

## Point:Counterpoint: Cardiovascular variability is/is not an index of autonomic control of circulation

### PURPOSE AND SCOPE OF THE POINT: COUNTERPOINT DEBATES

This series of debates was initiated for the *Journal of Applied Physiology* because we believe an important means of searching for truth is through debate where contradictory viewpoints are put forward. This dialectic process whereby a thesis is advanced, then opposed by an antithesis, with a synthesis subsequently arrived at, is a powerful and often entertaining method for gaining knowledge and for understanding the source of a controversy.

Before reading these Point:Counterpoint manuscripts or preparing a brief commentary on their content (see below for instructions), the reader should understand that authors on each side of the debate are expected to advance a polarized viewpoint and to select the most convincing data to support their position. This approach differs markedly from the review article where the reader expects the author to present balanced coverage of the topic. Each of the authors has been strictly limited in the lengths of both the manuscript (1,200 words) and the rebuttal (400). The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.

### POINT: CARDIOVASCULAR VARIABILITY IS AN INDEX OF AUTONOMIC CONTROL OF CIRCULATION

Blood pressure (BP) and heart rate (HR) continuously fluctuate over time (18), under the influence of control mechanisms aimed at maintaining cardiovascular homeostasis. This term, from the Greek *homeo* (similar) and *stasis* (steady), indicates a condition that dynamically aims at achieving stability, without entirely reaching it. Indeed, daily life BP fluctuations are generated by external perturbations and by neural control mechanisms opposing their effects in the attempt to bring BP back toward a reference “set point” (24). As a result of these complex interactions, cardiovascular (CV) variability (V), rather than being “undesirable noise,” reflects the activity of cardiovascular control mechanisms, representing a rich source of information on their performance in health and disease. The methods used to analyze this phenomenon include several approaches, respectively aimed at estimating BP or HR variance, their spectral powers (30) and coherence, HR turbulence (3), entropy, self-similarity and symbolic logic (11, 32), or BP-HR interactions to quantify the baroreflex sensitivity on HR (BRS) (15).

Evidence that CVV does represent an index of autonomic control of circulation, comes from three types of studies: 1) animal studies showing univocal changes in BPV or HRV after blockade, amplification or selective interference with autonomic cardiovascular regulation; 2) human studies in which manipulation of autonomic cardiovascular control through drug administration or laboratory stimulations induced consequent changes in BPV or HRV; and 3) studies focusing on changes in BPV and/or HRV in patients affected by diseases where the autonomic nervous system was primarily or indirectly affected. The former include pure autonomic failure or spinal lesions, whereas examples of the latter are diabetes

mellitus, congestive heart failure, acute myocardial infarction, obstructive sleep apnea, and arterial hypertension.

The link between autonomic function and CVV can be better appreciated by separately focusing on HRV and BPV, as well as on their mutual interaction as a means to quantify BRS (22, 24).

*HR variability.* Vagal and sympathetic cardiac controls operate on HR in different frequency bands. Electrical stimulation of the vagus nerve and left stellate ganglion in dogs showed that vagal regulation has a relatively high cut-off frequency, modulating HR up to 1.0 Hz, whereas sympathetic cardiac control operates only below 0.15 Hz (4, 24, 29). In dogs and humans, parasympathetic blockade by atropine eliminates most HR fluctuations >0.15 Hz [high frequency (HF)], whereas only partly reducing those <0.15 Hz; conversely, cardiac sympathetic blockade with propranolol reduced HR fluctuations below 0.15 Hz only, leaving those at HF largely unaffected (4, 29). After combined sympathetic and parasympathetic blockade, and after cardiac transplantation, a small HF HRV persists, probably due to mechanical modulation of sinus node by respiration (5).

