

## Heart Rate Variability: A Neuroscientific Perspective for Further Studies

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Heart rate variability (HRV) has proven to be a useful tool for studies of autonomic control and its central integration. Technical and analytical developments continue to advance the available methods for extracting accurate estimates of the components of heart rate variability, and two international committees of scientists have now recognized the potential utility of these measures for both research and clinical applications [1,2]. Additional research is necessary, however, to more fully elucidate the mechanisms of HRV and to refine approaches to the interpretation of these measures.

### Neuroscientific Background

As noted by Malliani, Montano and Pagani [3] in the previous (1997) issue on Noninvasive Cardiac Electrophysiology, neural regulation of the heart entails a complex interplay of central integrating mechanisms and peripheral feedback loops. The dynamic interactions of these processes result in rhythmical fluctuations in heart rate within several frequency bands. The high frequency (HF) band (~0.15–0.4 Hz in adults), associated with respiratory sinus arrhythmia (RSA), is considered to reflect vagal modulation of the heart, as sympathetic sinoatrial synapses and their intracellular signaling pathways effectively filter out periodic fluctuations beyond about 0.15 Hz [1–5]. At lower frequencies, however, sympathetic as well as vagal rhythms can translate into periodic fluctuations in heart rate. Consequently, lower frequency rhythms in heart rate in the low frequency (LF) range (~0.05–0.15 Hz; also referred to as the 0.1 Hz rhythm) or the very low frequency range (~0.003–0.05 Hz) can reflect the joint action of both sympathetic and parasympathetic neural influences.

Although HF rhythms in heart rate can reasonably be interpreted to reflect fluctuations in vagal cardiac control, there remain important caveats in interpretation. These fluctuations arise from the inspiratory-related inhibition of vagal outflow, and thus would be expected to correlate with the overall level of vagal control. But vagal inhibition may not be complete with typical inspiratory volumes, so the magnitude of vagal fluctuations and associated HRV is also a function of tidal volume [6]. Moreover, higher frequency respiratory fluctuations in vagal control are not as effectively

transferred to variations in heart rate as are lower frequency respiratory rhythms [7]. Finally, respiratory frequencies can sometimes fall below the typical 0.15 Hz band pass for HF variability, and thus appear in lower frequency bands. These considerations indicate the need for greater attention to respiratory parameters in interpreting HF variability [2].

Interpretation of HRV at lower frequencies is even more problematic. Although measures of LF variability are sometimes considered an index of sympathetic control, both sympathetic and parasympathetic branches can contribute to these rhythms. In fact, vagal blockade with atropine can dramatically reduce LF variability [8]. A proposed interpretive approach is based on the fact that the two autonomic branches are often reciprocally controlled, with increases in the activity of one branch associated with decreases in the other [3]. To the extent to which a reciprocal relationship holds among the autonomic branches, it is argued that the problem of specifying the state of autonomic control may be reducible to a bipolar dimension of sympathovagal balance, an index of which (LF/HF ratio) may be derivable from HRV measures [3,9]. An example of reciprocal regulation can be found in basic brainstem reflexes such as baroreceptor heart rate reflex, although this is not an invariant pattern. Hypoxia [10,11] or atrial stretch [12,13], for example, can yield a reflex coactivation of both autonomic branches. This raises an important issue for measures of sympathovagal balance.

Although there are important feedback influences on HRV, the crucial role of central integrative mechanisms is increasingly recognized, and these mechanisms are not limited to the brainstem [14,15]. In fact, basic cardiovascular reflex substrates can be modulated or even bypassed by rostral neural systems. These systems include the hypothalamus, the amygdala and the medial prefrontal cortex, which have been

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shown to issue monosynaptic projections to brainstem reflex networks as well as autonomic source nuclei [16]. Rostral systems appear to be more flexible in the pattern of autonomic control that they exercise, and can yield reciprocal, independent, or coactive changes in the activities of the autonomic branches [17,18].

Even in cases where rostral influences foster a general reciprocal mode of autonomic control, there appears to be an important difference from the pattern of reciprocal control exerted by baroreceptor reflexes. Selective pharmacological blockades revealed that an orthostatic challenge and standard psychological stressors (e.g., mental arithmetic, reaction time task) yield a similar pattern of reciprocal sympathetic activation and vagal withdrawal in human subjects, when considered at the group level [19]. The response to orthostatic stress displayed minimal individual variation, so the reciprocal changes in the autonomic branches were highly correlated across subjects. In contrast, psychological stressors, typical of those encountered in daily life, yielded wide individual differences in the mode of response, with some subjects consistently showing predominantly sympathetic activation, others primarily vagal withdrawal, and still others a reciprocal pattern of autonomic response [19].

These neurobehavioral influences highlight the need for a more comprehensive and realistic framework for models of central autonomic control. The neurobiological perspective also focuses on a relatively neglected source of variance in autonomic regulation, related to the feedback consequences of autonomic state on the operations of rostral neural systems [16,20]. Peripheral feedback loops in basic autonomic reflexes are central concepts in cardiovascular physiology, but the role of ascending visceral afference in the functions of higher neural control systems has received less attention. In fact, there are relatively direct ascending pathways, such as the noradrenergic projection from the locus coeruleus and the corticopetal cholinergic projection of the basal forebrain, whereby activities in autonomic source nuclei and brainstem reflex networks can modulate higher neural processes [16,20]. These relationships have important implications for future studies.

