Chapter 5
HRV and Alterations in the Vegetative Nervous System

Introduction

Heart rate variability is often discussed synonymously with imbalance within the autonomous system. HRV has been seen not only as an indicator for probable disturbances in the autonomous system. In a significant number of publications, it is even regarded as proof for ANS dysfunction without other kind of evidence (e.g., in Mazzeo et al. 2011). In this chapter I intend to review this hypothesis.

One basic problem is to find methods to examine the autonomic nervous system. There is no gold standard to evaluate the ANS, and it is rather arguable whether there are evaluation methods that can display the real situation of the ANS.

Dysfunction of ANS can be caused or impaired by several clinical and subclinical conditions, summarized in the following Table 5.1.

We still have an insufficient understanding of the exact underlying mechanisms that induce alterations of HRV in CHF (Tulppo and Huikuri 2004) or in healthy persons.

Is There an Accordance Between Anatomical Structures Involved in HRV and Supraspinal Structures Related to ANV?

Given the increased possibilities of in vivo studies of the human brain, it is not surprising that several studies have been conducted focusing on HRV.

Critchley used functional MRI experiments with simultaneous electrocardiography to examine regional brain activity associated with autonomic cardiovascular control during performance of cognitive and motor tasks. Activity in the dorsal anterior cingulate cortex (ACC) related to sympathetic modulation of heart rate was observed using indices of heart rate variability and high- and low-frequency power in the cardiac rhythm. This could indicate that during effortful cognitive and motor

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Table 5.1 Principal causes of autonomic nervous system dysfunction

Degenerative disorders	Acute and subacute disease	Chronic diseases	Others
Pure autonomic failure (PAF)	Heart failure	Diabetes mellitus	Drugs acting on ANS
Multiple system atrophy (MSA)	Myocardial infarction	Hypertension	Cardiac transplant
Parkinson's disease	Severe brain injury	Idiopathic orthostatic hypotension	
	Spinal cord injuries	Increased intracranial pressure	
	Guillain–Barré	Hereditary neuropathies	
	Paraneoplastic neuropathies	Dopamine beta-hydroxylase deficiency	
	Botulism	Uremia	
	Drug-induced neuropathies	Alcoholism	
	Toxic neuropathies	Liver disease	
	Porphyria	Chronic pulmonary diseases	
	Immune autonomic neuropathies	Amyloidosis	
		Infective neuropathies	
		Chronic immune demyelinating polyneuropathies	
		Connective tissue diseases	

Modified from Mazzeo et al. (2011)

behavior, the dorsal ACC supports the generation of associated autonomic states of cardiovascular arousal. This idea was tested on three patients with damaged ACC regions who, in contrast to healthy volunteers, showed blunted autonomic arousal to mental stress (Critchley et al. 2003).

Matthews used a test that presented incongruent (INC) and congruent (CON) stimuli at two speeds to probe dorsal (dACC) and ventral (vACC) using functional magnetic resonance imaging (fMRI). He was able to distinguish functional subdivisions within the ACC and to link the processes of cognitive interference and parasympathetic modulation with activation in specific subregions of the ACC, a structure that is critical for the interface between cognition and emotion. This activation correlated significantly with HF and might represent the parasympathetic modulatory role of the vACC (Matthews et al. 2004).

Napadow and colleagues developed and implemented a new method that relates cardiac-gated fMRI time series with continuous-time heart rate variability (HRV) to estimate central autonomic processing. The ECG was analyzed with a novel point process adaptive-filter algorithm for computation of HF simultaneously. This combined HRV–fMRI approach demonstrated HF correlation with fMRI activity in the hypothalamus, cerebellum, parabrachial nucleus/locus coeruleus, periaqueductal gray, amygdala, hippocampus, thalamus, and dorsomedial/dorsolateral prefrontal, posterior insular, and middle temporal cortices (Napadow et al. 2008).

Lane correlated HF-HRV with measures of regional cerebral blood flow (rCBF) derived from positron emission tomography (PET) and (15)O-water in 12 healthy women during different emotional states. Three different emotional states and three neutral conditions were each induced by videos or through recall of personal experiences. A 60-s HRV was analyzed with the help of frequency domain. The six emotional and six neutral conditions were grouped together and contrasted. Substantial overlap was found between emotion-specific rCBF and the correlation between emotion-specific rCBF and HF-HRV, particularly in the medial prefrontal cortex. The study also observed that the elements of cognitive control had clear neural substrates that correlated with HF-HRV and to a large extent differed from the emotion-specific correlates of HF-HRV. The study proposed that the medial visceromotor network is a final common pathway by which emotional and cognitive functions recruit autonomic support (Lane et al. 2009).

