Hot Topic Review

Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes

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Power spectral analysis of heart rate variability has often been used to assess cardiac autonomic function; however, the relationship of low-frequency (LF) power of heart rate variability to cardiac sympathetic tone has been unclear. With or without adjustment for high-frequency (HF) power, total power or respiration, LF power seems to provide an index not of cardiac sympathetic tone but of baroreflex function. Manipulations and drugs that change LF power or LF:HF may do so not by affecting cardiac autonomic outflows directly but by affecting modulation of those outflows by baroreflexes.

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The autonomic nervous system plays major roles in maintaining cardiovascular homeostasis and in the pathophysiology of a wide variety of disease states. The system includes vagal cholinergic and sympathetic noradrenergic nerves that supply the heart and sympathetic noradrenergic nerves that enmesh arterioles, which are a major determinant of total peripheral resistance to blood flow in the body and therefore of the blood pressure. Clinicians and researchers have long sought valid, non-invasive, quantitative means to identify pathophysiologically relevant abnormalities of these systems.

As will be emphasized later, one must distinguish autonomic 'tone' from modulation of that tone. If one considers a home heating system, there is a difference between measuring how much the furnace is working and measuring how much one can regulate the furnace by adjusting the thermostat. We will be proposing that power spectral analysis of heart rate variability (HRV) provides a means to evaluate the ability to modulate autonomic outflows via baroreflexes rather than a means to evaluate autonomic tone *per se*.

Low-frequency power is unrelated to cardiac sympathetic tone during supine rest

About a century ago, the great Dutch cardiologist, Karel Frederik Wenckebach (the same Wenckebach for whom a type of second degree heart block still bears his name) wrote that a variable pulse rate is a sign of a healthy heart (Wenckebach, 1914). Since then, many studies have shown that both tachycardia and decreased HRV are adverse prognostic signs in a variety of common conditions, such as ischaemic heart disease, congestive heart failure, myocardial infarction, and stroke.

Heart rate variability can be assessed in the time and frequency domains. Measures in the time domain include the standard deviation of heart rate and the standard deviation of heart rate normalized for absolute heart rate. It is generally accepted that under resting conditions HRV in the time domain mainly reflects respiratory sinus arrhythmia, which is mediated by parasympathetic cardiovagal outflow. Respiratory sinus arrhythmia corresponds to Wenckebach's sign of a healthy heart. In heart failure, myocardial infarction, and stroke,

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respiratory sinus arrhythmia usually is either blunted or absent. In the frequency domain, the most commonly used approach is based on power spectral analysis of HRV and in particular quantification of low-frequency (LF) and high-frequency (HF) power. The latter corresponds to the frequency of breathing, and most investigators agree that just as for HRV in the time domain, HF power in the frequency domain mainly reflects respiratory sinus arrhythmia.

The origins and clinical significance of LF power have aroused intense interest and persistent controversy (Akselrod *et al.* 1981). The source and meaning of LF power are the main subject matter of this review. Many studies have presumed that LF power, especially if adjusted for HF power, total power or respiration, provides an index of cardiac sympathetic 'tone' and that the ratio of LF to HF power indicates 'sympathovagal balance'. Thus, a PubMed search on low-frequency power of heart rate variability and cardiac sympathetic tone yielded 227 citations.

Several lines of evidence, however, argue against the validity of LF power, with or without adjustment for HF or total power, as an index of sympathetic outflow especially to the heart.

(1) The rate of entry of the sympathetic neurotransmitter, noradrenaline, into the cardiac venous drainage (cardiac noradrenaline spillover) provides a 'gold standard' index of cardiac sympathetic outflow. Individual values for LF power and LF:HF are not correlated with cardiac noradrenaline spillover (Kingwell *et al.* 1994; Alvarenga *et al.* 2006; Moak *et al.* 2007; Baumert *et al.* 2009).

