 14, No. 5
November 1, 1989:1139-48

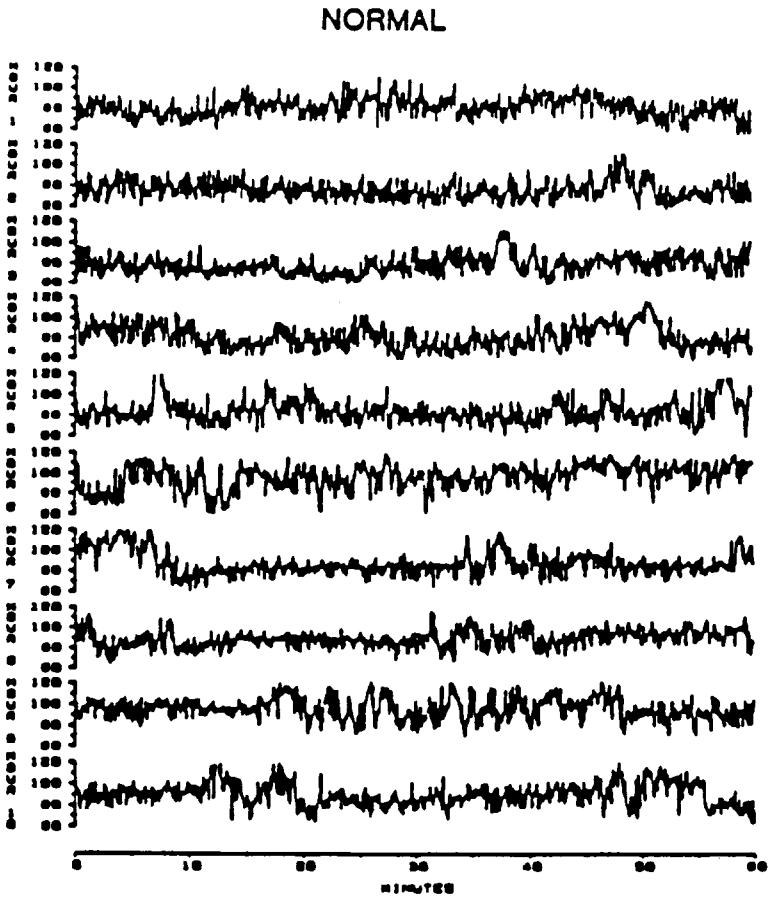


Figure 11. Ten hour heart rate tracing (**upper**) and corresponding power spectrum (**lower**) from a 24 h record of a normal subject.

nans" preceding the onset of reentrant rhythm disturbances in almost every instance (Fig. 12). Electrical alternans is a conduction pattern involving an ECG complex configuration that alternates every other beat between two morphologies resulting in an ABABAB type of pattern. Electrical alternans in the computer model resulted from alternating conduction patterns attributable to regions of tissue with refractory periods longer than the interbeat interval.

Electrical alternans and ventricular fibrillation. Electrical alternans in humans often occurs in the setting of pericardial effusion (31) and, under such circumstances, is associated with mechanical alternation of the position of the heart, and would not be expected to be associated with arrhythmias per se. Accordingly, we developed computer algorithms to specifically identify alternation (QRS, ST or T wave) in the pattern of electrical conduction in the analysis of ECG

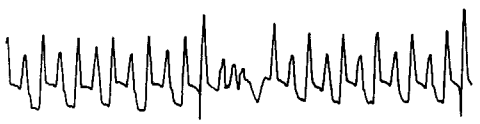


Figure 12. Simulated electrocardiogram of a paced ventricle showing the presence of electrical alternans before and after a burst of reentrant activity (reproduced from reference 28 with permission).

recordings. These algorithms were designed specifically to reject variations attributable to mechanical alternation and can quantify electrical alternans generally not detectable by visual inspection. We found that susceptibility to ventricular fibrillation, as measured by the ventricular fibrillation threshold technique, correlated with the presence of electrical alternans in dogs. A similar correlation was also observed in a pilot study (30) of patients undergoing invasive electrophysiologic testing in which the presence of alternans correlated with inducibility of ventricular tachycardia or ventricular fibrillation under a standard protocol. Taken together, these results suggest that beat to beat variability in excitation and repolarization processes in the pattern of electrical alternans may reflect decreased electrical stability. Analysis of beat to beat variability in ECG complex morphology may provide a noninvasive means of assessing susceptibility to cardiac arrhythmias.

