CROSSTALK

The Journal of Physiology

Comments on CrossTalk 42: Heart rate variability is/is not a valid measure of cardiac autonomic responsiveness

Dependence of heart rate variability on heart rate: insight from graded head-up tilt in healthy subjects

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Boyett *et al.* (2019) have stated that autonomic markers derived from heart period (HP) changes are fundamentally flawed by their relationship with HP mean. This dependence is indisputable given that, regardless of actual autonomic tone, any fluctuation of autonomic activity acts on the rate of change of membrane potential and this action will produce a greater variability in the time required to reach the threshold potential at longer cycle durations. However, this geometrical relationship does not fully explain the physiological complexity of cardiac control observed at the sinus node. For example, our graded head-up tilt data (from 0° to 90°, step = 15°) from healthy humans (Porta *et al.* 2007, 2011) indicate that the strength of the link between HP mean and tilt angle ($r = -0.68$, $P = 1.77 \times 10^{-15}$) is not fully mirrored by that of HP variance ($r = -0.34$, $P = 4.29 \times 10^{-4}$). More remarkably, the low frequency (LF) power expressed in absolute units (0.04–0.15 Hz) was not correlated with tilt angle at all ($r = 0.01$, $P = 9.03 \times 10^{-1}$), while the high frequency (HF) power expressed in absolute units (0.15–0.5 Hz) was significantly and negatively correlated ($r = -0.53$, $P = 7.15 \times 10^{-9}$). Our data are incompatible with the view articulated in Boyett *et al.* (2019) and suggest that HP variability markers add information that cannot be fully gathered from the HP mean. Conversely, they are in agreement with Malik *et al.* (2019) if one assumes that, in healthy individuals during head-up tilt, sympathetic and vagal modulations follow opposite trends leading to the stability of the LF power and the decrease of the HF power.

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Additional information

Competing interests

None declared.

HRV 'autonomic indexes': interpretations and misinterpretations

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In isolated sinoatrial myocytes, acetylcholine challenge prolonged the cycle length (CL) and increased its variance. Because this occurred without concomitant changes in the variance of any of the cycle components determining CL (diastolic depolarization rate, activation threshold etc.), we concluded that the increase in CL variance could only be accounted for by non-linearity of the 'mathematical' relationship between diastolic depolarization rate (the parameter acetylcholine modulates) and CL (Rocchetti *et al.* 2000). We then tested, by numerical modelling, the relevance of this finding to 'HRV' (actually CL variability) measurements commonly used as 'autonomic indexes'. This led to the conclusion that all 'time domain' HRV indexes and absolute power of spectral components are fraught with mathematical dependence on mean CL and, as such, are inadequate to assess autonomic balance (Zaza & Lombardi, 2001), regardless of whether tonic or in response to perturbations. Notably, we also concluded that, if normalized to total 'power' (or expressed as the LF/HF ratio), 'frequency domain' (spectral) indexes were immune from such a problem (Zaza & Lombardi, 2001). Dominant dependency of 'time-domain' HRV indexes on mean CL was confirmed '*in vivo*' by direct recording of sympathetic neural activity during ivabradine-induced bradycardia (Dias da Silva *et al.* 2015). Thus, I support the view, expressed in this CrossTalk debate by Dr Malik and coworkers, that 'normalized spectral power' and LF/HF may be sound 'autonomic indexes'. This does not apply to 'time-domain' HRV measurements, described as proper 'autonomic indexes' in the 1996 HRV Guidelines (Heart rate variability, 1996), and still widely used as such. Overlooking their dependency on mean CL leads to countless misinterpretations; we would expect Dr Malik and colleagues to point this out.

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Additional information

Competing interests

None declared.

