Assessment of autonomic function in humans by heart rate spectral analysis

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Department of Medicine, Division of Behavioral Medicine, Beth Israel Hospital, The Charles A. Dana Research Foundation, The Thorndike Laboratory, Brigham and Women's Hospital, and Departments of Medicine and Physiology, Harvard Medical School, Boston 02115; Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge 02139; and Children's Service Pediatric Pulmonary Unit, Massachusetts General Hospital, Boston, Massachusetts 02114

POMERANZ, BRUCE, ROBERT J. B. MACAULAY, MARGARET A. CAUDILL, ILAN KUTZ, DAN ADAM, DAVID GORDON, KENNETH M. KILBORN, A. CLIFFORD BARGER, DANIEL C. SHANNON, RICHARD J. COHEN, AND HERBERT BENSON. *Assessment of autonomic function in humans by heart rate spectral analysis.* Am. J. Physiol. 248 (Heart Circ. Physiol. 17): H151–H153, 1985.—Spectral analysis of spontaneous heart rate fluctuations were assessed by use of autonomic blocking agents and changes in posture. Low-frequency fluctuations (below 0.12 Hz) in the supine position are mediated entirely by the parasympathetic nervous system. On standing, the low-frequency fluctuations increase and are jointly mediated by the sympathetic and parasympathetic nervous systems. High-frequency fluctuations, at the respiratory frequency, are decreased by standing and are mediated solely by the parasympathetic system. Heart rate spectral analysis is a powerful noninvasive tool for quantifying autonomic nervous system activity.

posture; sympathetic; parasympathetic

WE ASSESSED AUTONOMIC nervous control of the heart by measuring the power spectrum of spontaneous heart rate fluctuations in humans. Recent studies in the conscious dog (1) show that low-frequency fluctuations in heart rate (below 0.1 Hz) are jointly mediated by the sympathetic and parasympathetic nervous systems, whereas higher-frequency fluctuations are mediated solely by the parasympathetic system. It was also shown that the renin-angiotensin system activity strongly modulated the amplitude of the low-frequency fluctuations. To determine whether heart rate fluctuations in humans are controlled by similar mechanisms, we used autonomic blocking agents and changes in posture to interpret the heart rate spectral analysis (HRSA) peaks. We found that low-frequency fluctuations (below 0.12 Hz) are increased by standing and are jointly mediated by the sympathetic and parasympathetic nervous systems. Higher-frequency fluctuations are decreased by standing and are mediated solely by the parasympathetic system.

Informed consent was obtained from eight healthy male volunteers between 22 and 36 yr of age (mean 27.8). The subjects were trained to breathe in synchrony with a metronome at 15 breaths/min (0.25 Hz) to ensure that respiratory-linked variations in heart rate did not overlap with low-frequency heart rate fluctuations (below 0.12 Hz) from other sources. A catheter was inserted in an antecubital vein at 12:30 P.M. of 2 consecutive days. Then HRSA measurements were obtained from 1 to 4 P.M. on each day. Two spectra were obtained with the subject supine and standing before and 5–40 min after each drug infusion. On *day 1*, atropine (a parasympathetic muscarinic blocker) was administered (0.03 mg/kg iv over 5 min) followed 40 min later by *d-l* propranolol, a β-sympathetic blocker (0.15 mg/kg iv over 5 min). On *day 2*, this order was reversed in six of the subjects. (Two subjects did not complete the study.) These doses were chosen to minimize the risk of arrhythmias or other potentially serious side effects while maximizing degree of blockade.

We continuously measured the surface electrocardiogram from standard lead II. The beat-to-beat instantaneous heart rate was measured with a Gould EKG-BIOTACH model 13-4515-65; the output was processed by a Hewlett-Packard 3582A spectrum analyzer and a Hewlett-Packard 85 microcomputer, which calculated the power spectral density from 0.02 to 1.0 Hz. The spectra were calculated on-line from 256 consecutive seconds of data (6, 7). On the basis of preliminary studies, we defined two frequency bands of interest: (LO-FR 0.04–0.12 Hz) and high frequency (HI-FR, 0.224–0.28 Hz). The effect of each drug on heart rate fluctuations on each day was determined by comparing the spectral area of each band with its average base-line (predrug) value for that day. All comparisons were subjected to an analysis of variance followed by Dunnett's comparison test. The effects of the drugs on heart rate fluctuations on each day were compared with the base-line fluctuations of the same day even though the base-line values of *day 1* and *day 2* were not significantly different.

