

Heartbeats, Hormones, and Health Is Variability the Spice of Life?

According to Heraclitus (sixth century B.C.): "Everything flows and nothing abides; everything gives way and nothing stays fixed" (1). Perhaps even more than the physical world around us, biological processes within us provide an endless and astounding source of complexity and flux. Yet, clinicians and investigators have traditionally been guided by a principle that has attained the status of a medical law—namely, homeostasis (2). According to this tenet, physiological regulatory mechanisms are "engineered" to reduce variability and maintain a constant type of steady state, which Walter B. Cannon referred to as the "wisdom of the body" (3). This notion, in part, underlies the widespread practice of summarizing and reporting physiological data as means and variances, while treating instant-to-instant fluctuations as uninformative "noise."

The apparent metronomic regularity of the healthy heartbeat would seem to confirm the assumption of homeostatic constancy. Closer scrutiny of "regular" sinus rhythm, even in resting subjects, however, uncovers remarkable variability with extraordinarily complex fluctuations across a wide range of time scales, ranging from milliseconds or less to hours or more. Furthermore, this variability is not simply attributable to random noise superimposed on a basically regular process. Instead, hidden in the interbeat interval cycles of apparently regular sinus rhythm are temporal structures at least as complex as the turbulent flows that pose some of the most challenging problems in contemporary physics (4). Equally interesting is the evidence from a growing number of studies indicating that changes in the patterns of complex variability in the heartbeat and other physiological signals—over both shorter (ultradian) and longer (circadian and infradian) time scales—may be important markers of numerous acute and chronic diseases (5–7).

Takabatake and colleagues, in this issue of the *American Journal of Respiratory and Critical Care Medicine* (pp. 1314–1319 (8)), provide further evidence to support the contention that reductions in certain statistical features of heart rate variability are important indices of perturbed physiological control. Their study was designed to probe mechanisms related to the unexplained weight loss commonly observed in patients with severe chronic obstructive pulmonary disease (COPD). They focused on two variables: serum leptin and heart rate. Leptin, an adipocyte-derived hormone, was studied because of its important role in the control of body weight and energy expenditure. Selected parameters of heart rate variability were measured as an indirect, useful assay of autonomic and neurohormonal control (6). The authors' leptin measurements indicate that patients with COPD with cachexia, when compared with noncachectic patients with COPD and healthy control subjects, have a blunted circadian pattern with marked attenuation of the usual nocturnal peak. They observed concomitant abnormalities in a number of indices of heart rate variability in the cachectic COPD group, including a higher

resting heart rate and lower overall spectral power. In addition, they reported significant diminutions in heart rate fluctuations in the so-called ultralow frequency (ULF) (< 0.003 Hz) and very low-frequency (VLF) bands (0.003–0.04 Hz).

What is the biological significance of these findings? The mechanism of circadian and ultradian "dysrhythmias" remains largely uncertain. Are they primary abnormalities or secondary epiphenomena? Can dynamic probes of heart rate and hormonal time series data provide useful new diagnostic and prognostic measures? Takabatake and coworkers (8) attempt to define a novel neurohormonal link by proposing that circulating leptin "at least in part, plays a determinant role" in regulating the VLF values of heart rate variability (8). Their inference relies primarily on the regression analysis of log VLF power versus log mean serum leptin levels, presented in their Figure 4 (8). However, this plot reveals a relatively weak positive correlation ($r = 0.388$), with a large amount of scatter around the regression line. Furthermore, for the cachectic subgroup alone, this relationship between serum leptin and VLF heart rate power appears to be even weaker, if present at all. The study, surprisingly, also did not reveal any significant differences between leptin levels (averaged over 24 h) in patients with COPD (cachectic or noncachectic) versus control subjects. In contrast, in their recent publication in this journal, the same group (9) reported a significant decrease in serum leptin (A.M. nadir values) in patients with COPD versus healthy control subjects.

The putative relationship between serum leptin and heart rate dynamics is also difficult to assess because the authors used 5-min segment lengths of R–R interval data to compute spectral power, a sample window just at the borderline for resolving frequencies around the threshold that separates the ULF from the VLF bands. As noted in Takabatake and coworkers (reference [23]), a report of the International Task Force on Heart Rate Variability (6): "VLF assessed for short-term (5 min) is a dubious measure, and should be avoided." Happily, the authors' data could be readily reanalyzed to compute VLF and ULF power over larger sampling windows (20–30 min) to provide more robust estimates that might strengthen their conclusions. Availability of the original data might also allow investigators to extend the authors' findings by using newer time series analysis techniques designed to cope with complex nonlinear and nonstationary signals (4, 10).

The report by Takabatake and colleagues (8) is, in my opinion, quite representative of the current explosion of publications on the variability of heart rate and other physiological signals. Such studies most often are based on invaluable but inaccessible databases, and present a bewildering "babelography" of different preprocessing and analytic algorithms. The current situation makes validation, interstudy comparisons, and clinical implementation of variability measures difficult, if not impossible—unless and until the biomedical community has access to the original data, and ideally, the source codes of the analytic algorithms. A highly successful precedent for such a "cultural change" in publication policies already exists in the biomolecular community (11). The impact of GenBank and related genomic and proteomic databases is a compelling

model for the institution of open-source policies with respect to all types of physiological signals (10, 12). By going beyond PubMed and publishing the original (versus reduced) data and analytic tools, we may finally be able to realize the 2500-yr-old "wisdom of the heterodynamic body" captured in the aphorisms of an ancient Greek philosopher.

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