(2) Cardiac sympathetic neuroimaging by ^{18}F-fluorodopamine or ^{11}C-hydroxyephedrine positron emission tomographic scanning or ^{123}I-metaiodobenzylguanidine single photon emission computed tomographic scanning enables quantitative assessment of noradrenergic innervation of the left ventricular myocardium. The imaging agents are taken up by sympathetic nerves and then translocated from the cytosol to intraneuronal vesicles. In other words, the scanning depicts the radioactivity in the vesicles in sympathetic nerves. As shown in Fig. 1, the log of LF power is not correlated with left ventricular myocardial concentrations of ^{18}F-fluorodopamine, nor is LF:HF (Moak *et al.* 2007). The LF to HF ratio is also unrelated to cardiac sympathetic innervation assessed by ^{123}I-metaiodobenzylguanidine scanning in patients with Parkinson's disease (Haensch *et al.* 2009). Analogously, LF power is not associated with myocardial sympathetic innervation by ^{11}C-hydroxyephedrine scanning (Vesalainen *et al.* 1999).

(3) Drugs that increase release of noradrenaline from cardiac sympathetic nerves (e.g. tyramine, yohimbine) increase LF power even in patients with neuroimaging evidence of cardiac sympathetic denervation (Moak *et al.* 2007).

(4) In patients with congestive heart failure, cardiac sympathetic outflow is known to be markedly increased (Eisenhofer *et al.* 1996), yet such patients have very low LF power (Adamopoulos *et al.* 1992; Creager, 1992; Guzzetti *et al.* 1995; Vesalainen *et al.* 1999). Low-frequency power in this setting and in the setting of pulmonary hypertension can even be negatively related to skeletal muscle sympathetic outflow (Notarius *et al.* 1999; McGowan *et al.* 2009).

(5) Blockade of preganglionic cardiac sympathetic outflow by segmental spinal anaesthesia does not affect LF power or LF:HF, although segmental spinal anaesthesia does attenuate the increase in LF:HF during head-up tilt (Hopf *et al.* 1995).

(6) With ageing, cardiac and total body noradrenaline spillover and skeletal muscle sympathetic outflow increase. That is, delivery of noradrenaline to its receptors increases with ageing. In contrast, LF power decreases, and LF:HF remains unchanged (Lipsitz *et al.* 1990; Ryan *et al.* 1992; Piccirillo *et al.* 1995; Karas *et al.* 2008).

(7) Bilateral thoracic sympathectomies or sympathotomies, which produce partial cardiac sympathetic denervation (Moak *et al.* 2005), do not decrease LF power or LF:HF (Noppen *et al.* 1996; Tedoriya *et al.* 1999). We recently confirmed this finding in a cohort of patients with bilateral thoracic sympathectomies (Fig. 1). In the study of Noppen *et al.* (1996), sympathectomized patients had decreased LF power during orthostasis, but in the study of Tedoriya *et al.* (1999) they did not.

(8) Cardiac β-adrenergic stimulation with isoprenaline, which increases heart rate and plasma noradrenaline levels (Goldstein *et al.* 1986), decreases LF power (Ahmed *et al.* 1994).

(9) Considering that LF power is influenced by respiration-related changes in cardiovagal outflow, it has been suggested that accounting for respiratory influences on LF power improves the accuracy of power spectral analysis of HRV in assessment of cardiac sympathetic tone (Aysin *et al.* 2007; Colombo *et al.* 2008). The ANSAR ANX 3.0 system (ANSAR Medical Technologies Inc., Philadelphia, PA, USA) is the only commercially available device that makes this adjustment. The ANX 3.0 uses a proprietary algorithm that yields a variable termed LFa. In conjunction with a testing protocol for beat-to-beat heart rate, respiration and blood pressure during baseline sitting, the Valsalva manoeuvre and standing, the ANX 3.0 calculates values for LFa and

interprets those values in terms of sympathetic and parasympathetic modulation and sympathovagal balance. Our recent findings that patients with low baroreflex-cardiovagal slopes have decreased values for LFa compared with subjects who have normal baroreflex slopes and that these decreases are independent of cardiac sympathetic innervation cast doubt on the notion that even with respiratory