Representative HRSA data and the effects of postural change are shown in Fig. 1. In the standing posture, each subject developed a heart rate oscillation with a period

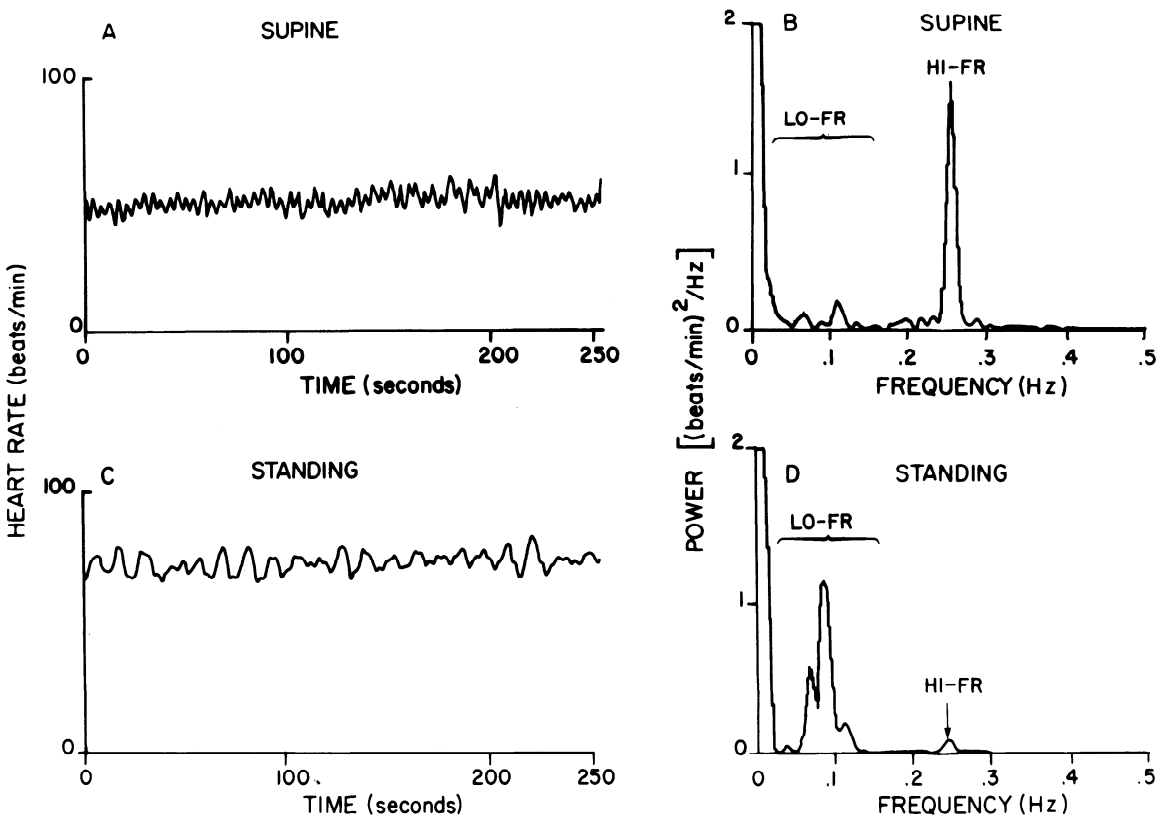

FIG. 1. Heart rate response to changes in posture. *A*: instantaneous heart rate in supine position. Note prominent high-frequency oscillations (respiratory sinus arrhythmia). *B*: power spectrum of *A*. Note small low-frequency (LO-FR) peak and prominent high-frequency (HI-FR) peak. *C*: instantaneous heart rate in standing position. Note prominent LO-FR oscillations. *D*: power spectrum of *C*. Note prominent LO-FR peak and small HI-FR peak.

of about 10 s, causing the peak within the LO-FR band (0.04–0.12 Hz) to increase 10-fold from his supine values. The mean areas (±SE) were as follows: supine 0.033 ± 0.008, and standing 0.33 ± 0.096 beats^2·min^{-2} ($P < 0.01$). The peak centered at 0.25 Hz is in the HI-FR band (0.224–0.28 Hz). This HI-FR peak is affected by depth of breathing (5) and varies in frequency with variations in respiratory rate. It constitutes a direct measure of the well-known respiratory sinus arrhythmia (4). The area of this peak decreased with the change of body posture from supine (mean area 0.065 ± 0.02) to standing (0.021 ± 0.005 beats^2·min^{-2}) on *day 1* ($P < 0.05$), with similar results on *day 2* ($P < 0.05$).

