Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of Beat-to-Beat Cardiovascular Control

Abstract. *Power spectrum analysis of heart rate fluctuations provides a quantitative noninvasive means of assessing the functioning of the short-term cardiovascular control systems. We show that sympathetic and parasympathetic nervous activity make frequency-specific contributions to the heart rate power spectrum, and that renin-angiotensin system activity strongly modulates the amplitude of the spectral peak located at 0.04 hertz. Our data therefore provide evidence that the renin-angiotensin system plays a significant role in short-term cardiovascular control on the time scale of seconds to minutes.*

In this report we demonstrate that random process analysis of beat-to-beat fluctuations in heart rate provides a sensitive, quantitative and noninvasive measure of the functioning of the principal rapidly reacting cardiovascular control systems: the sympathetic, parasympathetic, and renin-angiotensin systems.

It has long been recognized that the instantaneous heart rate, arterial blood pressure, and other hemodynamic parameters fluctuate on a beat-to-beat basis. This beat-to-beat variability was documented by Stephen Hales (*1*) in the 18th century when he performed the first quantitative measurements of arterial blood pressure. He noted the correlation between the respiratory cycle, blood pressure level, and interbeat interval. Although physicians have long considered the beat-to-beat variation in heart rate or "the normal sinus arrhythmia" as a salutary cardiovascular sign, its direct clinical importance was perhaps first demonstrated in the area of fetal monitoring (*2*). The diminution of the beat-to-beat variation in the fetal heart rate during labor signifies fetal distress and the need for rapid delivery. Despite the long-standing recognition of beat-to-beat variation in hemodynamic parameters and the established clinical relevance of this variation, there have been remarkably few efforts to characterize mathematically the physiologic mechanisms that generate these fluctuations.

