The following letters are in response to the Point:Counterpoint series “Cardiovascular variability is/is not an index of autonomic control of circulation” that appears in this issue.

To the Editor: The Point:Counterpoint article (5) stimulates a third way of thinking. Since our first study (4) we attempted to obtain noninvasive markers of autonomic cardiovascular regulation. In relation to a simple physiological hypothesis, the sympathovagal balance, we stressed two components of heart rate variability spectrum (LF and HF), normalizing their values to evaluate them independently of variance. We also proposed the LF/HF ratio, and, as an index of vasomotor modulation, LF of blood pressure variability. Evaluation of direct recordings of peripheral nerves and central neurons (1) strengthened the conceptual basis of the approach. Obviously the new tool, like all others, cannot apply to “all conditions,” and sympathovagal balance is not a linear phenomenon. The sentence “if one simply knows the angle of tilt, there is no need to assess heart rate variability” (5) indicates that irony is not the only key for understanding. Similarly, there is no paradox in the fact that both vagal and sympathetic recordings may furnish a window on the same central rhythmicity (3). Finally all authors (5) disregarded the study that has proven beyond any doubt the relationship between low-frequency power and cardiac sympathetic regulation. Neither low frequency (LF) nor high frequency (HF) power is simply watched the body position?

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actually elicited significant reductions in this variable (1). Sympathetic activity can also modulate the high-frequency component of heart rate variability (4), albeit to a lesser extent than parasympathetic influence on low-frequency power. Although the vast majority of clinical and experimental studies demonstrate a strong association between high-frequency power and cardiac parasympathetic activity (2), this relationship is qualitative rather than quantitative in nature (i.e., low HRV = low parasympathetic, high HRV = high parasympathetic activity, as opposed to X units = Y nerve impulses/s). Thus, even if data are interpreted with appropriate caution, HRV provides only a qualitative marker of cardiac parasympathetic regulation.

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To the Editor: Finding bold correlations is a difficult art that requires experience and competence: to correlate the number of personal computers sold per year with the number of publications on heart rate variability (HRV) may bring one to the conclusion that babies are brought by storks either in Strasbourg or in South Africa by simply correlating the peak of births with the incidence of arrival of storks.

Both parts agree on the fact that obtaining parameters that could “measure” at some extent autonomic control is a challenging (and probably not yet solved) task. Our group was involved in the two milestone papers (3, 5) also reported by (4). Previously (1), we set up original methods of signal processing with a parametric approach able to detect efficiently the possible presence of rhythmic components embedded in wide-band noise, according to a simple model of sympatho-vagal balance. Nobody may state that cardiovascular variability parameters (CVV) are quantitative measures of autonomic outflow, but certainly they helped many researchers of the >8,500 papers actually cited on Medline to provide some physiological interpretation and possible clinical application. CVV does not reflect “simple” mechanisms: the community of Biomedical Engineers and Computer Scientists have greatly contributed to the studying of the “complexity” of the various signals related to it. A recent issue of IEEE Trans BME was dedicated to “Recent Advances in HRV Signal Processing and Interpretation” (2) and original and different approaches have been suggested, thus indicating multiple new roads open to build bridges between CVV signal processing and physiological modelling.

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To the Editor: Heart rate variability (HRV) provides valuable prognostic information. Attenuation of HRV and baroreflex sensitivity (BRS) predicts poor outcome after myocardial infarction and in patients with chronic heart failure (2, 3). Limitation points have restricted the diffusion of these methods. HRV assessment is available from 24-h Holter monitoring, but accurate analysis is time consuming, dependence on multiple uncontrolled physiological stimuli mars interpretation (5). Conventional measures of BRS require the beat-to-beat measurement of blood pressure either invasively or noninvasively with expensive equipment. Taylor and Studinger who clearly express the skepticism of the clinical community toward these indexes indicates our study as a further demonstration of the HRV shortcomings (1). We assessed BRS by asking subjects to breathe gently at 0.1 Hz. Breathing at 0.1 Hz provides a standard blood pressure (BP) stimulus and concentrates spectral power of heart rate at one frequency, enabling simple evaluation of BRS even when BP measurement is not available. This entrains oscillations in blood pressure, which act via the baroreflex to cause oscillations in heart rate. BRS measurement by this technique was found to be highly reproducible (by comparison with conventional techniques) and to agree well with conventional measures (1). This method was validated in heart failure and diabetes mellitus patients. The widespread use of simple, cheap, and easy methods of identifying patients at high risk of adverse cardiovascular events should be promoted because it would therefore allow the correct allocation of limited resources and of potentially dangerous interventions.