HRV saturation in HCN4 mutation carriers, athletes and patients with anorexia nervosa

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In view of known signalling pathways, it is considered that heart rate variability (HRV) is partly caused by fluctuating levels of cyclic adenosine monophosphate (cAMP) receptor protein. cAMP binds directly to HCN4, which is responsible for the funny current in the heart. Parasympathetic stimulation lowers cAMP, while sympathetic stimulation elevates cAMP (Gordan *et al.* 2015). In athletes and subjects with pharmacologically induced parasympathetic dominance, HRV saturation has been observed (Plews *et al.* 2013). Goldberger showed that the HRV/RR interval relationship is described by a quadratic function. Accordingly, HRV increases with parasympathetic stimulation until it reaches a peak; HRV then decreases, while parasympathetic activity continues to increase. We also observed HRV saturation in patients with anorexia nervosa (AN) (Baumann *et al.* 2019). Goldberger suggested that the underlying mechanism of HRV saturation is a sustained parasympathetic control of the sinus node (Goldberger *et al.* 2001). This theory suggests that increased vagal tone causes bradycardia in athletes and patients with AN. Interestingly, HRV saturation has been reported in bradycardic patients with a HCN4 mutation, which affects cAMP binding (Hategan *et al.* 2017; Baumann *et al.* 2019). The mutation may make HCN4 less sensitive to cAMP, which elevates the threshold potential. Therefore, while speculative, we believe that a sustained parasympathetic control of the sinus node is not the only possible explanation for HRV saturation and the associated bradycardia. One possible theory is as follows. If cAMP insensitivity and low cAMP levels delay and prolong diastolic depolarization drastically, other mechanisms that are less influenced by autonomic tone become dominant to prevent complete sinus arrest (Lakatta *et al.* 2010). This would explain the phenomenon of a low HRV at long RR intervals.

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Additional information

Competing interests

None declared.

Heart rate variability as a measure of cardiac autonomic responsiveness: the beat goes on, and on, and on

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We read with interest the thought-provoking and sometimes cross-purpose CrossTalk pertaining to heart rate variability and cardiac autonomic tone/responsiveness. We have three brief comments. (1) It is important to remember that heart rate is not exclusively under autonomic control. During a variety of physiological perturbations, including exercise, endocrine agents also contribute to chronotropic regulation. Thus, relying exclusively on heart rate derived parameters as an indicator of cardiac autonomic tone/responsiveness can be problematic and the interpretation confounded. (2) We disagree with the assertion presented in the Rebuttal that athletes remain in bradycardia during autonomic blockade. During intravenous administration of the ganglionic blocker trimethaphan, resting heart rate is increased by approximately 15 beats min^{-1} resulting in heart rates in excess of 70 beats min^{-1} (Jones *et al.* 2002; Christou *et al.* 2003). These autonomically independent heart rates are consistent with reviewed responses to administration of atropine, with and without β-adrenergic antagonists (Boyett *et al.* 2013), and also with data cited in the Rebuttal (D'Souza *et al.* 2017). Further, 70+ beats min^{-1} clearly exceeds the standard definition of sinus bradycardia (heart rate <60 beats min^{-1}). (3) In response to the question posed in the Rebuttal, we suggest that heart transplant recipients may represent a unique model of heart rate variability that is independent of autonomic tone/responsiveness and perhaps heart rate, at least during the early stages of recovery prior to re-innervation (Singh *et al.* 2007; Williams *et al.* 2017).

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Additional information

Competing interests

None declared.

Physiology of low-frequency heart rate oscillations

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The prerequisite for using HRV indices to evaluate cardiac autonomic responsiveness is to understand the physiological mechanism of their production. The statement that 'LF modulations reflect a combined vagal and sympathetic control' (Malik *et al.* 2019) is highly disputable, simply because it has been reported that acute β-adrenoceptor blockade has minor, if any, effects on these oscillations (Grasso *et al.* 1997; Taylor *et al.* 1998). One major argument that has been frequently, and still is (Malik *et al.* 2019), put forward to attribute LF oscillations of HR to sympathetic activation is the enhancing effect of active standing or head-up tilt on these oscillations. These observations are fundamentally misinterpreted for the simple reason that, during these manoeuvres, there is a concomitant augmentation of the sympathetically mediated LF oscillations of blood pressure (Mayer waves), which are strongly coherent with those of HR. Direct evidence in sino-aortic baroreceptor denervated rats (Cerutti *et al.* 1994) and indirect evidence in healthy humans (Grasso *et al.* 1997) support the conclusion that LF oscillations of HR are a vagal baroreflex response to underlying Mayer waves. It is thus not surprising that their amplitude increases when Mayer waves are amplified. To evaluate the mean level of activity (tone) or responses to provocative manoeuvres (responsiveness) of the cardiac autonomic nervous system, the gold standard method is to compare resting HR with intrinsic HR. It has been shown in humans (Goldberger, 1999) and in rats (Sayin *et al.* 2016) that HRV indices do not concord with this approach.

