

I'm Glad we can add: Finally Accurate Measurement of Both Components of Heart Rate Variability Can be Applied Routinely Clinically

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One century ago, the critical role of the Autonomic Nervous System (ANS) in health and disease was prophesized. In 1990, Heart Rate Variability (HRV = Sympathetic-tone [S] + Parasympathetic-tone [P]) was 1st used in clinical cardiology. Emphasizing the reduction in HRV was associated with a poor prognosis in all major cardiovascular illness. In 2000, HRV was included in Sudden Cardiac Death (SCD) risk stratification.

There are over 350,000 SCDs/yr. in the USA. High S and critically low P are associated with increased mortality, life-threatening ventricular arrhythmias, congestive heart failure (CHF), and acute coronary syndromes (ACSs). Two common autonomic dysfunctions are Sympathetic Withdrawal (SW, an abnormal alpha-adrenergic response to head-up postural change underlying Orthostatic dysfunction) and Parasympathetic Excess (PE, an abnormal cholinergic response to stress, amplifying the stress response, as in difficult to manage blood pressure (BP), blood glucose, hormone levels, or Anxiety syndromes). Both SW and PE contribute significantly to the worldwide pandemic of uncontrolled Hypertension (HTN). Both result in poor brain perfusion leading to an increase in resting BP as compensatory, an increase in resting BP that is largely resistant to anti-hypertensives. On average, only 35% of Hypertensives are well managed, increasing the mortality risk of 1.5 billion people with HTN [1-9]. And yet, ANS testing is very rarely used in patient management, probably mainly due to difficulty in directly measuring P. All non-invasive ANS measurements only measure total autonomic activity, resulting in assumptions and approximations of the independent contributions of S and P to total HRV. Since $HRV = S + P$, both S and P must be accurately identified.

However, there is one exception. A technologic breakthrough was developed, validated, and verified by the 1st joint Bio-Medical Engineering program group from Massachusetts Institute of Technology and Harvard [10-14], and is now available for user-friendly routine clinical use. It is P&S Monitoring. The breakthrough quantifies the independent contributions of S and P to total HRV through two simultaneous measurements: (1) ECG monitoring which establishes total HRV (Low Frequency area [0.04-0.15 Hz] under the HR time-frequency spectral curve), simultaneously with (2) Impedance Plethysmography which independently quantitates P (a 0.12 Hz-wide window area under the HRV spectral curve centered on the modal peak of the time-frequency Respiratory Activity (RA) spectral curve; HRV due to RA is solely P-dependent). Therefore, $S = HRV - P$; where P is no longer assumed to be the area under the curve between 0.15-0.40 Hz, but now is quantitatively measured as the Respiratory Frequency area. The curves are analyzed using continuous wavelet transforms rather than the frequency-only fast Fourier transforms. The latter, although accurate for stationary signals,

compromises time and frequency resolution due to the fixed length windows used in analysis. The value of routinely using this new technology is illustrated by our following studies.

Hypertension

Comparing ANS-assisted to JNC 8 treatment, 74% of the ANS-assisted patients reached JNC 8 treatment control goals vs. 30.4% of the JNC 8 patients within 9 mo. ($p < 0.001$ for both systolic and diastolic BP) on 2.3 vs. 3 prescription anti-hypertensives. Final S was lower and P higher (both $p < 0.001$) in the ANS-assisted group [9].

Autonomic Balance in CHF

Beta blockers are the cornerstone of CHF pharmacologic therapy. Of concern, 59% of 54 patients had either high (>3) Sympathovagal Balance (SB, a resting measure, = S/P), Cardiovascular Autonomic Neuropathy (CAN, a resting measure, $P < 0.10$ bpm²) or both, despite guideline-mediated treatment. Off-label Ranolazine corrected most of these treatment failures [15]. In another study of 109 patients [16], in addition to improving SB and relieving CAN, Ranolazine (titrated with ANS guided therapy) independently improved left ventricular ejection fraction in 70% of patients; on average 11 units, $p = 0.018$ (vs. no change in the usual treatment group). In this other study, by titrating Ranolazine to normalize SB and thereby helping to relieve CAN, the outcome was to reduce cardiac deaths, acute CHF, and malignant ventricular arrhythmias in the ANS assisted therapy patients as compared with the usual treatment group. Given the critical role of beta blockade in CHF, it seems essential to measure S on therapy and adjust accordingly. Presently, this is never done.

Risk Stratification in Patients at Risk for Cardiovascular Disease or with Established Disease

In 483 patients (127 with risk factors, 224 with coronary disease, 132 with chronic CHF) followed for a mean of 4.92 yrs., SB > 2.5 outperformed myocardial perfusion imaging (MPI) and echocardiography (2DE) ($p = 0.001$) with a sensitivity of 0.59, OR = 7.03 (CI: 4.59-10.78), specificity of 0.83, PPV = 0.64, and NPV = 0.80 for predicting cardiac death, ACS, acute CHF, and malignant ventricular arrhythmias [17]. Since only 31% of the patients had SB > 2.5, perhaps they require MPI and/or 2DE, and the other 69% of stable patients can avoid expensive imaging procedures.

Neurogenic Orthostatic Hypotension (Noh)

Ten to 30% of the elderly experience Orthostatic Hypotension (OH), resulting in profound morbidity and increased mortality. Currently, routine management consists of compression stockings, vasopressors, mineralocorticoids, fluids, and more recently Droxydopa. Low S in response to standing (SW) is a very common cause of NOH, not always addressed by stockings, vasopressors, mineralocorticoids, fluids; and Droxydopa is expensive. In 109 patients with low-S Orthostatic Intolerance, the OTC antioxidant (r-) Alpha Lipoic Acid (ALA) had a 66% response rate via increasing S and avoiding the inconvenience, expense, and side effects of current therapies, such as supine/sitting HTN, [18].

Conclusion

In the 2nd century AD, Wang Shu Ho stated, “If the heart beat gets as regular as the knocking of the woodpecker or the dripping of the rain on the roof, the patient will die within 4 days”. And yet, analysis of HRV remains unused. What a shame; science has made it easy: with P&S Monitoring, now HRV DOES = S + P.

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