Heart rate variability is a valid measure of cardiac autonomic responsiveness

by

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Heart rate variability (HRV) has now been investigated for a number of decades. Different investigations linked HRV to the autonomic nervous system (ANS). Among these links, two clearly distinct facets need to be distinguished. Ongoing debate relates to HRV used a measure of autonomic tone. Nevertheless, this is very different from the present discussion which deals with HRV used as an indicator of autonomic responsiveness, i.e. the usefulness of assessing whether ANS responds to provocations and whether HRV can detect changes in ANS influence.

Autonomic control of heart rate

ANS control of sinus nodal periodicity is well established. Efferent vagal activity hyperpolarizes sinus nodal cells and decreases their spontaneous depolarization rate. In man, the baseline vagal 'tone' reduces the resting heart rate to about 50-70 beats per minute (bpm) from its intrinsic 110-120 bpm level (Parker et al, 1984; Hainsworth, 1998). The sympathetic supply to the heart has the opposite effect, increasing the sinus nodal depolarization rate. These mechanisms differ in response latency. Whilst vagal activity or withdrawal can influence the immediately subsequent heartbeat, responses to sympathetic activity occur more slowly with an initial delay of some 5 seconds and maximal effect occurring after some 20-30 seconds (Furnival et al, 1973; Hainsworth, 1998).

Respiratory sinus arrhythmia with cardiac periods shortened and prolonged during inspiration and expiration, respectively, also manifests vagal control (Farmer et al, 2016), especially if observed during undisturbed stable conditions without physical activity and/or respiratory rate and tidal volume changes (Grossman et al, 2004; Grossman & Taylor, 2007).

Heart rate variability

The autonomic background of the cardiac periodicity control has implications for the interpretation of the HRV measurements (Task Force, 1996). Different HRV assessments range from simple statistical variance to non-linear estimates (Task Force, 1996; Sassi et al, 2015). Of these, spectral HRV analysis of short-term recordings is perhaps the closest to the estimates of autonomic influences although other methods also estimate the degree of autonomic control.

The spectrum of stable undisturbed cardiac periods allows distinguishing the very low (VLF, ≤0.04 Hz), low (LF, 0.04-0.15 Hz) and high (HF, 0.15-0.4 Hz) frequency components (Task Force, 1996). Under normal circumstances, the respiratory frequency falls within the HF range linking the HF components to vagally driven heart period modulations whilst LF modulations reflect a combined vagal and sympathetic control. This allows assessing the relationship between sympathetic and vagal control by either the LF/HF proportion or by the so-called normalised LF and HF components, expressing their contribution to the total spectral power excluding the VLF components (Task Force, 1996). The LF/HF ratio becomes problematic when HF components converge to zero; the normalised components do not suffer from this problem. Spectral HRV components have also their counterparts in other HRV indices.

Importantly, HRV components express the degree of modulation due to the sympatho-vagal influences rather than the direct extent of the tone of ANS branches (Malik & Camm, 1993). Under normal circumstances, there is some correlation between the modulations and the underlying tone but this relationship breaks under extreme conditions (Malik & Camm, 1993; Casadei et al, 1995).

Physiologic studies

Already the seminal canine HRV study showed that parasympathetic blockade practically abolishes the HF components while total autonomic blockade almost eliminates any heartbeat period variability (Akselrod et al, 1981). This observation was subsequently replicated in many physiologic human studies (Martinmäki et al, 2006; Ng et al, 2009; Bolea et al, 2014). Some partially conflicting results (Warren et al, 1997; Højgaard et al, 1998) have been attributed to additional factors, e.g. condition instabilities (Pyetan & Akselrod, 2003).

Importantly, autonomic provocation studies were consistent with the vagal-sympathetic association of the HF and LF components. When challenging healthy subjects by autonomically active, e.g. postural, manoeuvres that boost sympathetic tone, the proportional shift between the HF and LF components corresponds to the underlying autonomic changes (Pomeranz et al, 1985; Vidigal et al, 2016). Compared to supine rest, standing increased and decreased the normalised LF and HF components, respectively (Task Force, 1996; Vidigal et al, 2016). Accurate HRV analysis performed in healthy volunteers during head-up tilt with gradual inclination changes showed only moderate heart rate increases but the normalised LF and HF components increased and decreased practically linearly and statistically significantly with the increasing tilt inclination from 0 to 90 degrees (Montano et al, 1994). This observation was followed by occasionally heated arguments of whether LF components reflect only sympathetic of both vagal and sympathetic ANS influences and whether different methods for spectral analysis (e.g. the methods for normalised components calculation) deserve different interpretation in terms of ANS tone assessment (Eckberg 1997). Nevertheless, even these discussions did not dispute that provoked ANS changes can be depicted by HRV analysis.