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Additional information

Competing interests

None declared.

The effect of frequency and depth of breathing on RR interval spectral power is sometimes mistakenly ignored

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Boyett *et al.* (2019) state that it is not even known whether autonomic nerve activity affects heart rate variability (HRV) and ask if there is any way to separate the effect of heart rate (HR) on HRV from an independent factor on HRV. In a study aimed at characterizing the relationship between breathing with or without tidal volume control, and blood pressure and RR interval variability, Cooke *et al.* (1998) showed that mean RR interval was comparable across a wide range of breathing frequencies (0.05, 0.1, 0.15, 0.20, 0.25 and 0.30 Hz), whereas total RR interval spectral power was highest at a breathing frequency of 0.1 Hz ($P < 0.05$). Brown *et al.* (1993) have also demonstrated this.

In a study comparing short-term cardiovascular regulation in subjects with recent-onset hypertension not taking antihypertensive medication, borderline hypertension, with age-matched normotensives, I and my colleagues found that mean RR interval at rest was comparable in these three groups, whereas heart rate variability during timed deep breathing at six breaths per minute was significantly diminished in the group with recent-onset hypertension (Prakash *et al.* 2005).

The magnitude of sinus arrhythmia observed in denervated hearts is 5- to 25-fold lower compared to that observed in age-matched healthy humans under resting conditions depending on breathing frequency and tidal volume, even though mean RR interval is about 25% lower in heart transplant recipients (Bernardi *et al.* 1989). This suggests that the contribution of mechanoelectric feedback, humoral factors, local reflexes mediated by the intrinsic cardiac nervous system, and or intrinsic sinus node cycle length variability to the observed sinus arrhythmia is much smaller compared to that due to the SA node's integration of phasic modulation of vagal and sympathetic outflows to the heart, as reviewed by Malik *et al* (2019).

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Additional information

Competing interests

None declared.

HRV gives information about the variability around the mean heart rate

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Boyett *et al.* suggest that the autonomic nervous system and the heart rate affect HRV. This is recursive. The single most important physiological factor that determines the instantaneous beat-to-beat heart rate is the autonomic nervous system inputs into the SA node. The mean heart rate over a period of 5 min is determined by the mean sympathetic and parasympathetic tones supplying the SA node. However, within the 5 min, the two autonomic limb inputs will be fluctuating continuously producing beat-to-beat variability in the heart rate. HRV quantifies the variability of the inter-beat intervals around the mean R–R interval (or mean heart rate). A report of 'low' HRV means that the extent of fluctuations of inter-beat intervals around the mean R–R interval is less, due to reduced modulations of the autonomic supply to the SA node, and inferred as a decrease in cardiac autonomic activity. This 'decrease in autonomic nerve activity' does not indicate a decrease in the autonomic tone or nerve traffic. Thus, for example, the mean level of the sympathetic tone may have increased in heart failure patients, raising the mean resting heart rate. If a study reports that amongst heart failure patients, those with greater resting HRV have a better prognosis, we conclude that heart failure patients whose autonomic nervous system was more responsive (more active) have a better outcome. Patel *et al.* did not analyse HRV in heart failure patients, but in a cohort who did not have even sub-clinical heart failure.

