

# Rebuttal

by

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The link of heart rate variability (HRV) to autonomic nervous system (ANS) encompasses different facets. When this Journal invited the present proponent-opponent debate, both sides agreed to discuss the usefulness of HRV in the assessment of ANS responsiveness rather than in the assessment of ANS tone. The difference is obvious to all even marginally involved in ANS studies. While assessing ANS tone means estimating the sympatho/vagal nerve traffic, the assessment of ANS responsiveness means estimating ANS responses to provocations. (The difference is as the difference between measuring the height of water waves due to wind and measuring the depths of a lake.)

Since the Journal confirmed that our opponents agreed to address ANS responsiveness and not the ANS tone, we read the contribution by Boyett et al (2019) with some bewilderment. Apart from the title, they do not mention responsiveness at all and write solely about ANS tone assessment. Is this because they agree with us and, similar to ourselves, cannot find any arguments against the use of HRV in the estimates of ANS reactions?

As our position is unopposed by Boyett et al, we should perhaps respond to their comments on HRV and ANS tone. First and foremost, the application of HRV to ANS tone assessment is complex and well beyond the limits of this text. While it would surely be inappropriate to state that HRV measurements always express ANS tone under all circumstances (Malik & Camm, 1993), the claim that HRV relationship to ANS tone is all wrong is equally misplaced. A new detailed review of this aspect is still needed. We only regret that Boyett et al contribute little to the existing conundrum of the links between HRV and ANS tone.

The notion that there is nothing in HRV beyond the underlying heart rate is clearly wrong. Even in the risk stratification studies, already the seminal work showed that compared to the underlying heart rate, HRV carries not only additional but also stronger risk information (Kleiger et al, 1987). This was subsequently repeatedly confirmed (Bauer et al, 2006). The claim that HRV spectral shifts due to autonomic blockades are just caused by heart rate changes lacks any justification.

Most of the text and data presentation by Boyett et al deal with SDNN, a measure of total heartbeat interval variance. For trivial mathematical reasons, SDNN is related to mean heartbeat interval and since heart rate is its reciprocal, a hyperbolic relationship is observed. This all is very well known (Sacha, 2014). More importantly, however, we do not understand how SDNN properties help the discussion on HRV and ANS tone. Can our learned colleagues cite any article in a reasonable physiology/cardiology journal that interpreted SDNN values as those of sympathetic or of vagal tone?

Disappointingly, Boyett et al do not distinguish absolute measurements of low (LF) and high (HF) frequency HRV components from their proportions and/or normalised expressions (Task Force, 1996). In their arguments, they mix both together and appear to have misunderstood the essence of the old discussion on how the spectral proportions relate to ANS tone (Pagani et al, 1997; Eckberg, 1997; Berntson et al, 1997). Although some spurious publications might have wrongly interpreted absolute values of spectral components, more serious debates have been about the relative values.

As we previously explained, both ANS limbs differ in their response lags. Under normal circumstances, when the tone is neither saturated nor suppressed, the closed loop mechanisms of ANS control lead to tone modulations with different frequencies of both limbs. Since the extent of the modulations relates (but is not equal) to the tone (in the same way as SDNN relates to heart rate), approximations are possible. The decades old dispute questioned under what circumstances the normalised HRV components express the tone of the ANS limbs and whether the interpretation

is different in different well-defined populations.<sup>†</sup> While general agreement exists on the vagal contribution to the HF modulations, the proportion between the vagal and sympathetic contribution to the LF modulations remains debated. Arguments about extreme situations, e.g. total pharmacology blockade, total physical exhaustion with sympathetic saturation, etc., are irrelevant because under these circumstances, the relationship between modulations and the underlying tone breaks down (Malik & Camm, 1993) in the same way as SDNN is nonsensical during constant pacing.

Importantly, it is not even obvious whether different method for spectral HRV analysis should be interpreted differently. The standard Fourier transformation leads to components defined by strict frequency bands when the total spectral power below 0.4 Hz equals to the sum of very low, low, and high frequency components. Consequently, normalised HF and LF components complement each other since  $nHF=HF/(HF+LF)$  and  $nLF=LF/(HF+LF)$  give  $nLF+nHF=1$ . On the contrary, autoregressive modelling, which depends on the model set-up, may identify additional components thus giving  $nLF+nHF<1$  (Task Force, 1996). Unfortunately, there has not been a systematic study comparing these different HRV analyses under strictly controlled conditions and it is unknown whether and how this technology difference influences detailed physiology interpretations. Whilst these nuances might be significant when talking about ANS tone assessment, they matter little when addressing ANS responsiveness.

The modulation of vagal tone by its responses to respiration also needs to be considered. It is not obvious whether controlled respiration increases sympathetic drive due to mental effort thus making the comparison between different methodologies even more complicated. Note that the possibility of pushing respiration-driven modulations into the LF band by very slow controlled respiration (Malik et al, 2016) is again beside the point.

In conclusion, we regret that Boyett et al did not follow the previously agreed discussion topic. While, as we already stated, overwhelming evidence demonstrates that HRV is a useful technique for the assessment of HRV responsiveness, the complex issue of HRV estimates of autonomic tone has still unanswered gaps and deserves different detailed discussion.

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<sup>†</sup> More than two decades ago, the first author of this text tried to moderate a face to face discussion between Drs Malliani and Eckberg. While both agreed to come to London and to participate, the meeting had to be unfortunately cancelled at the last moment and never took place.

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