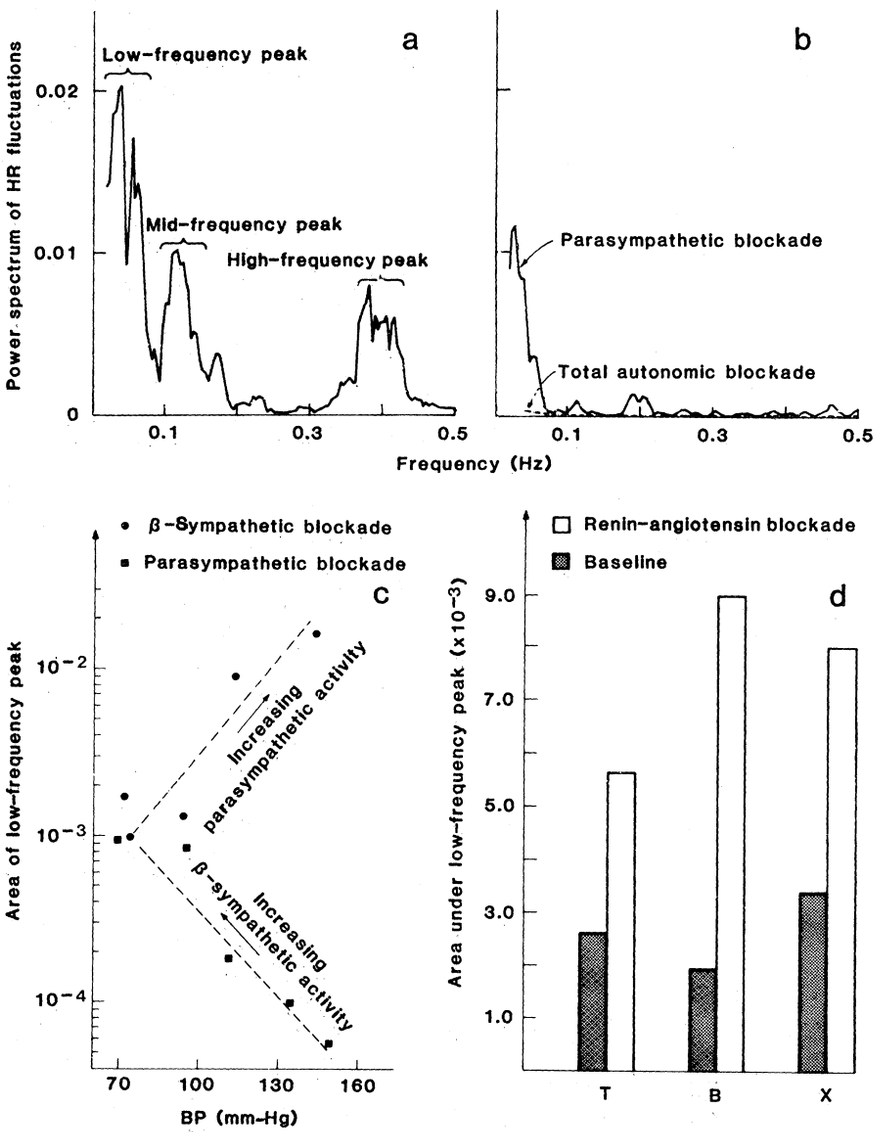

Fig. 1. (a) Power spectrum of heart rate fluctuations in the adult conscious dog. Power spectrum is normalized so that the integral of $S(\nu)$ is the variance of the heart rate fluctuations divided by the square of the mean heart rate. (b) Power spectrum of heart rate fluctuations under parasympathetic blockade and combined parasympathetic and sympathetic β-adrenergic blockade. (c) Area of low-frequency peak as a function of mean aortic blood pressure during sympathetic and parasympathetic blockade. (d) Area under low-frequency peak before and after renin-angiotensin system blockade by converting enzyme inhibitor, in dogs T, B, and X.

It is currently believed that beat-to-beat fluctuations in hemodynamic parameters reflect the dynamic response of the cardiovascular control systems to a host of naturally occurring physiological perturbations. For example, central arterial and venous blood pressures are continually perturbed as a result of the cyclic variation in intrathoracic pressure associated with respiration and also by fluctuations in peripheral vascular resistance resulting from the autoregulation of local blood flow in tissue beds. The sympathetic and parasympathetic nervous systems are usually considered to be the principal systems involved in short-term cardiovascular control on the time scale of seconds to minutes. It has been suggested that the renin-angiotensin system could also play a role in short-term cardiovascular control (*3*), although direct evidence has not been available to demonstrate such a role under normal physiologic conditions.

The rapidly reacting control systems maintain cardiovascular homeostasis by responding to beat-to-beat perturbations that are sensed by a variety of pressoreceptors and chemoreceptors. The efferent limbs of these control systems impinge both on cardiac function, altering heart rate, atrioventricular conduction, and contractility, as well as impinging on the peripheral vasculature, altering arterial and venous vasomotor tone.

Sayers and other (*4*, *5*) analyzed the frequency content of heart rate fluctuations by measuring their power spectrum. In this pioneering work, they showed that in addition to the well-known fluctuations in heart rate associated with the respiratory cycle, there are

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also periodic fluctuations in heart rate occurring at lower frequencies. Accordingly, the power spectrum (see Fig. 1a) of the heart rate fluctuations contain not only a peak centered at the respiratory frequency but also peaks at two lower frequencies, typically 0.04 and 0.12 Hz. The work of Hyndman and Kitney (*6*) suggests that the low-frequency peak is related to cyclic fluctuations in peripheral vasomotor tone associated with thermoregulation, whereas the mid-frequency peak is related to the frequency response of the baroreceptor reflex.

To study the frequency-specific contributions of each of the principal cardiovascular control systems to the genesis of the heart rate fluctuations, we have measured the power spectrum of these fluctuations in trained, conscious, unanesthetized dogs. In these experiments the different cardiovascular control systems were selectively blocked by means of specific pharmacologic agents: glycopyrrolate (0.01 mg/kg, administered as an intravenous bolus) to block muscarinic parasympathetic transmission; propranolol (0.1 mg/kg, intravenous bolus) to block the sympathetic β-adrenergic receptors; and nonapeptide converting enzyme inhibitor (0.3 mg/kg, intravenous bolus followed by infusion, 0.003 mg/kg per minute) to block the renin-angiotensin system. Adequacy of blockade was demonstrated by abolition of response to administration of, respectively, acetylcholine, isoproterenol, or angiotensin I.

Arterial and venous indwelling catheters were implanted in the trained dogs. During each experiment the arterial blood pressure, surface electrocardiogram (ECG), and respiratory activity were continuously monitored and recorded on a Hewlett-Packard 3968A FM magnetic tape recorder. An electronic device was used to detect the R waves from the recorded ECG and then to automatically measure and digitize the RR interval sequence; a NOVA computer was used to compute the power spectrum of the heart rate fluctuations from the RR interval sequence. Typically, 5 minutes of real-time stationary data were used to compute the power spectrum in the band from 0.02 to 1.0 Hz. Prior to each pharmacologic intervention, 20 minutes of baseline data were obtained. To confirm the stationarity of the data, and the reproducibility of the measurements, we examined multiple consecutive 300-second blocks of data under both control and postintervention conditions. We found that the spectral peak areas varied by no more than 5 to 10 percent. Multiple experiments were performed on each of seven conscious, trained dogs.