Heart rate variability is valid for athletes but not for exercise

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Malik *et al.* reported convincing examples of the usefulness of heart rate variability (HRV) for diagnosing autonomopathies and neuropathies in patients. At the same time, Boyett *et al.* clearly showed that HRV is largely affected by heart rate and that the expected decrease in HF and increase in LF powers during exercise are equivocal and unclear. These two apparently opposite views are, however, complementary for using HRV in the field of exercise physiology. HRV is an effective means for diagnosing overreaching and overtraining in athletes if used in standardized protocols investigating the supine-to-standing changes (so-called 'active tilt test') (Schmitt *et al.* 2015*b*) at wake-up (for minimizing the circadian influence), with frequency-domain analysis (absolute and normalized LF and HF) (Schmitt *et al.* 2015*a*) and the control of respiratory sinus arrhythmia influence (Mirmohamadsadeghi & Vesin, 2016). In this context, repeated HRV recordings give similar heart rates but very different LF–HF patterns, that allow the diagnosis of autonomic disbalance. Contradicting this, HRV *per se* is inaccurate as a surrogate of the 'thresholds' for determining intensity domains during exercise (Buchheit *et al.* 2007) since HRV is largely influenced by the ventilatory and adrenergic responses.

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Additional information

Competing interests

None declared.

Heart rate variability is due to autonomic nervous system variations

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The CrossTalk between Malik's and Boyett's groups reads like that of the two blindfolded men who describe an elephant: they feel the same beast but different parts of it.

Strangely, the phenomenon underlying most HRV is not mentioned, i.e. *blood pressure variability*. Both HF and LF variations are highly correlated to concurrent variations in blood pressure, to such an extent that this may be used to find a running estimate of baroreflex sensitivity (Wesseling *et al.* 2017). This requires activity of the cardiac vagus nerve; in its absence little HRV will be observed, e.g. in heart failure, when sympathetic activity is high and blood pressure very stable.

Malik does not go into the reasons why LF and HF appear: HF coupled to respiration, via mechanical blood pressure variations (Zhang *et al.* 2002) and via coupled vagal outflow from the medulla (Farmer *et al.* 2016); LF comes into existence as an eigenfrequency of the sympathetic control of the vasculature (deBoer *et al.* 1987), LF in HRV is, as it were, 'riding the wave' via the vagal baroreflex. Boyett is treating the ANS influence as if we have to do

with a simple oscillator. In fact, the vagus nerve–sinus node interaction is complicated (Karemaker, 2015). If vagal pulses reach the sinus node in a critical stage, just before the moment of firing, small changes in their number may have dramatic effects and induce large HRV. If the same occurs earlier or later in the cycle, the effects are minimized. Therefore, HRV is not a simple measure of ANS activity, but the two go, certainly, together.

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Additional information

Competing interests

None declared.

Heart rate variability is not merely a surrogate for heart rate

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We agree with all comments raised by Malik and colleagues (Malik *et al.* 2019*a*,*b*) and would like to add some remarks to reinforce the value of heart rate variability (HRV). First, HRV is fundamentally an appraisal of autonomic modulation instead of a measurement of nerve activity (autonomic tone), even though the two concepts are linked. Second, the mathematical/statistical dependence of HRV to the mean level of heart rate (or cardiac interval) is well recognized (Akselrod *et al.* 1985; Sacha, 2014). However, there is evidence that the heart rate cannot be taken as a surrogate for HRV (Stauss, 2014). For instance, the selective blockade of the cardiac autonomic receptors by atenolol or atropine elicits changes of HR in the opposite directions, while the overall HRV variability (SDNN) decreases in both situations (Silva *et al.* 2017*a*). Third, HRV is a general terminology that encompasses a large number of indexes. Many of them are not dependent on the mean level of heart rate, such as the normalized spectral components (LF and HF powers in normalized units) and several non-linear indices (Silva *et al.* 2017*b*). The short-term fractal index, for example, was demonstrated as the most powerful mortality risk predictor in patients after myocardial infarction (Mäkikallio *et al.* 1999; Huikuri *et al.* 2000). In this case, the prognostic cannot be attributed to changes in heart rate, but to dynamical properties of short-term HRV, which certainly are influenced by the autonomic nervous system.