Low frequency (LF; 0.04–0.14 Hz) fluctuations in HR are affected by electrical stimulation of both vagal and sympathetic cardiac nerves in animals (4). Similarly, in humans, LF powers are reduced by either parasympathetic or sympathetic blockade (29); moreover, they increase with sympathetic activation achieved by lowering BP (31). Also, fluctuations <0.04 Hz [very low frequency (VLF)] are reduced by autonomic blockade, but they may also depend on other factors such as slow respiration and hemodynamic instability (24). Thus HRV at HF is a satisfactory, although partly incomplete, measure of vagal cardiac control, whereas LF components reflect both sympathetic and parasympathetic modulation, without excluding a role of humoral factors, gender and age. The occurrence of resonance in the baroreflex loop can also play a role (13). Normalization of LF powers by total variance, or computation of the LF/HF power ratio, helps increasing the reliability of spectral parameters in reflecting sympathetic cardiac modulation (30), particularly when cardiac sympathetic drive is activated (4, 24, 29). The clinical relevance of these findings is related to the well-established link between autonomic cardiac control and cardiovascular mortality, including sudden cardiac death, with HRV being a key marker of such a relationship (10). In fact, reduced HRV is associated with increased mortality after myocardial infarction (12, 14) and increased risk of sudden arrhythmic death (10). This association is paralleled by BRS reduction and by signs of increased sympathetic cardiovascular drive. Recently, changes in HRV have been shown to identify favorable changes in cardiac autonomic control after cardiac resynchronization therapy in patients with severely symptomatic heart failure (1). These observations strongly suggest that HRV, in addition to representing a research tool, should become a more widely employed clinical parameter.

*BPV.* BPV increases in conditions characterized by sympathetic activation. Indeed, increased daytime BPV in humans is associated with an increase in sympathetic efferent traffic in the

peroneal nerve (20). When considering BP spectral powers, HF fluctuations depend on the mechanical effects of respiration, being largely unmodified in patients with denervated donor hearts (5). Conversely LF and VLF powers are predominantly caused by fluctuations in the vasomotor tone and systemic vascular resistance and are influenced by neural, humoral, and endothelial factors and by thermoregulation (24). LF powers increase or decrease with stimuli or conditions that, respectively, increase or decrease sympathetic cardiovascular influences, such as head-up tilt or mental stress in the former case, sleep or  $\alpha$ -adrenergic blockade in the latter case (17, 24). The specificity of BP LF powers in reflecting sympathetic activation is limited; however (24), because these components are also affected by resonance in the baroreflex loop (13). These observations, on one side, suggest caution in regarding LF powers as specific markers of sympathetic cardiovascular drive, but, on the other side, further emphasize their dependence on autonomic cardiovascular modulation.

**BRS.** The ability of CVV to reflect autonomic cardiovascular control is improved by use of multivariate models for its assessment. The simplest ones consider the relationship between spontaneous fluctuations in BP and HR, either in the time (sequence technique) (6, 23) or frequency domain ( $\alpha$ -coefficient, transfer function analysis) to assess BRS (21, 27). This is done at BP levels where the baroreflex usually works in real life, with no need of external interventions either on the baroreceptor areas or on the cardiovascular parameters under evaluation, as with conventional laboratory maneuvers (22). The methods assessing “spontaneous” BRS are used also to investigate the BRS dynamics, which reflect changes of baroreflex control associated to modulations of autonomic activity during daily life, or to the occurrence of autonomic impairments (Fig. 1). A number of papers support the pathophysiological and clinical relevance of spontaneous BRS estimates. Their ability to explore the baroreflex function was demonstrated by animal studies where surgical denervation of arterial baroreceptors was followed by disappearance of significant links between BP and HR fluctuations in the above models (6, 19). It was also demonstrated in humans by relating spontaneous BRS estimates with those measured by injection of vasoactive drugs (7, 25, 26). Although quantitatively different, as expected, BRS estimates provided by spontaneous CVV and by laboratory methods displayed high correlation in most instances, confirming their ability to provide complementary information on baroreflex HR modulation (22). The clinical relevance of spontaneous BRS analysis is shown by its ability to detect early impairment of autonomic function (9) and to provide information of prognostic value, as in patients after stroke (28) or myocardial infarction (14), or in the diagnosis of brain death (8).