Beat to Beat Variability During Arrhythmias

This review has focused on beat to beat variability of cardiovascular signals during apparently normal conduction processes. Another whole range of analyses can be made to probe mechanisms of arrhythmias by analyzing variability in timing or morphology of complexes during frank arrhythmias. For example, analysis of RR interval variability during atrial fibrillation can provide insight into the electrical interaction of the atria and atrioventricular junction during atrial fibrillation and the effects of pharmacologic intervention (32,33). The occurrence of ventricular premature depolarizations can be treated as stochastic process reflective of the underlying mechanisms involved with the generation of ventricular ectopic activity (34,35). Parasystolic mechanisms give rise to a rich range of dynamic behavior (36). A review of this fertile area of investigation is beyond the scope of this report.

Conclusions

Cardiovascular signals do indeed fluctuate on a beat to beat basis throughout one's lifetime. These fluctuations reflect the dynamic interplay of diverse physiologic processes. Traditionally, these fluctuations have escaped serious scrutiny. With modern techniques of analysis, such fluctuations can reveal the delicate dynamics involved in beat to beat cardiovascular control. Analysis of these fluctuations may provide a powerful, quantitative means of characterizing these physiologic processes. This approach may also provide a noninvasive or minimally invasive means for clinically assessing alterations in closed loop cardiovascular regulation and stability in a wide range of pathophysiologic states.

It may soon become common to assess autonomic function, baroreceptor function and cardiac electrical stability by mathematical analysis of commonly monitored signals such as heart rate, blood pressure and the ECG. Such an assessment could be used diagnostically as well as to guide and monitor therapeutic interventions. Fluctuations in cardiovascular signals should be considered not as noise but as music to be appreciated with a properly tuned mathematical ear.

References

1. Hales S. Haemastaticks. In: Hales S, ed. Statistical Essays. London: Innys and Manby, 1735:II, 1–186.
2. Hon EH, Lee ST. Electronic evaluation of the fetal heart rate patterns preceding fetal death, further observations. Am J Obstet Gynecol 1965; 87:814–26.
3. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. IEEE Trans Biomed Eng 1986;33:900–4.
4. Hyndman BW, Gregory JR. Spectral analysis of sinus arrhythmia during mental loading. Ergonomics 1975;18:255–80.
5. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
6. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 1985;249:H867–75.
7. Pomeranz B, Macaulay RJB, Caudill MA, et al. Assessment of autonomic function in man by heart rate spectral analysis. Am J Physiol 1985; 248:H151–3.
8. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure as a marker of sympatho-vagal interaction in man and conscious dog. Circulation 1986;59:178–93.
9. Rosenblueth A, Simeone FA. The interrelations of vagal and accelerator effects on the cardiac rate. Am J Physiol 1934;110:42–55.
10. Berger RD, Saul JP, Cohen RJ. Transfer function analysis of autonomic regulation: I. The canine atrial rate response. Am J Physiol 1989; 25:H142–H152.
11. Baselli G, Cerutti S, Civardi S, Malliani A, Pagani M. Cardiovascular variability signals: towards the identification of a closed-loop model of the neural control mechanisms. IEEE Trans Biomed Eng 1988;35:1033–46.
12. Madwed JB, Albrecht P, Mark RG, Cohen RJ. Low-frequency oscillations in arterial pressure and heart rate: a simple computer model. Am J Physiol 1989;25:H1573–9.
13. Madwed JB, Sands KEF, Saul JP, Cohen RJ. Spectral analysis of beat-to-beat variability in HR and ABP during hemorrhage and aortic constriction. In: Lown B, Malliani A, Prosdocimi M, eds. Neural Mechanisms and Cardiovascular Disease. Fidia Research Series, Padova: Liviana Press, 1986;5:291–301.
14. Taratuta E, Albrecht P, Dennis R, Akselrod S, Valeri CR, Cohen RJ. Analysis of blood pressure in conscious baboons. Proceedings of the

9th Annual Conference of the IEEE Engineering in Medicine and Biology Society 1987:94–5.