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Additional information

Competing interests

None declared.

Potential divergence between heart rate and heart rate variability

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Boyett and colleagues hypothesized that HRV 'is primarily determined by heart rate and cannot be used in any simple manner to determine cardiac autonomic tone' (Boyett *et al.* 2019). We disagree with this statement because heart rate (HR) and its variability may be disjoined both in physiological and pathophysiological conditions. A −20 mmHg lower body negative pressure increased HR in healthy volunteers despite unchanged HRV (Furlan *et al.* 2001). In patients with Pure Autonomic Failure, a rare neurodegenerative disorder characterized by cardiac pan-dysautonomia, HR was identical to age-matched healthy controls but their HRV was about 10-fold lower (Furlan *et al.* 1995). These findings suggest that HR control may differ from its neurally controlled variability (Furlan & Barbic, 2012).

A question was raised: 'Is there any way to separate the effects of HR on HRV from the effect of an independent factor on HRV?' From our experience the answer is yes. Trained and detrained athletes had identical HR and HRV, but

different HRV autonomic spectral profiles. Trained athletes showed greater LF/HF (Task Force of ESC and NASPE, 1996) than detrained ones (Furlan *et al.* 1993), suggesting maintained cardiac sympathetic over-activity and reduced cardiac vagal modulation, likely reflecting the previous day's training session effects (Furlan *et al.* 1993). In individuals with prodromes before syncope, time-variant spectrum analysis of HRV showed early LF/HF decrease during tilt despite unchanged HR (Furlan *et al.* 1998). Parkinson's disease patients with dysautonomia had lower LF/HF, analogous HR and slightly lower RR interval variance than those without dysautonomia (Barbic *et al.* 2007).

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Additional information

Competing interests

None declared.

Heart rate dynamics: more than a measure of cardiac autonomic responsiveness

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Malik focuses entirely on the frequency spectrum and Boyett on the heart rate. Left unmentioned are heart rate dynamics that need not affect either. For example, abnormal heart rate characteristics of reduced variability and transient decelerations precede the clinical diagnosis of neonatal sepsis to a very great deal larger extent than does heart rate (Griffin & Moorman, 2001; Lake *et al.* 2012). Display of the risk of sepsis based on this analysis saves babies' lives (Moorman *et al.* 2011), the only application that we know of in which heart rate variability analysis has been clinically useful. We understand why it was neglected by the discussants – these are aperiodic and non-stationary phenomena and thus unsuited for Malik's frequency domain analysis, and the large abrupt changes in heart rate exclude them from Boyett's considerations of how the mean heart rate is related to its standard deviation.

Where Malik and coworkers see waves in the heart rate and Boyett and coworkers see the mean, we see interesting and informative dynamics. We especially look for how the heart rate changes with respect to other cardiorespiratory signals such as the breathing rate and the blood oxygenation (Moss *et al.* 2016, 2017; Fairchild *et al.* 2017). We see an entrained network of signals reporting on the autonomic nervous system and other regulatory paths. Most importantly, we think about the patients who emit those signals, and how their health status might be changing for the better or for the worse.

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Additional information

Competing interests

J. R. Moorman is Chief Medical Officer and shareholder in Advanced Medical Predictive Devices, Diagnostics, and Displays, Charlottesville, VA, USA, which has licensed University of Virginia technologies relevant to predictive analytics monitoring. D. E. Lake is a shareholder, Medical Predictive Science Corporation, Charlottesville, VA, USA, which has licensed University of Virginia technologies relevant to predictive analytics monitoring and markets the neonatal HeRO monitor.

HRV: a precious tool for investigating and estimating cardiac autonomic responsiveness

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Cardiac autonomic responsiveness quantifies how the ANS responds to external physiological stimuli (e.g. during a tilt or stress test) or to pathological states affecting autonomic responses (ischaemic diseases, diabetes and many others). This is certainly rather different from measuring the autonomic 'tone' and we agree on this with Malik *et al.* (Malik *et al.* 2019).