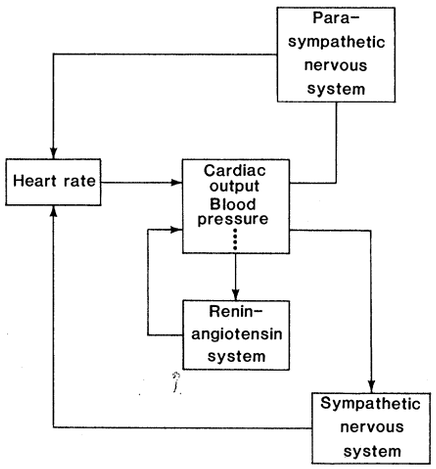

Fig. 2. Block diagram of short-term cardiovascular control, illustrating primary independent actions of the parasympathetic, β-sympathetic, and renin-angiotensin systems.

The heart rate power spectrum in the dog contains the three peaks described in the human by Sayers (*4*) (Fig. 1a). In any given spectrum one or more of the three peaks may not be evident because of low amplitude or overlap. Furthermore, the high-frequency peak will not be present if the respiratory rate exceeds the mean heart rate. Figure 1b illustrates the effect of parasympathetic blockade with glycopyrrolate; the mid- and high-frequency peaks are abolished, while the amplitude of the low-frequency peak is reduced. Combined β-sympathetic and parasympathetic blockade abolishes all heart rate fluctuations leading to a metronome-like heartbeat (Fig. 1b). Sympathetic blockade alone tends to reduce the low-frequency peak's amplitude, but this effect is not consistent because of the low tonic level of sympathetic activity in the resting dog. To better characterize the effects of autonomic activity on the low-frequency peak, we varied the levels of autonomic nervous activity reflexogenically by varying arterial blood pressure. Arterial pressure was manipulated by continuous intravenous infusion of either the vasodilator sodium nitroprusside or the vasoconstrictor methoxamine. Under conditions of β-sympathetic blockade, increasing arterial pressure—which reflexively increases parasympathetic activity—increases the area under the low-frequency peak. Under conditions of parasympathetic blockade, decreasing arterial pressure—which reflexively increases β-sympathetic activity—also increases the area under the low-frequency peak (Fig. 1c). Thus, increasing the activity of either the sympathetic or parasympathetic nervous system augments the area under the low-frequency peak. Therefore, our data indicate that the parasympathetic nervous system mediates heart rate fluctuations at frequencies corresponding to the mid- and high-frequency peaks of the power spectrum, whereas both the sympathetic and parasympathetic systems may mediate the low-frequency fluctuations.

Finally, we tested the effect of selective blockade of the renin-angiotensin system. In three of four animals so studied we observed a 2- to 4.5-fold increase in the area under the low-frequency peak (Fig. 1d). In the fourth dog, which was at autopsy found to have heartworms, this response was not noted.

In the resting dog on a normal salt diet, blockade of the renin-angiotensin system leads to little or no change in mean heart rate or mean arterial pressure. However, the data presented here clearly indicate that such blockade can lead to a dramatic alteration in low-frequency heart rate fluctuations. We believe that this noninvasive analysis provides the first direct evidence that the renin-angiotensin system plays a significant role in short-term cardiovascular regulation.

The physiologic basis for our results can be understood in terms of a simple block diagram (Fig. 2). The sympathetic and parasympathetic nervous systems are directly responsible for modulating heart rate in response to fluctuations in sensed variables such as arterial blood pressure. However, the response time of the parasympathetic nervous system is much shorter than that of the sympathetic nervous system (*7*). Therefore, only the parasympathetic nervous system reacts rapidly enough to mediate high-frequency fluctuations in heart rate corresponding to the mid- and high-frequency peaks of the spectrum. Both the sympathetic and parasympathetic systems are capable of mediating heart rate fluctuations in the range of the low-frequency peak. Thus the change in power spectrum of heart rate fluctuations with autonomic blockade can be understood simply in terms of the band-pass properties of these systems.

To understand the effect of converting enzyme inhibitor, we note that the origin of the low-frequency peak in the heart rate power spectrum probably originates from fluctuation in peripheral vasomotor tone, leading to perturbations in central venous and arterial pressures (*6*). Our data suggest the possibility that the tonic activity of the renin-angiotensin system normally damps the amplitude of these fluctuations in peripheral vasomotor tone; blocking the renin-angiotensin system leads to a large increase in the

amplitude of these fluctuations in vasomotor tone and thus the perturbation to sensed blood pressures. These larger perturbations, occurring at frequencies of about 0.04 Hz, are in turn translated into heart rate fluctuations at these frequencies through the mediation of the autonomic nervous system (*8*). Our data strongly suggest that the renin-angiotensin system indeed plays an important role in maintaining the short-term stability of the cardiovascular system under conditions of normal salt intake. Previously, blockade of the renin-angiotensin system could only be demonstrated to lead to physiologically significant changes in the salt-deprived, or otherwise stressed, animal (*3*).