In conclusion, available data unequivocally indicate that CVV analysis provides important information on the autonomic control of circulation, in normal and diseased conditions. The importance of this approach is related to its ability to offer information on cardiovascular regulation in daily life (16) and without using stimulations which may interfere with the measured parameters. Progress offered by multivariate models has allowed for the evaluation of the interactions between BP, HR, and other biological signals, further approaching the physiological complexity of cardiovascular regulation. Demonstration of the prognostic value of these methods calls for

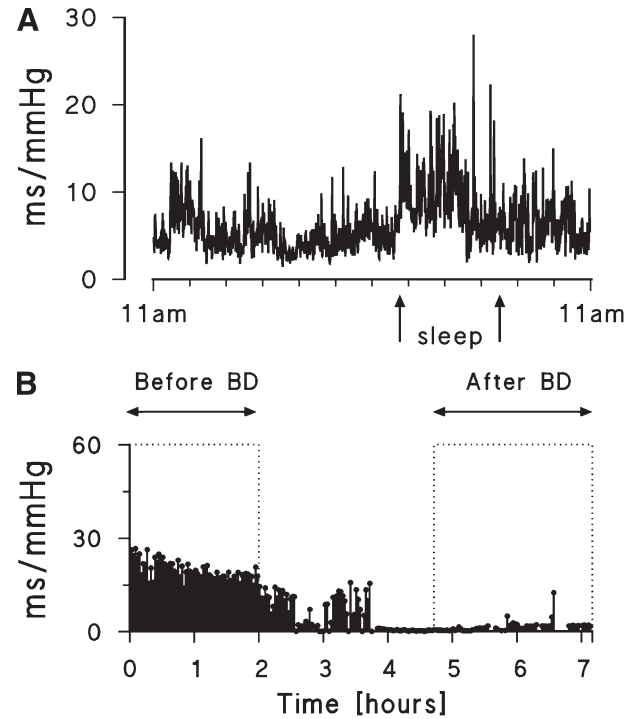


Fig. 1. Dynamic assessment of spontaneous baroreflex sensitivity (BRS). *A* (sequence technique): data obtained during 24 h in a healthy subject; *B* [redrawn from (8), spectral approach]: data obtained in a patient before and after the time of brain death (BD).

their larger use not only in research but also in a clinical setting.

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#### COUNTERPOINT: CARDIOVASCULAR VARIABILITY IS NOT AN INDEX OF AUTONOMIC CONTROL OF THE CIRCULATION

Cardiovascular variabilities were first observed over 250 years ago (11) and first associated with physiological control 140 years ago (15). However, it is only in the past 20 years, with the advent of readily accessible and unparalleled computing power, that their apparent utility has come to be appreciated. Heart rate variability measurements were introduced into clinical practice in 1965 by obstetricians who found decreased variability indicated fetal stress and compromised viability (12). Since then, the availability of high-resolution, digitized ECG recordings and computers capable of easily and quickly solving complicated mathematical equations greatly expanded this area of inquiry. The ostensible clinical relevance of heart rate variability led to development of standards for quantitative measurement for both clinical application and physiological research (28). By 2005, an average of 10 scientific articles on heart rate variability were published each week (see Fig. 2) and cardiovascular variabilities had achieved amazingly wide application as indexes of autonomic outflow from dinosaurs (1) to dinghy sailors (26), from sex (5) to religion (4).

Work in the area of cardiovascular variabilities has been termed “a new field of impetuous research” (17). Indeed, a range of indexes have been derived from fluctuations not just in heart period, but also in blood pressure (20), sympathetic nerve activity (21), and blood flows (27). Parallel oscillations in cardiovascular parameters have been used to create “spontaneous” baroreflex sensitivity (23) or cerebral “autoregulation” (22). Beat-by-beat vascular resistances (i.e., pressure/flow) have been derived and cross-correlated with the numerator in an attempt to probe vascular control (19). Quantitative approaches have included not only time- and frequency-domain statistics (28), but have also ranged across the spectrum of nonlinear models (24). However, greatest physiological