No doubt that: (i) HR and HRV are both sensitive to autonomic stimuli; (ii) SDNN is related to HR (Zaza & Lombardi, 2001), (iii) the analysis of HRV is not limited to the total power (SDNN) and other metrics are largely independent of HR, such as LF/HF (Zaza and Lombardi); advanced HRV methods proved stronger predictors of mortality, e.g. after AMI, than HR, with increased relative risks (Sassi *et al.* 2015).

While it is difficult to find out a mathematical model which exactly describes autonomic responsiveness, many papers have demonstrated that HRV is a valuable 'indirect estimator'. If the same information were present in HR and HRV, it is reasonable to think that, historically, the easier to quantify would have been always selected. But, objectively, a wide literature has approached the topic and demonstrated the opposite: HRV is able to better describe pathophysiological conditions than HR alone (Lombardi *et al.* 1987; Task Force of ESC and NASPE, 1996; Malik *et al.* 2019).

While it is good to remember the link between SDNN and HR, as Boyett *et al.* (2019) did, as well as the limited number of clinical applications of HRV (Sassi *et al.* 2015), our opinion is that bold statements such as HRV is 'flawed' may only over-simplify the still open issues and cast shadows over many important results that have been obtained (Task Force of ESC and NASPE, 1996; Sassi *et al.* 2015). We encourage clinicians and scientists to go along in the research.

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Additional information

Competing interests

None declared.

Heart rate variability – what are we talking about?

In all science error precedes the truth, and it is better it should go first than last.

Horace Walpole (1717–1797).

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Forty years of research in heart rate variability (HRV) as a measure of autonomic nervous system (ANS) activity are characterized by 'truths and errors', which is well reflected in the CrossTalk debate between M. Malik *et al.* and M. Boyett *et al.* on the validity of heart rate variability as a measure of ANS responsiveness (Malik *et al.* 2019; Boyett *et al.* 2019).

Although HRV has potential to characterize patients at risk for ventricular tachyarrhythmic events (La Rovere *et al.* 1998), efforts to use HRV to *prospectively* identify high risk patients ended up disappointingly since specificity and positive predictive accuracy for selecting patients prone to therapy with implantable cardioverter defibrillators (ICDs) turned out to be too low. This holds true for both time and spectral measures of HRV. Thus, more subtle measures of heart rate (HR) fluctuations such as *deceleration capacity of HR* are currently studied for this purpose (Bauer *et al.* 2006; Rizas *et al.* 2018). In contrast, physiological studies – such as those cited by Malik *et al.* – strongly support that HRV is influenced by the activity of the ANS and can be used to assess the effect of provocative manoeuvres affecting the ANS, thus characterizing ANS responsiveness.

Boyett *et al.* are not wrong when they state that HRV is dependent on HR. However, this holds true only for those HRV time domain parameters which reflect a direct statistical characterization of HR, such as the standard deviation of normal RR intervals measured over 24 h (named as 'SDNN' or 'SD'). In contrast, HRV parameters that reflect subtle short-term changes in HR – such as pNN50 (proportion of NN intervals differing more than 50 ms from the previous NN interval), spectral HRV measures, HR turbulence, or deceleration capacity of HR – do perform independently of HR, are much more related to ANS activity, yield better predictive values for arrhythmic events, and are more suitable to characterize ANS responsiveness.

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Additional information

Competing interests

None declared.

Heart rate does not always walk hand in hand with heart rate variability: the case of post-exercise recovery

