Editorial

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Measuring Activity of the Autonomic Nervous System in Humans

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It has been hypothesized that obesity is an abnormally high setting of a regulatory system controlling the level of fat storage in adipose tissue (1). The regulation is achieved by the operation of many elements and is determined by genetic variation and environmental factors. The autonomic nervous system (ANS),[1] with both sympathetic and parasympathetic controls (SC and PC, respectively), is believed to play a particularly important role. SC has been intensively studied in obesity; in fact one theory of obesity causation is the Mona Lisa Hypothesis, an acronym for "most obesities known are low in sympathetic activity" (2). A widely used technique for evaluating SC in humans and in experimental animals is dependent on the turnover rate of norepinephrine as measured by the decline in plasma norepinephrine specific radioactivity after injection of tritiated norepinephrine (3). In experimental animals, direct measure of turnover in heart muscle has been a valuable tool. The most direct method for measuring SC is microneurography, using an electrode in the peroneal nerve (4).

PC is also likely to be a player in fat storage, as suggested by the profound effect of vagotomy in ameliorating the effects of ventromedial hypothalamic lesioning. Some vagal effects may be related to insulin release, but there are likely other more direct relations of PC to fat storage, such as the marked bradycardia—probably not insulin related—occurring with weight reduction. Variations in heart rate, in particular, the waxing and waning of heart rate with respiration, or so-called sinus arrhythmia, is an effect of PC and thus has been used to estimate the degree of PC.

In 1981, a research group at the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology and the Massachusetts General Hospital published findings on formal spectral analyses of heart rate fluctuations to evaluate PC and SC (5). Modern electronic and computer technology enable rapid analysis of the "power" of various fluctuating or periodic inputs to heart rate at frequencies from 0 to 0.5 Hz (0 to 30 cycles/min). High-frequency peaks at ~0.4 Hz are the result of sinus arrhythmia. Because sinus arrhythmia can be completely alleviated by atropine, a muscarinic parasympathetic blocker, its measure is believed to be a "pure" measure of the parasympathetic input to heart rate variability at the frequency of respiration. Lower frequency peaks were found to be a mixture of SC and PC, and another input from the renin–angiotensin system was also identified. The equipment to perform such analyses is now readily available and has often been used to evaluate SC and PC in humans, both obese and non-obese, under a variety of conditions. In this issue of *Obesity Research*, Nagai et al. (6) make use of this method to evaluate the relationship of ANS activity to the development of obesity in Japanese school children. We have studied spectral analyses of heart-rate variability in human subjects (7), hoping that this relatively simple and noninvasive method would give reliable measures of SC and PC in human subjects as levels of fat storage are modified by feeding low or high calorie diets. For the reasons given below, we have found that the method has several shortcomings, and a more complex approach using pharmacological blockade becomes necessary for accurate assessment of ANS (8).

The beat-to-beat interval (RR) in milliseconds is shown in the Nagai et al. study (6) of autonomic activity in obese and non-obese Japanese children. They illustrate the variation of heart rate in the "time domain," and the same figure shows how these data can be reanalyzed in the "frequency domain," indicating the influence or power of inputs at various frequencies. Peaks at ~0.3 Hz in the children were attributable to respiration and used to measure PC, and the lower frequencies were ascribed to SC.

Our approach to the evaluation of the ANS is shown in Figure 1. Heart rate variability in the time domain as was obtained with the Japanese children is shown in Figure 1A. A periodic function derived from the beat-to-beat variation in RR by spectral analysis is shown in Figure 1B as a series of regular undulations, cycling at the same rate as respiration. As shown in Figure 1C, when heart rate changes under

[1] Nonstandard abbreviations: ANS, autonomic nervous system; SC, sympathetic control; PC, parasympathetic control; RR, beat-to-beat interval.