Thayer and colleagues executed a meta-analysis of this and four other imaging studies using Multilevel Kernel Density Analysis (MDKA). The study treats MDKA contrast maps as the unit of analysis and is therefore suitable for evaluating the consistency of activation across studies (Thayer et al. 2012). They identified three regions associated with emotion tasks investigated in earlier studies together with HRV (Thayer 2006), the right pregenual cingulate (BA 24/32) in the medial prefrontal cortex, the right subgenual cingulate (BA 25), and the left sublenticular extended amygdale/ventral striatum (SLEA). The latter region extends into the basolateral amygdale complex, the superior amygdale (central nucleus), and into the ventral striatum. Especially the involvement of SLEA is in accordance to its central role in ANS. One problem is that due to temporal aspects of the imaging investigations, only HF (needing the shortest time periods) could be tested.

In conclusion, newer studies support the assumption developed in animal studies that ANV correlates in the brain and structures involved in HRV are largely similar.

Is There General Increased Autonomic Activity That Might Correlate with HRV Measures?

In frequency-domain analysis the idea of a possible correlation between alterations of the HF, or LF component and parasympathetic, or sympathetic activity comes largely from pharmacological studies in both humans and other animals. The basic idea that HRV measures could correlate with the functional state of the vegetative nervous system assumes a synchronicity between different parts of it. In other words it assumes that the vegetative nervous system is in either a sympathetic or parasympathetic state, and this regards all parts simultaneously. This is probably only partially true. There is evidence for quantitative regional differences in sympathetic outflow, particularly in patients with heart failure, with a bigger activation at the heart compared to the real noradrenaline spillover (Hasking et al. 1986). These differences occur not only between different functional systems but also temporally. The increase in cardiac adrenergic drive precedes the rise in sympathetic nerve traffic to the skeletal muscle measured by MSNA (Rundqvist et al. 1997). Therefore, it

is difficult to sustain the idea of a generalized sympathetic or parasympathetic state. HRV might or might not mirror a generalized state, but it may also simply show just the sympathetic or parasympathetic state of the parts of the ANS involved in HRV (and not, for instance, ANV states in peripheral nerves).

Does HF Correlate with Parasympathetic Tone?

[*Pros*:] Early evidence was interpreted to suggest that HF power can be promoted as a noninvasive index of vagal-cardiac nerve traffic in humans (Eckberg 1983; Fouad et al. 1984). Administration of atropine or other parasympathetic blocking agents can abolish the high-frequency component of heart rate variability (Rimoldi et al. 1990). High-dose atropine was thought to block vagal parasympathetic activity, and it was shown to eliminate nearly all HF (and LF) in studies (Pomeranz et al. 1985; Koh et al. 1994). Using an experimental approach in which sympathetic influence was blocked by propranolol and vagal influence was blocked gradually with atropine under controlled respiration, HF (both calculated with autoregressive spectrum analysis and fast Fourier transformation) correlated strongly with vagal tone (Hayano et al. 1991). In volunteers after beta-adrenergic blockade with propranolol, phenylephrine and nitroprusside were used to achieve baroreflex-mediated increases and decreases of the parasympathetic activity, with a dose–response experiment. In the analysis, which used linear and quadratic models, quadratic models proved superior. The authors conclude that the relationship between HRV parasympathetic activities can be described best by a function with an ascending part that goes over to a plateau level (Goldberger et al. 2001). In post-AMI patients, plasma noradrenaline correlates with HF (Oya et al. 1999).

[*Cons*:] Kollai and Mizsei compared respiratory peak minus valley RR interval changes with RR interval shortening provoked by large-dose atropine after β-adrenergic blockade. Although their study supported the use of respiratory RR interval fluctuations as indexes of vagal-cardiac nerve traffic, it showed that this measure is not a perfect index (Kollai and Mizsei 1990). After β-adrenergic blockade, there was a reasonable correspondence between RR interval fluctuations and vagal-cardiac neural outflow but only when respiration was controlled. When respiration was not controlled, respiratory frequency RR interval fluctuations bore no significant relation to tonic vagal-cardiac nerve activity (Grossman et al. 1991). Casadei noted a difference between absolute power of the HF component and the normalized power. The former increased, but the latter decreased at the onset of exercise (Casadei et al. 1995).