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In the recent CrossTalk series, both contributors (Boyett *et al.* 2019; Malik *et al.* 2019) discuss the use of heart rate (HR) variability (HRV) to assess cardiac autonomic nervous system (ANS) responsiveness and/or tone. Based on the previously described biophysical/mathematical relationship between HR and HRV (Monfredi *et al.* 2014), Boyett and colleagues argue that HRV does *not* reflect ANS tone but rather a simple mathematical consequence of HR change. Although we appreciate the points raised by Boyett *et al.*, we have previously reported a lack of association between HR and HRV during rest following chronic training (Leicht *et al.* 2003) and during the post-exercise period (Pecanha *et al.* 2014). Specifically, the post-exercise return of HR and HRV to their respective pre-exercise values was different, with HR returning within the first minutes whereas HRV took much longer (60 min to 24 h) (Pecanha *et al.* 2014). Based on Boyett and colleagues' proposal, we would expect that HRV (which is decreased during exercise) would present with a mathematically corresponding increase immediately following exercise. However, several studies have reported no increase in HRV immediately after maximal–supramaximal exercises (Niewiadomski *et al.* 2007; de Oliveira *et al.* 2013). The relationship between HRV and HR appears to be inconsistent with Boyett and colleagues' argument. Given the evidence to date, we agree that HRV is a useful tool to assess ANS responsiveness (*not* tone) with the post-exercise recovery period, a time of profound physiological change (Luttrell & Halliwill, 2015), an interesting condition to assess HRV responsiveness.

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Additional information

Competing interests

None declared.

Some changes of heart rate variability related to depressiveness and anxiety are not accompanied by changes of heart rate

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In our research on the clinical applicability of heart rate variability (HRV) in the field of psychiatry, its responsiveness was examined by incorporating the measurement during a mental task (Task) (Shinba *et al.* 2008; Shinba, 2014, 2017). The results showed that the responses to the task as well as the baseline scores (Rest) of HRV were related to depressiveness and anxiety, and were useful in differentiating mental disturbances, supporting the comments by Malik *et al.* (2019).

Further analyses on heart rate (HR) showed that in generalized anxiety disorder, HR was not different from control in spite of the significantly increased high frequency component (HF) of HRV (Shinba, 2017). When examining the responses of HRV and HR to task (Task/Rest ratio) in depression, abnormalities were found for HF but not for HR (Shinba, 2014). In depression, a rebound-like increase of HF was observed after the task without changes of HR (Shinba, 2014). In normal controls, depressiveness evaluated by a Self-rating Depression Scale was correlated with the Task/Rest ratio of HF but not with that of HR (Shinba *et al.* 2008). The response of the low frequency component (LF) of HRV to the task was also different from that of

HR in normal, depressive and anxious states (Shinba, 2017).

These discrepancies between HRV and HR in relation to mental disturbances indicate that in contrast to the opinion by Boyett *et al.* (2019), some aspects of HRV are independent of HR, and can be used as an autonomic parameter to analyse the pathophysiology of psychiatric disorders.

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Additional information

Competing interests

None declared.

We should be careful when physiologically interpreting heart rate variability

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Malik *et al.* (2019) and Boyett *et al.* (2019) have advanced sophisticated opinions regarding the validity of heart rate (HR) variability (HRV) to study cardiac autonomic responsiveness. Based on the two cited references, some points need highlighting.

Firstly, when we quote 'cardiac autonomic' evaluations, we need to distinguish that 'cardiac autonomic' analysis contains variables relating to blood pressure and heart periods, including baroreflex, chemoreflex and cardiopulmonary reflexes. Instead, HRV only measures inter-beat interval oscillations, indicating heart period. Thus, we raise the following question: should we be more cautious when inferring that HRV indicates 'cardiac autonomic' regulation?

Secondly, previous studies have suggested that the sympatho-vagal balance index calculated by the LF/HF ratio is theoretically flawed (Heathers, 2012; Billman, 2013). The most serious concern is that LF does not represent sympathetic HR regulation. Consequently, there is a lack of justification and compelling evidence regarding the HF components' adequacy to index the relative strength of vagal and sympathetic signalling.

Thirdly, sympathetic and parasympathetic activities can be measured through invasive techniques, such as electro-neuromyography, gastric vagal nerve activity, renal sympathetic nerve activity and blood catecholamine levels. HRV evaluates fluctuations in heart rhythm. Considering this: should we be more careful when promoting that HRV provides measures of sympathetic or parasympathetic activity?

We acknowledge this opportunity to discuss this globally implemented technique in this important journal.

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Additional information

Competing interests

None declared.