15. Shannon DC, Carley DW, Benson H. Aging of modulation of heart rate. Am J Physiol 1987;253:H874–7.
16. Gordon D, Herrera VL, McAlpine L, et al. Heart rate spectral analysis: a noninvasive probe of cardiovascular regulation in critically ill children with heart disease. Pediatr Cardiol 1988;9:69–77.
17. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. Am J Cardiol 1988;61:1292–9.
18. Sands KEF, Appel ML, Lilly LS, Schoen FJ, Mudge GH, Cohen RJ. Assessment of heart rate variability in human cardiac transplant recipients using power spectrum analysis. Circulation 1989;79:76–82.
19. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
20. Myers GA, Martin GJ, Magid NM, et al. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. IEEE Trans Biomed Eng 1986;33:1149–65.
21. Saul JP, Berger RD, Chen MH, Cohen RJ. Transfer function analysis of autonomic regulation: II. Respiratory sinus arrhythmia. Am J of Physiol 1989;25:H153–61.
22. Ljung L. System Identification: Theory for the User. Englewood Cliffs, NJ: Prentice Hall, 1987.
23. Kalli S, Suoranta R, Jokipii M, Turjanmaa V. Analysis of blood pressure and heart rate variability using multivariate autoregressive modelling. Computers in Cardiology 1986;13:427–30.
24. Appel ML, Saul JP, Berger RD, Cohen RJ. Closed-loop identification of cardiovascular regulatory mechanisms. Computers in Cardiology 1989; 15 (in press).
25. Saul JP, Albrecht P, Berger RD, Cohen RJ. Analysis of long term heart rate variability: methods, 1/f scaling and implications. Computers in Cardiology 1987;14:419–22.
26. Kobayashi M, Musha T. 1/f fluctuation of heartbeat period. IEEE Trans Biomed Eng 1982;29:456–7.
27. Goldberger AL, West BJ. Applications of nonlinear dynamics to clinical cardiology. Ann NY Acad Sci 1987;504:195–213.
28. Smith JM, Cohen RJ. Simple finite element model accounts for wide range of cardiac dysrhythmias. PNAS 1984;81:233–7.
29. Kaplan DT, Smith JM, Saxberg BEH, Cohen RJ. Nonlinear dynamics in cardiac conduction. Math Biosci 1988;90:19–48.
30. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac electrical instability. Circulation 1988;77:110–21.
31. Goldberger AL, Shabetai R, Bhargava V, West BJ, Mandell AJ. Nonlinear dynamics, electrical alternans and pericardial tamponade. Am Heart J 1984;107:1297–9.
32. Cohen RJ, Berger RD, Dushane TE. A quantitative model for the ventricular response during atrial fibrillation. IEEE Trans Biomed Eng 1983;30:769–81.
33. Berger RD, Bailin MT, Pollick F, Cohen RJ. Experimental application of a computer model for atrial fibrillation. Computers in Cardiology 1983; 10:197–200.
34. Lovelace DE, Knoebel SB. Time series analysis in predicting ventricular arrhythmias. Computers in Cardiology 1982;9:45–7.
35. Albrecht P, Cohen RJ, Mark R. Stochastic characterization of chronic ventricular ectopic activity. IEEE Trans Biomed Eng 1988;35:539–50.
36. Glass L, Goldberger AL, Belair J. Dynamics of pure parasystole. Am J Physiol 1986;20:H841–7.
37. Chen MH, Berger RD, Saul JP, Stevenson K, Cohen RJ. Transfer function analysis of the autonomic response to respiratory activity during random interval breathing. Computers in Cardiology 1987;14:149–52.