Does LF Correlate with Sympathetic Tone?

[*Pros*:] Low frequency is thought to be associated with changes of sympathetic outflow. In dogs, an increase in low-frequency power was observed during baroreceptor unloading with nitroglycerin and was prevented by prior bilateral

stellectomy (Rimoldi et al. 1990). In four of ten subjects studied, a significant correlation between sympathetic nerve activity and normalized LF was found (Saul et al. 1990). Malliani and coworkers argued with parallel changes of increased sympathetic activity and LF increase (Malliani et al. 1991); their review and data however have been recalculated and challenged (Eckberg 1997). In decerebrated cats, increased activity of cardiac sympathetic nerves and reflex sympathetic excitation induced an increase in LF and a reduction in HF, the opposite effect occurring in sympathetic reflex inhibition (Montano et al. 1992). Another argument for the correlation of LF and sympathetic outflow came from studies showing synchronous changes of LF and HF oscillations of MSNA recordings and HRV recordings under stimulation with nitroprusside (Pagani et al. 1997).

[*Cons*:] Pagani reported that propranolol 0.2 mg/kg iv does not reduce normalized 0.1-Hz RR interval spectral power (Pagani et al. 1986). Low-dose scopolamine as cholinergic blocking drug increases LF (Vibyral 1990). In healthy supine subjects there was no significant correlation between myocardial noradrenaline spillover and absolute or relative 0.1-Hz RR interval spectral power (Kingwell et al. 1994). High-dose atropine should block vagal parasympathetic activity and thus increase sympathetic activity. By contrast, high-dose atropine abolished nearly all LF (and HF) in studies (Pomeranz et al. 1985; Koh et al. 1994). Heart rate variability recorded during severe exercise in healthy subjects (a condition known to increase sympathetic outflow) has been shown to decrease (Casadei et al. 1995). Two groups measured RR interval spectral power before and after high spinal anesthesia. Sympathetic blockade in the supine position did not alter absolute or relative 0.1-Hz RR interval spectral power significantly (Hopf et al. 1995; Introna et al. 1995). Short-term β-blockade can increase HF power (Jokkel 1995). In a mice model, cardiac-specific GTP-binding protein, $G_s\alpha$, which plays an important role in β-adrenergic signal transduction, was overexpressed. Contrary to expectations, the LF component was reduced in the mutant mice compared to wild-type mice, and the LF/HF ratio was also reduced (Uechi et al. 1998). LF however contains also vagal influence (Eckberg 1997). MIBG-SPECT used to examine postganglionic sympathetic innervation showed reduced activity, whereas frequency-domain and time-domain values did not differ to the controls apart from a subgroup of patients (Druschky et al. 2001).

Some of the studies reporting associations between LF and sympathetic outflow have been criticized. The study of Saul et al. (1990) was not able to show the correlation in six of ten subjects. The study of Pagani et al. (1997) was criticized for not using fixed breath frequencies, using wrong statistic algorithms, and not normalizing the data (Eckberg 1997).

To explain the disconcordance of LF and known conditions with high sympathetic outflow, the hypothesis was developed stating that under conditions of complete receptor saturation or blockade, the modulation of autonomic activity is abolished and the relevant frequency band disappears (Malik and Camm 1993). The loss of LF in chronic heart failure can be viewed as evidence for a decrease in modulation of sinoatrial discharge, which may be due to constancy of sympathetic and parasympathetic firing rates or to a loss of pacemaker responsiveness to neurally released noradrenaline and acetylcholine (Notarius and Floras 2001).

In patients with severe heart failure, the LF pattern can be virtually absent in muscle sympathetic nerve activity, which correlates again close with HRV LF (van de Borne et al. 1997). A breakdown of fractal properties of HRV is often related to an unfavorable prognosis. In a study using an experimental stress model, fractal breakdown was associated with simultaneous activation of SNS and PNS (Tulppo et al. 2005).

In rats, there is a correlation between sympathetic nerve activity and blood pressure in power spectra at 0.4 Hz, but not with heart rate (where the majority of spectral power was lower than 0.4 Hz) (Brown et al. 1994).