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To the Editor: Sir, Taylor and Studinger use “heart” rate variability (HRV) arguments to attack circulatory variability indices of “circulatory” control (4), ignoring the role of activity or breathing (1, 2, 3, 5) and much favorable evidence (1, 2, 3, 5). Citations are misquoted; our physiological study of slow breathing is described as a study of religion! Their main argument against blood pressure (BP) low-frequency components (LF) as an index of sympathetic activity is the lack of “perfect” correlation between sympathetic nerve activity (MSNA) and LF-BP, while admitting the existence of significant correlations. They regard MSNA as their gold standard, but the circulatory response depends on the hypertrophy responsiveness of the target (5)—negating their interpretation of their Ref. 29. Taking this into account, their Ref. 29, Fig. 3, correlates BP-LF with MSNA within each group, even if at rest and supine. Parati’s group rely mainly on consistent human indices of “circulatory” control (4), ignoring the role of activity responsiveness of the target (5)—negating their interpretation of their Ref. 29. Taking this into account, their Ref. 29, Fig. 3, correlates BP-LF with MSNA within each group, even if at rest and supine. Parati’s group rely mainly on consistent human studies of blockade, disease, or prognosis. Neither group reports the tight coherence between single sympathetic bursts and BP-LF (Ref. 2, Fig. 1)—clear evidence that BP-LF is indeed related to sympathetic activity. In cardiac transplantation studies, before/during reinnervation, spectral analysis and specific interventions demonstrate neural and nonneural components of circulatory variability, and LF dependence on sympathetic activity (1). Although we agree with Parati (although encouraging also a more physiological approach), Taylor and Studinger require perfect correlation with sympathetic nerve recordings; not finding perfection, they then reject existing reasonable correlations (e.g., their Refs. 21, 25, 29), considering them as “contamination by lack of validation.” Perfect correlations do not exist in biology.

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To the Editor: Both the Point and Counterpoint (4) agree that heart rate variability (HRV) is related to the activity of the autonomic nervous system (ANS) and that spectral variation of the heart rate in the lower (LF) and higher (HF) frequencies typically have a stronger relationship to sympathetic activity and vagal outflow, respectively. What is at issue is whether HRV is an index, or “a benchmark of activity or performance” of ANS. Only an explicit definition will make this assessment concrete. The counterpoint shows the difficulty of such a definition.

This comes as no surprise. HRV, produced as a by-product of homeostatic function of ANS (4) is in turn one of many inputs to the ANS via “sensors” (1) such as baro- and chemoreceptors. However, so far, only a few, if any, of the quantitative relationships between the specific mechanisms of control and the sensor inputs have been investigated and explained (2). HRV reflects both the operation of multiple controllers such as the sympathovagal input to the sinoatrial nodes, or prior calibration of one of the sensor inputs (3). Thus without explicit knowledge of these relationships, the point cannot be established. Nonetheless, rough mutable correlations between the properties of controlled cardiac output and the ANS input are to be expected.

The authors of the point also propose that HRV should be used in clinical practice. We all welcome better diagnosis and treatment of heart disease. To date, HRV has not been shown to be better than standard clinical tools for individual treatment. Because these measures are relatively cheap and noninvasive, we look forward to this demonstration.

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To the Editor: The Point:Counterpoint article (3) poses the problem of the relevance of indexes derived from blood pressure (BP) and heart rate (HR) variability.

The most convincing index of autonomic function is by far respiratory sinus arrhythmia (RSA), studied by Pyetan et al. (1), Médigue et al. (2), and others. The study by Médigue et al. (2) showed that an infusion of atropine induced changes in amplitude of RSA. This RSA follows perfectly atropine infusion and corresponding changes in vagal tone. At low doses of atropine, the amplitude of RSA was increased and then decreased at higher doses. This study shows that RSA was sensitive to slight changes in vagal activity resulting from the vagometric and the vagolytic effect of atropine.

Also, indexes derived from rapid reflex HR changes produced good markers of the vagal activity. Furthermore, the estimation of baroreflex sensitivity (BRS), by combining the BP and HR fluctuations, offers some benefit in the early detection of autonomic neuropathy in animals (1) and humans (5). The study by Ziegler et al. (5) compared different indexes derived from BP and HR variability. This shows that some of them followed the degree of neuropathy in diabetic subjects. But only a few of them, such as the slope of the sequence method, were able to show significant modifications at an early stage of neuropathy, when conventional autonomic function tests were unable to detect any alterations. This estimate of BRS provides a powerful tool for the assessment of autonomic neuropathy, with direct implications in clinical practice.