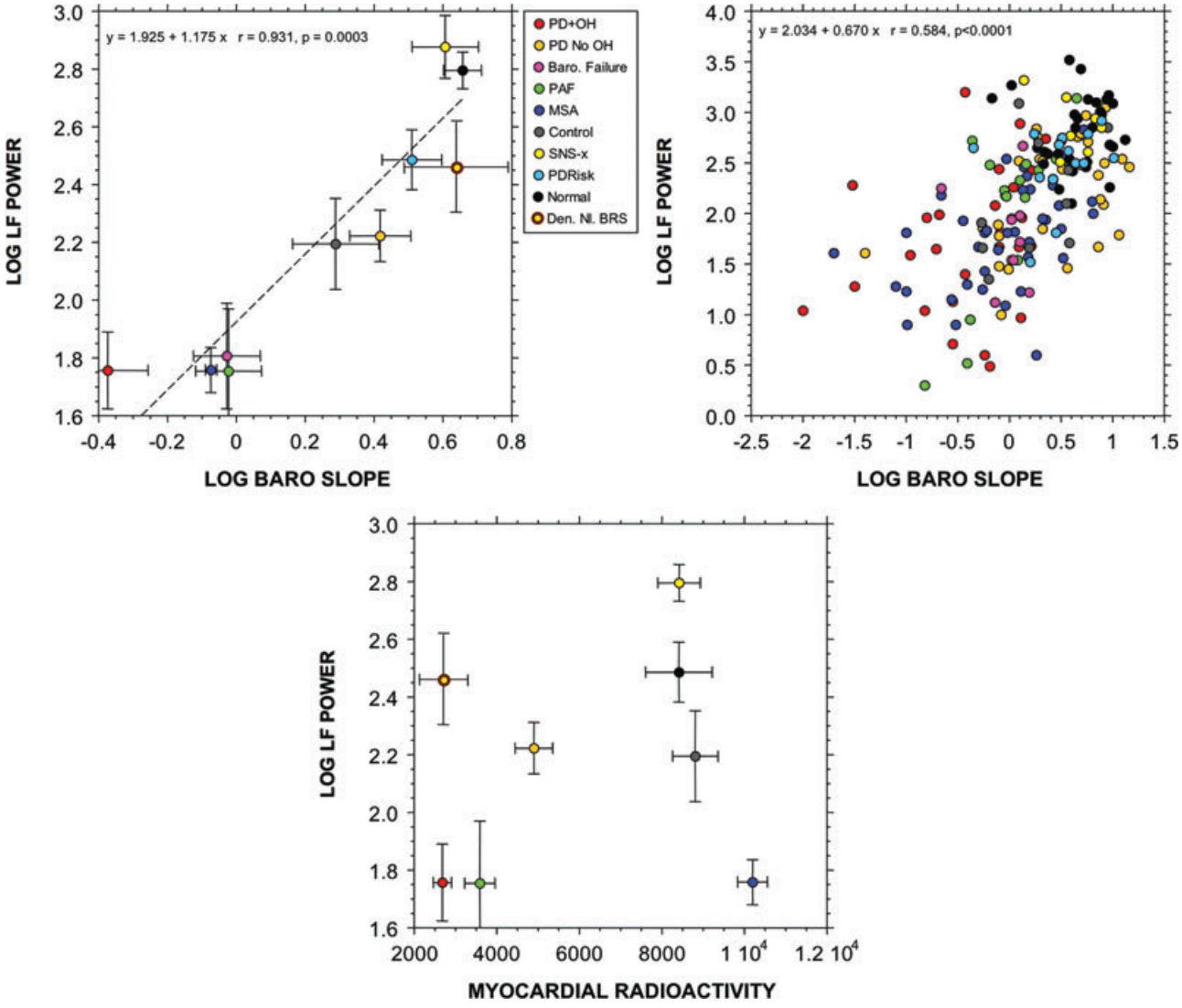

Figure 1. Relationship between LF power and measures of baroreflex function and cardiac sympathetic innervation