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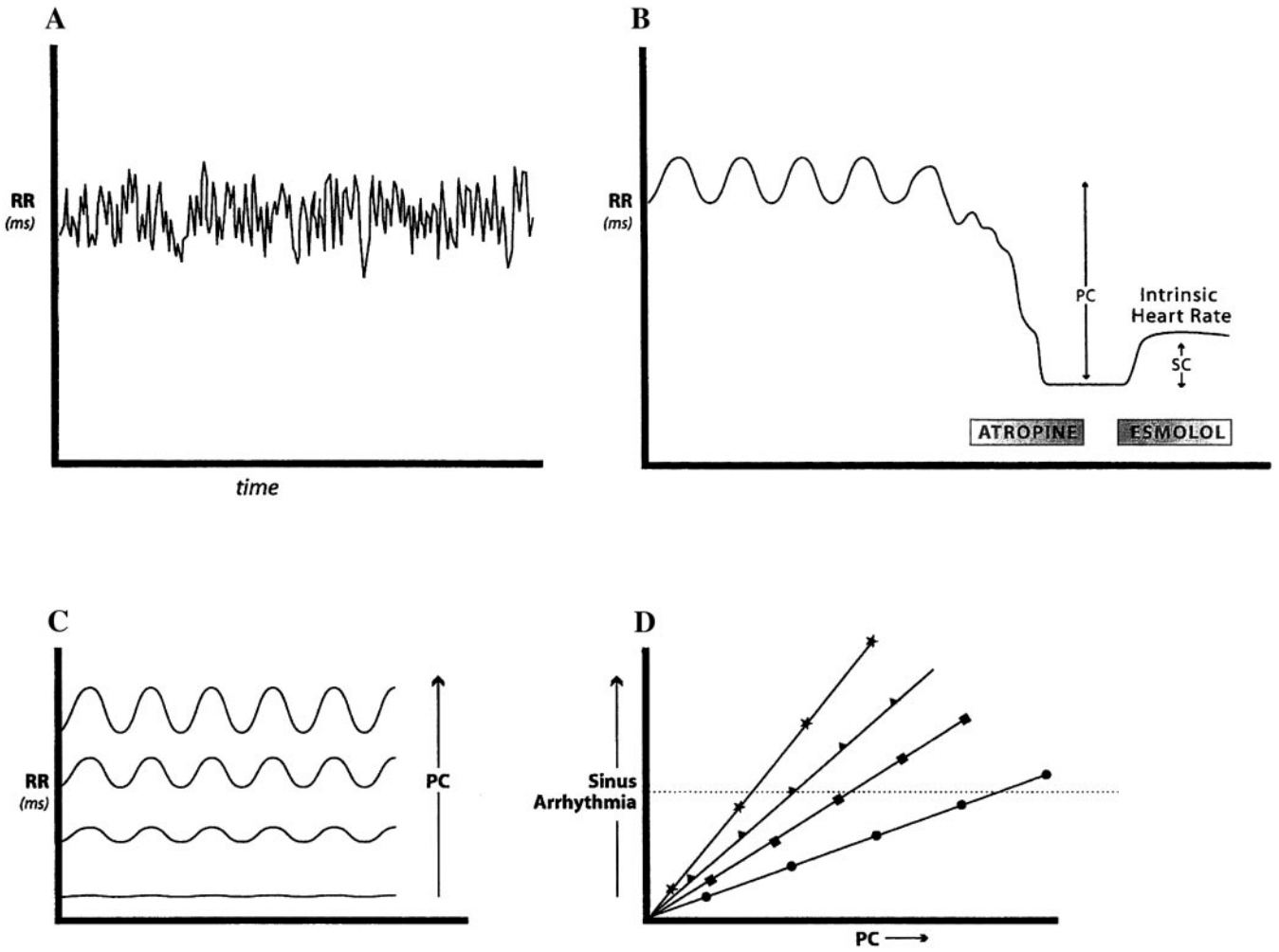

Figure 1: ANS analysis. (A) Typical heart rate variability in the time domain. (B) A periodic element of heart rate variability such as respiratory sinus arrhythmia. The effect of drugs on heart rate as used to calculate PC and SC is shown. (C) The effect of PC on sinus arrhythmia. (D) Individual differences in the PC–sinus arrhythmia relationship. (See text for further details.)

the influence of increasing or decreasing vagal activity, the level of sinus arrhythmia changes as well. When the respiratory input to heart rate variability is completely blocked by full doses of atropine, sinus arrhythmia disappears. This drug effect, shown in Figure 1B, was used to measure PC. After atropine blockade, the administration of full doses of esmolol, a cardio-selective β-blocker, leads to a slowing of heart rate or increase in the RR interval as shown. This serves as the measure of SC. RR interval or heart rate, after both drugs are given, becomes free of the moment-to-moment variations related to the ANS and is termed the intrinsic heart rate. Data on PC and SC obtained in this way clearly indicate that the ANS has both phasic and tonic components. Note that sinus arrhythmia is only a small fraction of the total input of PC, and thus, cannot be assumed to be an accurate measure of total PC. Although sinus arrhythmia may give an estimate of vagal activity or total PC as it varies in a given individual, as shown in Figure 1C, this relationship is dependent on such factors as respiratory kinetics, age, and physical training and hence varies markedly from one person to another (9). Therefore, the level of sinus arrhythmia cannot be used as an accurate measure of differences in PC between groups of individuals. This is shown in hypothetical data in Figure 1D. The different slopes of various individuals are shown to illustrate the person-to-person variation in PC to heart rate variability. This portion of the diagram is modeled on the data of Katona and Jih (9). Note the dotted line drawn to show that different individuals with the same degree of sinus arrhythmia may have marked differences in PC. Thus, using the power of heart-rate variability at the frequency of respiratory rate can be a highly inaccurate measure of PC when used to compare different groups of individuals such as the obese vs. the non-obese.

SC is even more difficult to estimate from spectral analysis. With atropine blockade of PC, there is also a marked

decline in low frequency variations, which are often attributed to SC when spectral analysis is used to evaluate ANS. This cannot be done with assurance, because low-frequency heart-rate variability is very much influenced by PC. After full blockade, there remains only a small measurable rhythmicity in heart rate at low frequencies.

Studies of the ANS using only spectral analysis such as the studies of development of obesity in Japanese children published in this issue are most important, but the results are difficult to interpret; for more definitive answers, analysis by pharmacological blockade will be required. When we applied the method of spectral analysis of heart rate to compare obese and non-obese humans, results were complex and difficult to interpret (7), but when the method of pharmacological blockade was applied to the study of heart rate and its variability, a much clearer picture emerged (10). We could conclude that obese humans have more SC and less PC than non-obese in contrast to the Mona Lisa Hypothesis related findings in experimental animals. Hopefully, other simpler and less invasive methods will be found for evaluating SC and PC in humans. Until that time, estimating SC and PC from power at various frequencies in spectral analyses of heart rate variability runs the risk of producing meaningless or erroneous results.

Acknowledgments

This research was supported in part by a General Clinical Research Center grant (M01-RR00102) from the National Center for Research Resources, NIH. We gratefully acknowledge the assistance of Karina Aberg in preparation of Figure 1.

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