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Is Heart Rate Variability the Spice of Life?

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It has been said that "variety is the spice of life." Most often, this is taken to mean that variability of extrinsic experiences enhances life. In this issue of *Pediatric Critical Care Medicine*, Dr. Badke and colleagues present data to further support the notion that *intrinsic* physiologic variability is also an important part of life (1). Using data from two observational cohorts of critically ill children from a single institution, the authors demonstrated that lower median age-normalized heart rate variability in the 12-hour period prior to biomarker collection was associated with higher levels of the pro-inflammatory cytokines interleukin (IL)-6, IL-8, and C-reactive protein (CRP). Although there was not an association with the earlier, more hyperacute cytokines IL-1β or tumor necrosis factor (TNF)-α, the correlation of heart rate variability with IL-6 persisted after adjusting for illness severity using PRISM-III and the correlation with CRP persisted after adjusting for both PRISM-III and age.

Heart rate variability is the fluctuation in time intervals between adjacent heartbeats. For this study, heart rate variability was measured using an integer calculation (termed HRVi) computed as the standard deviation of the heart rate sampled every 1 second over five consecutive minutes from the beside monitor rather than more complex time-domain, frequency-domain, or non-linear measures that are ascertained from electrocardiogram waveforms (2, 3). A strength of this study is that, because HRVi only requires routine measurements of heart rate, it provides a practical and readily available estimate of heart rate variability without the need for sophisticated waveform data capture and analysis. However, this simplicity may be a double-edged sword, as it also has the potential to miss subtle, but potentially informative physiologic signals more readily ascertained from the electrocardiogram. Thus, specific study of the clinical utility of HRVi is important. The

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finding that low HRVi is associated with increased systemic inflammation is an important step towards better understanding how this physiologic marker may inform risk prediction and clinical care.

To fully appreciate the clinical applicability of HRVi, it is necessary to understand the physiology and pathophysiology that drives normal and perturbed heart rate variability, respectively. In general, heart rate reflects the balance between sympathetic and parasympathetic autonomic nervous system (ANS) activity (3). The sympathetic ANS enervates the entire myocardium, while the parasympathetic ANS largely drives the sinus node, atrial myocytes, and atrial atrioventricular node (4). Natural oscillations of the heart, leading to observed (though subtle) beat-to-beat variability in heart rate, reflect the ever-changing myriad of inputs to the ANS from baroreceptors, chemoreceptors, atrial receptors, and ventricular receptors, along with feedback from the respiratory, vascular, renin-angiotensin-aldosterone, and thermoregulatory systems (5). Healthy physiological systems exhibit marked signal variability and complexity that tends to produce higher heart rate variability. In contrast, severe illness can disrupt this homeostatic sympathetic-parasympathetic balance to decrease physiologic complexity and mute the usual variability across organ systems (6). The importance of such altered signaling is exemplified by a rather consistent finding that lower heart rate variability is associated with decreased survival in a number of severe illnesses, including sepsis, trauma, diabetes, respiratory failure, heart failure, seizure, and stroke (7). Decreasing heart rate variability has also been seen an important indicator of evolving intrapartum fetal distress for decades (8).

As it is unlikely that heart rate variability in and of itself is a critical component of cardiovascular function or contributes substantially to cardiac output, interest in this measure has largely focused on its role as a biomarker of ANS dysfunction, including increased sympathetic or decreased parasympathetic activity (9). Notably, in inflammatory disorders such as sepsis and trauma, emerging data support that down-regulation of parasympathetic inputs, largely mediated through the vagus nerve, promotes increased release of pro-inflammatory cytokines (10). Such findings have inspired efforts to enhance vagal tone as a novel therapeutic strategy to modulate inflammation, restore immunologic homeostasis, and attenuate organ dysfunction (10, 11). Stimulation of the efferent fibers of the vagus nerve releases acetylcholine in the spleen and other organs which, through the nicotinic acetylcholine receptor (nAChR) family expressed by macrophages and other cytokine-producing cells, inhibits release of proinflammatory cytokines in a process termed “the inflammatory reflex” (10). Moreover, pharmacologic modulation of sympathetic activity that shifts the ANS toward the parasympathetic, such as with dexmedetomidine, has also been shown to tamp down inflammation, increase vascular responsiveness to catecholamines, and potentially enhance patient outcomes (12, 13).

By testing the association of heart rate variability with pro-inflammatory cytokines, Dr. Badke and colleagues have addressed an important question of whether HRVi is a useful biomarker of the downstream effects of ANS dysfunction (i.e., systemic inflammation). Although the relevant biologic phenomenon is ultimately the causal effect of ANS dysfunction on systemic inflammation, neither this cause (ANS dysfunction) nor its effect (inflammation) is currently easily measured at the bedside. Data from this study suggest

that HRVi may provide a practical surrogate measure—one that could be made available to clinicians using routinely monitored patient heart rate data—to discern ongoing or worsening inflammation attributable, at least in part, to ANS dysfunction.

Of course, the clinical utility of HRVi to monitor ANS-driven inflammation requires additional study. As with most biomarkers, the scatterplots from this study suggest that while median differences in HRVi differentiate groups of patients by cytokine concentrations, the wide distribution of HRVi values within groups will present an interpretative challenge when applied to individual patients (14). The authors also only tested a single median HRVi value from a 12-hour period, but it is more likely that HRVi will be most useful as a continuous measure over time in which trends within individuals may be more informative than comparisons between patients (15). Specific testing of the association of longitudinal trends in HRVi with serial changes in inflammation is, therefore, necessary. Moreover, the complexity of the inflammatory profile will require testing HRVi against more than the few targeted cytokines, as was done in this study.

Despite these challenges, evidence that HRVi, as a rather straight-forward indicator of heart rate variability, is associated with common inflammatory biomarkers in children is an important preliminary step towards understanding, monitoring, and (potentially) treating ANS dysfunction as an under-appreciated component of neurologic injury in critically ill patients. It certainly seems that variety (or variability) really is the spice of life—even in illness.

Copyright Form Disclosure:

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