Baroreflex Gain

The baroreflex manages blood pressure homeostasis in different body positions. Baroreceptors located in major systemic arteries monitor blood pressure. If PB decreases, sensory impulses transmitted to the vasomotor center in the brainstem also decrease, resulting in adjustment of ANS activity to increase heart rate and vascular resistance. This basic reflex can be attenuated by higher brain centers and the limbic system. Blushing during an embarrassing moment involves the vasomotor center but originates in the frontal association cortex, much like fainting reactions, cold sweating, and racing heart rate.

The baroreflex feedback theory describes low oscillations observed as a consequence of changes in blood pressure (e.g., due to respiration). Arterial baroreceptors detect such changes and lead the central nervous system to adjust the heart rate through both fast vagal action and slower sympathetic action. The baroreflex also adjusts sympathetic outflow to the vasculature and therefore peripheral resistance, leading to a change in blood pressure in an attempt to buffer the initial change in blood pressure (Malpas 2002). The critical point is that the combination of a series of time delays present among baroreceptors, the central nervous system, sympathetic outflow, and the response of the vasculature means that the input change in blood pressure results in an output change in vasculature resistance that is slightly delayed in time. Instead of buffering the initial change in blood pressure, this leads to the development of yet another change in blood pressure. This was showed in a model that accounted for oscillations at 0.1 Hz in the human (DeBoer et al. 1987). Sympathecomy or combined alpha- and beta-adrenergic blockade leading to reductions of the spectral power at 0.1 Hz may be interpreted as interruption of the reflex feedback loop (Malpas 2002). Some refined models have been presented to show this. Linear models seem to require strict relationships between the vasculature and the central nervous system (Burgess et al. 1997). A nonlinear model, however, needed only a set of rather mild assumptions to show a similar behavior of the system (Ringwood and Malpas 2001). But even if the baroreceptor reflex is removed by denervation, a reasonable amount of variability remains around this frequency (Cerutti et al. 1994; Julien et al. 1995). This can be due to other reflex pathways or central nervous system components (Malpas 2002).

LF spectral power is influenced by the baroreflex function, cardiac beta-adrenoreceptor sensitivity, post-receptor signal transduction and parasympathetic modulation (Adamopoulos et al. 1992; Saul et al. 1990). By contrast, values for cardiac noradrenaline spillover are not affected by postsynaptic mechanisms, but may be influenced by changes in reuptake of noradrenaline (Notarius and Floras 2001).

Frequency-domain measures have been challenged as too insensitive for individual measures because of relatively large intersubject variability and dependency on the measurement conditions (Gregoire et al. 1996; Notarius and Floras 2001).

Coupling between the three main rhythms of respiration, HF and LF oscillations were determined to be weak (Janson et al. 2001). However, they tend to synchronize (Prokhorov et al. 2003). The high degree of nonlinear coordination between HRV and SPV may be mainly influenced by the respiratory component. If this was filtered, the coupling was significantly reduced in an animal model (Gonzalez et al. 2000).

Conclusion

In a critical review, Eckberg considers the existing evidence about how heart rate variability reflects the sympathovagal balance. He comes to the following conclusions:

- Vagal contributions to baseline LF RR interval fluctuations are great, and there is no evidence that baseline LF RR interval spectral power is related quantitatively to sympathetic-cardiac nerve traffic.
- Most evidence refutes the notion that LF RR interval spectral power tracks baroreflex-mediated changes of sympathetic nerve activity.
- Baseline respiratory frequency RR interval fluctuations are related significantly but imperfectly to the level of human vagal-cardiac nerve traffic.
- Moderate changes of arterial pressure, which alter vagal-cardiac nerve activity, do not change HF RR interval fluctuations, and changes of breathing frequency and depth, which profoundly alter HF RR interval fluctuations, may not change vagal-cardiac nerve activity at all.
- Some physiological interventions provoke parallel, not reciprocal, changes of vagal and sympathetic nerve activity, and other interventions, such as baroreceptor stimulation, provoke reciprocal changes but only over a very limited range of arterial pressure.
- Measures of sympathovagal balance are not valid in heart failure patients and may not be valid in hypertensive or sleep apnea patients.
- Neither upright tilt nor light or heavy exercise provokes the reciprocal changes of sympathetic and vagal nerve traffic predicted by calculations of sympathovagal balance.

He does not dispute the value of heart rate variability in stratifying risk in patients with cardiovascular diseases or in better understanding autonomic mechanisms, but argues against using the term “sympathovagal balance” because this relationship is not proven (Eckberg 1997).

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