The effects of autonomic blockade on both the LO-FR and HI-FR bands are summarized in Table 1. In the supine position, atropine reduced the LO-FR area by 84% ($P < 0.01$), and addition of propranolol 40 min after the atropine to produce a double blockade did not further reduce this area. On *day 2*, the effect of propranolol alone on the LO-FR area in the supine position was inconsistent and not significant. Addition of atropine to propranolol was not different from atropine alone. Thus in the supine position, LO-FR heart rate fluctuations are largely mediated by parasympathetic activity. In contrast, in the standing posture the suppression of the LO-FR peak by atropine was only −72% of base line ($P < 0.05$). This was further decreased by addition of propranolol to −89% of base line ($P < 0.05$). Propranolol alone reduced the area by 73% ($P < 0.05$), indicating the presence of a strong sympathetic influence on LO-FR fluctuations in the standing posture.

TABLE 1. *% Change in areas of low- and high-frequency heart rate power spectrum bands after administration of atropine and propranolol*

Posture	*Day 1*		*Day 2*	
	Atropine	Atropine + Propranolol	Propranolol	Propranolol + Atropine
	Low frequency (0.04–0.12 Hz)			
Supine	−84† ±4.6	−83* ±5.6	+47 ±23.3	−90† ±2.5
Standing	−72* ±4.4	−89* ±1.7	−73* ±5.3	−90* ±2.6
	High frequency (0.224–0.28 Hz)			
Supine	−92* ±4.2	−80* ±1.7	+18 ±25.0	−92* ±2.9
Standing	−95† ±1.8	−93† ±1.1	+11 ±48.9	−96* ±1.1

Values are means ± SE. * $P < 0.05$. † $P < 0.01$.

Atropine practically abolished the HI-FR area (Table 1) in both the supine (−92%, $P < 0.05$) and standing (−95%, $P < 0.01$) postures. The addition of propranolol caused no additional reduction. On *day 2*, propranolol given alone had no effect on HI-FR for either posture. Thus, at a respiratory rate of 15 breaths/min, the HI-FR peak is mediated entirely by the parasympathetic system and has no sympathetic component.

These pharmacologic studies in humans confirm previous observations in the conscious dog that showed that the parasympathetic system mediates heart rate fluctuations at all frequencies between 0.024 and 1.0 Hz, while the sympathetic system mediates only LO-FR heart rate fluctuations (1). The present study in humans extends the previous observations in the dog, by determining the effect of posture. We find that in humans sympathetic influences are normally present in the LO-FR band only in the standing posture, whereas vagal activity influences heart rate at low and high frequencies in both supine and standing postures.

Heart rate fluctuations in the LO-FR regime may reflect a baroreceptor response to blood pressure fluctuations in this frequency band (1). The marked increase in the area of the LO-FR peak in the upright position then could be attributed either to an increase in LO-FR fluctuations in blood pressure, which then elicit increased heart rate fluctuations, or to an increased gain of the baroreceptor in the upright position (3) over this frequency range. Increased sympathetic activity in the upright position, as demonstrated by Burke et al. (2) in healthy humans, might increase the gain of sympathetic baroreceptor reflex in the LO-FR regime and account for increased power in the heart rate fluctuations in this frequency band. Decreased parasympathetic activity would account for the marked diminution in the HI-FR peak area. These results suggest that autonomic control of the heart in response to postural movements strikes a balance between the activities of the parasympathetic and sympathetic nervous systems and that HRSA may provide a quantitative measure of this balance.

In summary, we have utilized heart rate power spectrum analysis in humans to characterize, quantitatively and noninvasively, autonomic nervous system regulation of cardiovascular activity during pharmacologic interventions and changes of body posture. To better understand short-term cardiovascular regulation, further studies will be needed to determine the phase relationships between fluctuation in heart rate, blood pressure, and autonomic nervous system activity. Furthermore, future studies will be required to examine in humans the important role played by the renin-angiotensin system in short-term cardiovascular regulation as manifested by its ability to modulate the amplitude of spontaneous fluctuations in heart rate and other hemodynamic variables (1). We believe that power spectrum analysis of hemodynamic variables may provide a very powerful technique for assessing cardiovascular regulation in health and disease.

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