Left panel shows group mean (±SEM) values for the log of low-frequency (LF) power of heart rate variability (in ms^2) as a function of mean values for the log of baroreflex-cardiovagal gain, calculated from the slope of the linear relationship between cardiac interbeat interval and systolic blood pressure during the descent of pressure in Phase II of the Valsalva manoeuvre (in ms $mmHg^{-1}$). Middle panel shows individual values for the log of LF power as a function of baroreflex-cardiovagal gain. Right panel shows group mean (±SEM) values for the log of LF power of heart rate variability as a function of mean values for septal myocardial ^{18}F-fluorodopamine-derived radioactivity in the 5 min interval beginning about 5 min after initiation of 3 min infusion of the tracer. Abbreviations: Den. Nl. BRS, denervated, normal baroreflex sensitivity; PD+OH, Parkinson's disease with orthostatic hypotension; PD No OH, Parkinson's disease without orthostatic hypotension; Baro. Failure, baroreflex failure from head/neck cancer and neck irradiation; PAF, pure autonomic failure; MSA, multiple system atrophy; SNS-x, bilateral thoracic sympathectomies; and PDRisk, individuals with multiple statistical risk factors for Parkinson's disease (at least three of the following: family history of Parkinson's disease; symptoms of rapid eye movement (REM) behaviour disorder; decreased olfaction; and orthostatic intolerance from orthostatic hypotension). Dashed line shows linear line of best fit. Note positive correlation between the log of LF power and baroreflex-cardiovagal gain and no correlation between the log of LF power and myocardial radioactivity. Data adapted and updated from Rahman *et al.* (2011).

adjustment LF power provides a measure of cardiac sympathetic tone (Rahman *et al.* 2011).

(10) Low-frequency power is unrelated to several measures of extracardiac sympathetic outflow, such as peroneal skeletal muscle sympathetic traffic and plasma noradrenaline levels (Saul *et al.* 1990).

(11) In dogs, heart failure increases sympathetic outflow as measured by direct recording of stellate ganglionic nervous activity, whereas in this setting LF power decreases (Piccirillo *et al.* 2009).

(12) Perhaps most convincingly, in sheep with pacing-induced heart failure, in which directly measured cardiac sympathetic outflow is increased markedly, LF power in not increased, with or without normalization for total or mid-frequency power (Watson *et al.* 2007).

Low-frequency power does not relate to sympathetic nervous responses to acute manipulations

One might propose that acute changes in LF power reflect phasic changes in sympathetic outflow, even if there were no relationship at baseline. We considered the following four manipulations used in clinical laboratory testing: head-up tilt, exercise, mental arithmetic and meal ingestion.

Many studies have noted increases in LF:HF and normalized LF power during orthostasis. In this setting HF power usually decreases, and so the ratio of LF:HF and LF power normalized for total power of HRV would be expected to decrease, even if LF power remained unchanged. Low-frequency power considered alone does not consistently increase with orthostasis (Lipsitz *et al.* 1990; Hopf *et al.* 1995; Peles *et al.* 1995; Piccirillo *et al.* 1995; Vicek *et al.* 2008), despite approximately a doubling of plasma noradrenaline levels, although there are exceptions (Peles *et al.* 1995).

Low-frequency power also does not increase during exercise, with or without normalization for total power (Warren *et al.* 1997), whereas there are clear-cut increases in cardiac and extracardiac sympathetic outflows (Eisenhofer *et al.* 1992).