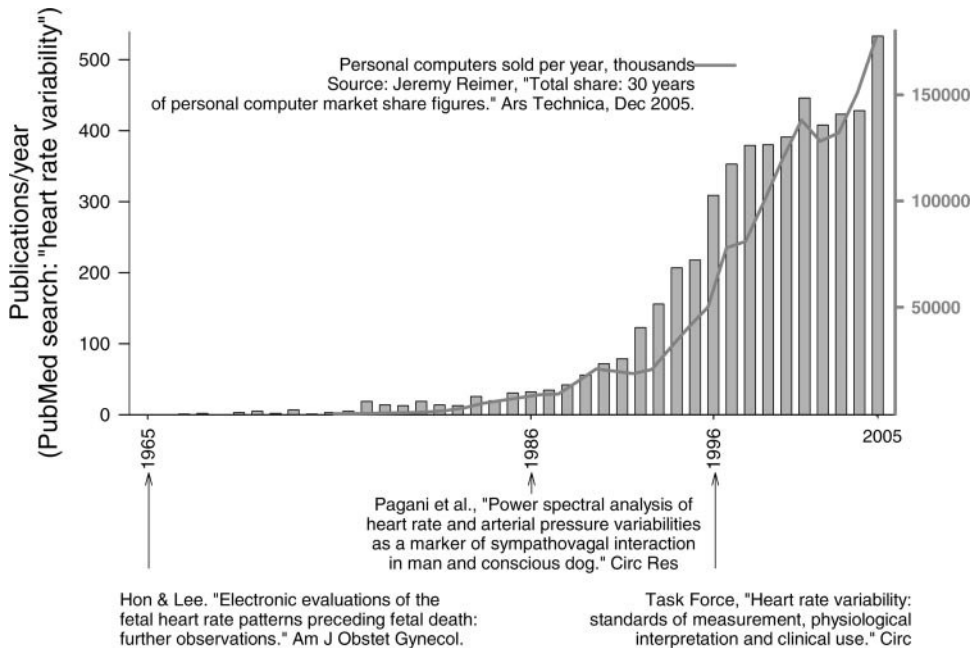


Fig. 2. Publications per year on heart rate variability.

significance has been ascribed to the two primary short-term oscillations in humans—those occurring at respiratory frequencies (sometimes termed the high-frequency component) and those occurring at a slower, approximate 10-s cycle (sometimes termed the low-frequency component). These cardiovascular variabilities have been used most often to index autonomic circulatory control (28).

The consensus of most large-scale studies is that heart rate variability has prognostic value, with reduced variance relating to increased cardiovascular morbidity and mortality (13). However, this prognostic capacity has led beyond the simple interpretation of variabilities as interesting and complex physiological (epi)phenomena worthy of study, to accepted status as true quantitative measures of autonomic outflows. The best example of this may be respiratory sinus arrhythmia. This variability is a key prognostic indicator of cardiac health and is thought by many to quantify tonic cardiac vagal activity (18). However, despite the fact that vagal outflow is the dominant contributor to heart rate variability, the assumption that a particular variability is always purely vagal is challenged by several observations. Heart rate variability across a wide range of frequencies is increased by cardioselective  $\beta$ -blockade, indicating an important modulatory role for cardiac sympathetic activity (29). In some conditions, significant respiratory sinus arrhythmia can be generated by non-neural mechanisms (6). In addition, stimuli aimed to increase vagal tone, such as direct vagus nerve stimulation in animals (3) and administration of vasoconstrictors in humans (10), do not produce changes in variability that linearly reflect the vagally mediated chronotropic response. Thus simple interpretation of respiratory sinus arrhythmia amplitude can lead to spurious conclusions about levels of cardiac vagal tone.