Consistent results were obtained with medical conditions associated with sympathetic tone increases. Among others, relative LF increases and HF decreases were seen in patients with fever (Lin et al, 2006; Carter et al, 2014), painful conditions (Sesay et al, 2015), or anxiety disorders (Shinba, 2017). Spectral HRV analysis also detects sex differences in baseline resting autonomic status (Smetana & Malik, 2013).

Clinical applicability

This association of cardiac ANS status with spectral HRV components (and their other measurement counterparts) makes HRV analysis suitable for detecting autonomopathies characterised by the loss of autonomic responsiveness. Numerous publications showed the clinical value of HRV in the early detection and type-classification of diabetic neuropathy (Howorka et al, 1998; Osterhues et al, 1998; Jirkovská et al, 2006; Andersen et al, 2018). This is not surprising; the assessment of autonomic responsiveness is also the basis of neuropathy detection by the seminal Ewing test (Ewing et al, 1985). Several studies reported that the HRV-based testing has not only the same efficacy as the Ewing test but also offers much easier clinical conduct (Howorka et al, 1998; Jirkovská et al, 2006). Similar autonomopathy detection has also been reported in many other clinical conditions.

As already discussed, particularly sensitive assessments of disturbed autonomic responsiveness utilise HRV responses to provocative tests leading, under normal circumstances, to known autonomic balance changes. Not only tilt testing and other instrumental interventions (Hohnloser & Klingeheben, 1998), but also postural provocations have been employed in different clinical settings (Jiang et al, 2015).

Short-term HRV shows reduction of vagal-respiratory sinus arrhythmia in coronary artery disease. The extent of these changes was reported to correlate with the degree and severity of myocardial ischemic changes (Hayano et al, 1990). This represents the autonomic response to cardiovascular abnormality which, like other homeostasis abnormalities, leads predominantly to sympathetic rather than vagal activation.

Short-term vs long-term recordings

Whilst short-term recordings obtained without external disturbances are suitable for HRV-based assessment of the proportions between vagal and sympathetic modulations, changes in long-term, e.g. 24-hour, HRV assessment are influenced by cardiac autonomic responses less systematically. Under normal conditions, vagal influence is increased during the sleep (Berlad et al, 1993). During the day, external provocative stimuli, physical and mental activity, and general responses to the environment including food intake lead to variable autonomic reactions with consequent heart rate adaptation. Therefore, under normal circumstances, the major component of long-term HRV reflects the heart rate circadian pattern, mainly influenced by the day-night differences.

Autonomic responsiveness of the organism is needed for heart rate to respond to sleep stages and to activity and external stimuli during the wakeful state. Nevertheless, since the responses to the surrounding environment are a major contributor to the circadian heart rate changes, the extent of external environmental demands influences long-term HRV profoundly. Therefore, long-term HRV analysis is less suitable for individual quantification of autonomic responsiveness since strict control of different environmental aspects including psychosocial and mental stimuli is practically unachievable.

Risk prediction

Long-term HRV has been repeatedly shown to provide powerful risk prediction mainly in cardiac patients (Kleiger et al, 1987; Task Force, 1996; Sassi et al, 2015; Steger et al, 2019). Powerful results were obtained in patients hospitalised for acute myocardial infarction or worsening heart failure. The hospitalisation leads to relative standardisation of the environment allowing reasonable of heart rate responses in different patients. Disease progression and clinical status worsening leads to overall increases in sympathetic tone which in turn leaves lesser room for autonomically triggered heart rate response to surrounding environment and to less marked day-night differences. In cardiac patients, these clinical indicators are further combined with increased arrhythmic susceptibility due to prevailing sympathetic tone (Lown & Verrier, 1976). Nevertheless, similar relationship between reduction of autonomically driven heart rate responses to external stimuli and poorer prognosis is also known in other patient populations, such as in patients with kidney and liver impairments.

Nevertheless, the HRV reduction in high-risk patients does not mean their primarily diminished autonomic responsiveness. Rather, the increased sympathetic tone in high risk patients reflects their clinical status and exists because the autonomic system reacts to the underlying condition. In advanced heart failure, ‘erratic’ heart period fluctuations may also artificially increase HF components despite a sympathetic tone elevation and vagal withdrawal.

Conclusion

The autonomic nervous system reacts to both internal and external stimuli and maintains the homeostasis of the organism. Because both sympathetic and vagal systems lead to differently frequent modulations of cardiac periodicity, the HRV is a suitable method for assessing the proportions between the strength of modulations by both limbs of the autonomic system. If such an assessment is combined with autonomically provocative tests, HRV offers a direct measure of autonomic responsiveness which is clinically very useful in the diagnosis and detection of autonomopathies and neuropathies.

Numerical values of HRV components cannot be confused with accurate measurements of autonomic tone (Malik & Camm, 1993). Nevertheless, as far as the assessment of autonomic responsiveness is concerned, the usefulness of HRV has already been proven beyond any reasonable doubt.

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Competing Interests

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