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To the Editor: In their Point:Counterpoint discussion (2) on whether cardiovascular variability is/is not an index of autonomic control of circulation, both groups present valuable points. However, we would like to press the point that to be an index of autonomic control, cardiovascular variability must be a quantitative measure of the autonomic control. In the following, we present one example of the inadequacy of respiratory sinus arrhythmia (RSA) on being an index of vagal tone in healthy humans.

In a healthy supine 19-yr-old female, we recorded heart rate and respiration. A beautiful, prominent RSA (amplitude ~15 beats/min) appeared and HR was about 60 beats/min when she performed a moderate dynamic leg exercise. In supine rest, her HR averaged 39 beats/min, indicating a pronounced vagal tone. However, RSA was of lesser amplitude (~6 beats/min) and the integration of the HR power spectrum in the interval 0.15–0.40 Hz was 0.9 beats/min² in rest compared with 7.8 beats/min² in exercise.

This is one example where RSA is not a quantitative index of vagal tone. If RSA is not an index of vagal tone in healthy young resting humans, we definitely need more knowledge before using RSA as a clinical tool to assess vagal autonomic control.

The phenomenon presented here may be caused by saturation of M2-receptors for ACh in SA node cells (3). In addition, to make sure all aspects are considered during discussion of RSA and its origin and function, it is important to include the respiratory variation in stroke volume (1, 4).

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To the Editor: Thank you for the opportunity to respond to the Point:Counterpoint cardiovascular variability (CVV) topic (4). For those of us who study healthy human volunteers, CVV indexes are our only noninvasive window into autonomic control and therefore this topic is of vital interest. We have used spectral power (in conjunction with plasma catecholamines) to gain insight into autonomic control associated with gender (2), simulations of spaceflight (5), cardiorespiratory interactions (3) and artificial gravity training (1). Currently we find that resting measures of spectral power predict the subsequent orthostatic tolerance limit of healthy women and discriminate levels of damage to cardiovascular regulation in spinal cord injured patients.

The principals in this argument actually agree on the potential of CVV to discriminate autonomic activity. They disagree as to where problems exist: Taylor and Studinger argue that quantification of autonomic activity has not been achieved, warn that achievement may not expose “complex and largely undiscovered, physiology,” and suggest that efforts be focused on establishing more direct links to underlying physiology. Parati et al. (4) propose that the field has already established a basis for autonomic interpretation of results and that future modeling will expose underlying physiology. We argue that, although currently limited in interpretation, indexes of autonomic change are legitimate research tools.

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The current argument highlights the fact that CVV results must be carefully examined by authors, editors, and reviewers of manuscripts for appropriate analyses and interpretation of autonomic control. However, it is our firm opinion that ever-increasing refinement of CVV indexes will lead to increasingly quantitative measures of autonomic activity.

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To the Editor: I agree with Taylor and Studinger (4) that there is more to be learned from cardiovascular periodicities than what they may or not say regarding baseline levels of autonomic nerve traffic.

Respiratory activity gates the responsiveness of sympathetic as well as vagal motoneurons to stimulatory inputs; therefore, both neural outflows fluctuate at respiratory frequencies (2). Respiratory fluctuations depend critically on the rate at which this gate is opened and closed (the breathing rate). Each breath releases boluses of acetylcholine and norepinephrine; at rapid breathing rates, each neurotransmitter bolus arrives on the heels of the preceding bolus, whose effects have not dissipated. Slow breathing fully expresses, and rapid breathing minimizes transmitter peaks and valleys, and corresponding neuroeffector responses. Proper understanding of high-frequency rhythms requires knowledge of respiratory activity.

Cardiovascular fluctuations also depend importantly on the intrinsic antagonism that exists between sympathetic stimulation and vagal inhibition. When breathing rate and depth are controlled, sympathetic activity reduces vagal heart period fluctuations at all, including low frequencies (5). Not surprisingly, there is no published evidence that low-frequency heart period oscillations—measured, or modified mathematically—correlate significantly with muscle sympathetic nerve activity or cardiac norepinephrine spillover (1).

Largely unexplored fluctuations of vagal baroreflex gain may explain disparities between pharmacological and spontaneous baroreflex measures. Prognostically important very low frequency heart period rhythms are associated strongly with very low frequency, major fluctuations of baroreflex gain (3).

I suggest that new insights into cardiovascular rhythms might be obtained by study of mechanisms modulating baroreflex gain, particularly at very low frequencies, and the physiological implications of intrinsic sympathetic-vagal antagonism.

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