Various efforts have been made to disentangle the complex interactions that underlie heart rate variabilities. One popular approach is to normalize both the high- and low-frequency oscillations to total variability and/or to use a ratio of these two oscillations (i.e., LF/HF) (20). The underlying presumption is

that a reciprocal "sympathovagal balance" is critical to cardiac autonomic control and can only be deciphered via these calculations. Support derives, in part, from the finding that normalized variability and the ratio between variabilities correlate best with tilt angle during orthostatic testing in humans (17). However, the presumed balance between parasympathetic and sympathetic outflows cannot apply to all conditions; for example, only cardiac parasympathetic withdrawal occurs at low exercise intensities, whereas both parasympathetic withdrawal and sympathetic activation occur at moderate and higher intensities in humans (8). Moreover, transforming variables to better correspond to an anticipated physiological response does not create a more valid measure and, in the case cited, the argument for transformation relies on a weak analogy. Upright tilt does increase sympathetic and decrease parasympathetic outflows; it may then follow that "sympathovagal balance" changes as some function of tilt angle. However, it does not follow that the best linear correlate to tilt angle is the best index of sympathovagal balance. By this reasoning, if one simply knows the angle of tilt, there is no need to assess heart rate variability! Although this may be ridiculous on its face, it is, in fact not the case that autonomic adjustments linearly increase with increasing tilt angle; they are progressively greater up to 60 degrees of tilt, after which they approach an asymptote (14).

There is one other important consideration for normalizing variability data. Normalizing the oscillations to each other can uncouple their amplitudes from the physiology. For example, full cholinergic blockade results in almost complete elimination of any beat-by-beat changes in heart period. However, normalized units of variability can indicate that significant oscillations remain despite a nearly monotonic heart rate (16). Thus transforming the amplitude of these oscillations can divorce them from their physiological (in)significance.

The above issues also apply to the use of variabilities in other parameters. For example, slow blood pressure waves relate best to slow oscillations in sympathetic activity when both are normalized (21). However, absolute values do not

relate to one another well: young females and older males have striking differences in low-frequency blood pressure wave amplitude, yet similar low-frequency sympathetic oscillations (29). Nonetheless, many still retain the concept that low-frequency pressure variability accurately reflects sympathetic outflow to the vasculature. In fact, the tendency to exploit normalized units of cardiovascular oscillations to represent autonomic outflows can lead to illogical conclusions. For example, correlations have been used to imply that a given autonomic activity can be quantified from a particular oscillation in any cardiovascular variability. This has led to the unique assertion that a central parasympathetic effect may only be revealed if one measures the pattern of activity in a sympathetic nerve (16).

The correlative parallel patterns in cardiovascular oscillations may provide better insight to autonomic regulation. A currently popular approach is to use beat-by-beat changes in pressure and heart period to produce spontaneous baroreflex indexes (23). Animal data do suggest an important baroreflex role in linking these variabilities (9), but do not resolve the extent to which they reflect baroreflex gain. Human data suggest a correlation between spontaneous indexes and pharmacologically derived baroreflex gain, but also indicate poor correspondence between them (25). This may be due to the fact that short-term fluctuations in heart period are not intimately and always linked to those in pressure via the baroreflex. These spontaneous indexes are more likely simple analogues of heart rate variability. If blood pressure oscillations are not statistically different across heterogeneous groups of subjects, differences in spontaneous indexes depend primarily on differences in heart rate oscillations. From this, it has been concluded that the spontaneous baroreflex can be measured without recording blood pressure (7)!

In the few words left, even ignoring the analytic shortcomings and lack of validation that contaminates much of the work in this area, cardiovascular variabilities should not be considered quantitative measures of autonomic outflow owing to their complex and largely undiscovered physiology.