## **Directions for Further Studies**

### **1. Improved methods for quantification of HRV components**

There are many analytical challenges in decomposing HRV into functional components that relate meaningfully to basic physiological mechanisms and processes [1,2]. Nonstationarities in RR-interval series, the presence of arrhythmias in clinical populations, and even the accurate measurement of cardiac events pose methodological problems for HRV studies. These issues are important for future studies, but will not be further dealt with here, as they are considered else-

where in this volume. At least as important, however, are empirical and conceptual developments in our understanding of the mechanisms of HRV.

### **2. Origins and mechanisms of autonomic control**

Although much is known of the multiple mechanisms contributing to HRV, the relative contributions of central and peripheral processes has not been fully settled [2,15,24]. Adding complexity to this issue is the fact that central cardiovascular control systems extend beyond the brainstem to the highest level of the neuraxis. Whereas the construct of sympathovagal balance may have applicability in limited contexts, it is less meaningful in situations where nonreciprocal patterns of control manifest [17,18,21]. The latter mandate more comprehensive model of autonomic control, and strategically derived measures that tap critical features of the broader cardiovascular control system. This does not imply that the construct of sympathovagal balance is meaningless—only that it is incomplete. In this regard, two important directions for future research are a) the delineation of conditions under which reciprocal and other patterns of autonomic control manifest, as well as the functional bases of these patterns of control, and b) the further development of measures that reflect more closely the broader underlying neurophysiology of cardiovascular control [21,22].

### **3. Validation of HRV indices as markers of physiological processes**

It is important to progressively advance HRV measures from the status of outcomes of a state or process to markers of that state or process [23]. Both outcome measures and markers capture the predictive relation from a physiological state to an experimental measure, but a marker also permits inferences concerning the physiological state from the experimental index, whereas outcome measures do not. The mere fact that a physiological state may be reflected in an experimental measure is not sufficient to infer the presence of that physiological state from the measured index. At this point, RSA may be considered a marker of vagal control of the heart, because if variables such as age, respiratory rate and depth, and other known determinants are taken into account, a change in RSA can be used to index changes in vagal control [1,2]. Although the LF/HF measure of sympathovagal balance may vary in the expected direction with reciprocal changes in activities of the autonomic branches during orthostatic challenges [3], a change in this index in other contexts does not necessarily imply a reciprocal change in autonomic control [2,21].

Outcome measures may be useful under some conditions, but the ultimate utility of experimental measures relates to their validity as markers of physiological states, a status that has not yet been established for indices of sympathovagal balance [2,21,24,25]. One ap-

proach to this issue is to identify more thoroughly the contextual determinants of patterns of HRV, as what might otherwise be an outcome measure could assume the status of a marker within a clearly defined set of conditions. Another approach is to more fully elucidate the physiological mechanisms that underlie these relations, including the influences of rostral neurobehavioral systems, which would permit a more critical evaluation and selection of relevant measures.

#### 4. Clinical applications

Patterns of heart rate variability have proven effective in risk stratification in premature infants, after myocardial infarction, and in other cardiovascular dysfunctions, and may have utility for diagnosis as well as elucidation of the basic pathophysiology of a range of disorders [1,2,26,27]. Moreover, because psychosocial factors can impact on autonomic control [26,28], HRV measures may offer the basis for clinical interventions [29]. Because clinical issues are considered elsewhere in this volume, we limit our attention to two perspectives for future studies. One important focus for further research concerns the specific cellular events and processes that mediate the links between patterns of autonomic control, HRV, and clinical outcomes. Another entails a broader perspective. Although the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system have been viewed as distinct functional domains, this view is no longer viable. It is now recognized, for example, that (a) the autonomic nervous system innervates immune tissues, (b) neuroendocrine hormones and immune-tissue cytokines impact on the central nervous system and autonomic functions, and (c) that central corticotropin-releasing-hormone systems exert important regulatory influences over a wide spectrum of behavioral, autonomic, neuroendocrine, and immune processes [30,31,32]. In view of these considerations, autonomic control can not be divorced from the broader range of physiological systems with which it is integrally linked. Patterns of autonomic control are both modulated by rostral neural systems and in turn impact on higher levels of the neuraxis [16], and these relations may have substantial health implications. For example, research in psychoneuroimmunology reveals that exaggerated heart rate reactivity to laboratory stressors can predict immune reactions, including the immune response to an influenza vaccine [33]. But recent research reveals that it is the sympathetic component of heart rate response, rather than heart rate reactivity *per se*, that underlies this predictive relationship [33]. Moreover, peripheral immune responses have been shown to impact importantly on central autonomic regulation (in part via a vagal afferent pathway) [32]. The complexity of the bidirectional influences between central systems and peripheral functional states may seem daunting, but the broader health implications of

autonomic control and HRV may require attention to this complex interplay.

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