Quantitative analysis of fluctuations in hemodynamic parameters is a powerful quantitative means of probing mechanisms of short-term cardiovascular control. We believe that this approach could provide a versatile, noninvasive clinical method for assessing the integrity of the cardiovascular control system in a variety of disease states.

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8. Lumbers *et al.* [E. R. Lumbers, D. I. McCloskey, E. K. Potter, *J. Physiol. (London)* **294**, 69 (1978)] have shown that angiotensin II inhibits vagal parasympathetic outflow through a central nervous mechanism. Thus blockade of the renin-angiotensin system might be expected to increase vagal activity, which should increase all peaks in the power spectrum. Our data show a dramatic selective effect on the low-frequency peak, which cannot be attributed therefore merely to an increase in overall vagal activity. We believe this frequency-specific effect is probably due to changes in the amplitude of the fluctuations of the peripheral resistance upon blockade of the renin-angiotensin systems.
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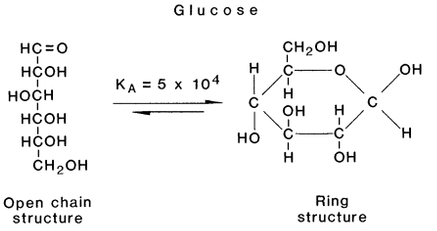
Reaction of Monosaccharides with Proteins: Possible Evolutionary Significance

Abstract. *Measurements were made of the rate of condensation of various monosaccharides with amino groups of hemoglobin to form Schiff base linkages. The reactivity of each sugar was dependent on the extent to which it exists in the open (carbonyl) structure rather than in the ring (hemiacetal or hemiketal) structure. Among the 15 monosaccharides tested, aldoses showed higher reactivities than ketoses. Glucose was the least reactive of the aldohexoses. The emergence of glucose as the primary metabolic fuel may be due in part to the high stability of its ring structure which limits potentially deleterious nonenzymatic glycosylation of proteins.*

As a rule chemical reactions in living tissues are under strict enzymatic control and conform to a tightly regulated metabolic program. One of the processes implicit in biomolecular evolution is the minimizing of unwanted side reactions. Nevertheless, uncontrolled and potentially deleterious reactions occur, even under physiologic conditions. Examples include deamidation, transamidination, sulfhydryl oxidation, and lipid peroxidation. Recently, attention has focused on the nonenzymatic condensation of glucose with proteins to form stable covalent adducts. Under physiologic conditions, glucose in solution exists as a stable pyranose ring structure in equilibrium with the open chain aldehyde form:



The most abundant minor hemoglobin component in human red cells, HbA_{Ic}, is formed by the reaction of the aldehyde

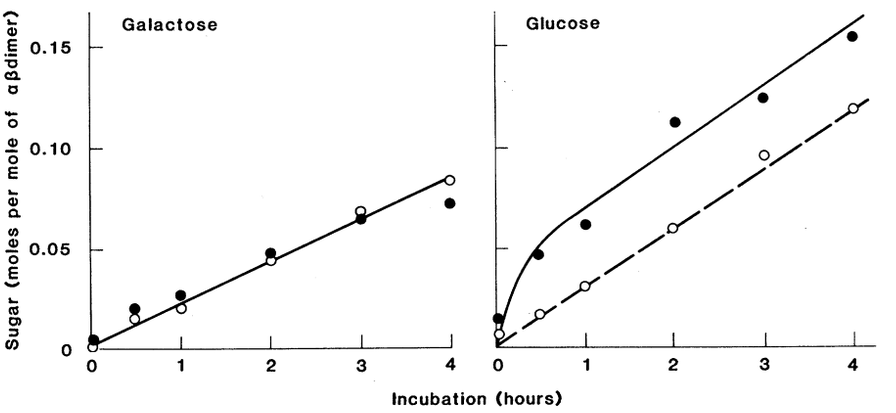


Fig. 1. Measurement of k_1, the rate of condensation of monosaccharide with hemoglobin, by two methods: (i) incubation with unlabeled sugar and reduction of aldimine linkage with ^3H-labeled cyanoborohydride (○); (ii) incubation with ^{14}C-labeled sugar and reduction with unlabeled cyanoborohydride (●); (left) 12 m*M* D-galactose; $k_1 = 1.9 \times 10^{-3}$ mM^{-1} per hour; (right) 42 m*M* D-glucose; $k_1 = 0.6 \times 10^{-3}$ mM^{-1} per hour. The initial rapid rate of incorporation of D-[^{14}C]glucose can be explained by the small amount of rapidly reacting impurity remaining in the preparation (*11*, *15*).

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