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#### REBUTTAL FROM DRS. PARATI, DI RIENZO, CASTIGLIONI, AND MANCIA

Taylor and Studinger raise a number of points that should be critically considered. First, the high number of papers published on cardiovascular variability (CVV) reflect persistent interest toward the physiological, pathophysiological, and clinical relevance of CVV phenomena (4, 6), rather than occasional attention toward a fashionable issue. Second, we agree that indexes of CVV should not be invariably taken as “quantitative measures of autonomic outflow,” because they do quantitatively reflect the dynamic features of autonomic CV modulation, rather than mean autonomic tone (3, 4, 7). Although the contribution to CVV modulation by sympathetic, parasympathetic, and respiratory influences can be identified by CVV changes in specific frequency bands, autonomic influences affect CVV through a wide range of frequencies, and more comprehensive information from CVV analysis can be obtained by methods providing a broad-band spectrum of cardiovascular fluctuations, including 1/f modeling (2, 7, 9). Finally, the reliability of methods for spontaneous baroreflex sensitivity (BRS) assessment is supported by experimental studies (1, 5), showing that surgical denervation of baroreceptor areas leads to disappearance of baroreflex-mediated coupling between blood pressure (BP) and heart rate (HR). It should be emphasized that spontaneous and laboratory-derived BRS indexes are closely related to each other (8), despite being characterized by somewhat different absolute values, and both quantify the slope of the R-R interval response to progressive BP changes, either spontaneous or pharmacologically induced. While laboratory estimates explore baroreflex cardiac modulation over a wide range of stimulus intensities, from threshold to saturation, spontaneous methods focus on reflex HR changes in response to smaller spontaneous BP fluctuations around the baroreflex “set point.” Both spontaneous and laboratory BRS indexes correlate negatively with BPV and positively with HRV. Thus these methods provide complementary information on BRS from a different perspective, and quantitative differences between their indexes should not be surprising. Overall, the “technical” points of criticism raised by Taylor and Studinger against the value of CVV analysis appear to be of questionable importance vis-à-vis the strong evidence, fairly acknowledged also by them, that this approach explores “interesting and complex physiological (epi)phenomena”, and has “prognostic capability.” Although sharing with laboratory methods the inability of being a perfect tool, CVV analysis is a useful noninvasive means to explore the dynamic features of neural cardiovascular regulation and its clinical relevance. It should therefore be more frequently considered in daily practice, too.

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#### REBUTTAL FROM DRS. TAYLOR AND STUDINGER

We should first assure the reader (and those on the opposite side of this debate) that we recognize the overextrapolations in our argument. Personal computers and heart rate variability are not necessarily comparable. Parasympathetic and sympathetic outflows can be related. Indeed, critical to this polemic is recognition of and avoidance of overextrapolations.

To this point, quantitation of any variability via whatever technique does not represent an analysis of the complex interactions underlying the variability, but merely a measurement of the resulting phenomenon. Therefore, we agree with our colleagues that observations of blood pressure “LF powers as specific markers of sympathetic cardiovascular drive” suggest caution. Although we too believe that they may have a “dependence on autonomic cardiovascular modulation,” this does not make them an adequate index of autonomic outflow. Both this dependence and this inadequacy applies to all cardiovascular variabilities.

Ratios (e.g., LF/HF) are a mathematical construct, not measured variables in physiological research. Ability to predict clinical outcomes may not relate to utility as a cardiovascular measure. Correlation between a proposed measure and an established one does not mean the two are equivalent, or even complimentary. What one may think works in “real life” is not necessarily borne out as true over time.

The value of cardiovascular variabilities lies not in their purported ability to measure autonomic control, but in their complex derivation from this control. Rather than exploiting the observation that these variabilities have autonomic components to justify them as measures, we should study them to better understand integrated control of the cardiovascular system. For example, probing the determinants for the synchrony

between heart rate and respiratory rhythm suggests that respiratory sinus arrhythmia has an intrinsic physiological role to optimize gas exchange, and further suggests that possible dissociation from vagal outflow reflects differential modulation from respiratory and vagal sources (1).

Our argument focuses on variabilities as measures of autonomic outflow. Most evidence put forth by our colleagues focuses on variabilities as signifying autonomic outflow. Unambiguous disappearance of variability with blockade or denervation does suggest they rely on autonomic cardiovascular regulation, but does not support them as quantitative measures

of that regulation. Despite the assertions of our colleagues, most data do not support correspondence of any cardiovascular variability at any frequency to any specific physiological controller or autonomic outflow at all times. This precludes their utility as clinical tools for tailoring therapy or as measurement tools for physiological studies.

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