During laboratory psychological challenges, such as mental arithmetic, video games or the Stroop color–word conflict test, total body and cardiac spillovers of noradrenaline increase (Eisenhofer *et al.* 1992; Esler *et al.* 1995), indicating increased sympathoneural outflows. Concurrently, normalized LF power may (Moriguchi *et al.* 1992) or may not (Sloan *et al.* 1996) increase. Without normalization or adjustment for HF power, LF power does not increase during laboratory psychological challenges (Madden & Savard, 1995; Sloan *et al.* 1996; Hoshikawa & Yamamoto, 1997; Bernardi *et al.* 2000).

Meal ingestion represents a situation in which both parasympathetic and sympathetic outflows might be expected to increase, the former as part of the cephalic phase of digestion and the latter as a response to a tendency towards decreased total peripheral resistance because of postprandial shunting of blood towards the gut. Studies have disagreed about LF and HF power responses to meal ingestion. Ryan *et al.* (1992) reported that LF power increases in young but not old subjects, and HF power does not change regardless of subject age; Miyajima *et al.* (2001) noted no change in LF power and an increase in HF power; Kamath *et al.* (2007) found a tendency to increase LF power and no change in HF power after sham feeding ('chew and spit'); Friesen *et al.* (2007), studying responses of children to meal ingestion, described increased LF and decreased HF power; and Vaz *et al.* (1995) reported no changes in LF or HF power, despite significant increases in total body noradrenaline spillover.

Low-frequency power is related to baroreflex function

A different perspective on the physiological meaning of LF power is based on a distinction between tone and modulation of autonomic outflows.

In the 1920s, Hering described reflexive falls in heart rate and blood pressure upon stimulation of a branch of the glossopharyngeal nerve located near the bifurcation of the carotid arteries or upon intravascular stretching of this carotid sinus area (Hering, 1927). Subsequent studies of reflexive responses to increases or decreases in blood pressure in the carotid sinus (the baroreceptor reflex or baroreflex) and of reflexive responses to hypoxia and hypercarbia in the nearby carotid bodies (chemoreflexes) led to the Nobel Prize for Corneille Heymans in 1938 (Heymans & Neil, 1958). Relevant to the current discussion, Heymans emphasized effects of baroreflex stimulation on respiration. Carotid sinus stretching decreases the frequency of breathing.

When blood pressure increases acutely, heart rate decreases because of baroreflex stimulation. In the late 1960s, Smyth, Sleight and Pickering described a clinical method to measure baroreflex-cardiovagal gain (often called baroreflex sensitivity), based on the slope of the linear relationship between cardiac interbeat interval and systolic blood pressure after bolus I.V. injection of a pressor agent (Smyth *et al.* 1969), originally angiotensin but replaced soon after by phenylephrine (Bristow *et al.* 1969). Responses also to I.V. injection of a vasodilator enabled construction of baroreflex function curves. It soon became clear that baroreflex-cardiovagal failure is associated with the conditions noted above that are associated with decreased HRV, such as congestive heart failure, hypertension, and myocardial infarction.

Several lines of evidence fit with the concept that LF power is of central origin (Cooley *et al.* 1998) and in

particular support an association between LF power and baroreflex modulation of autonomic outflows (Saul *et al.* 1990), as summarized below.

(1) Sleight *et al.* (1995) demonstrated that carotid sinus stimulation produced by neck suction increases LF power only in individuals with normal baroreflex function and not in those with impaired baroreflex sensitivity.
(2) Patients with baroreflex failure, whether from carotid endarterectomy (Timmers *et al.* 2004), head and neck irradiation (Timmers *et al.* 1999; Sharabi *et al.* 2003), mixed cranial nerve neuroma (Guasti *et al.* 2010), neurosarcoidosis (Jardine *et al.* 2000) or brainstem stroke (Phillips *et al.* 2000), have very low values for LF power. Patients who have undergone neck irradiation also have attenuated responses of LF power to drugs that increase noradrenaline release from sympathetic nerves (yohimbine, which increases exocytotic release, or tyramine, which increases non-exocytotic release, independently of cardiac sympathetic innervation (Moak *et al.* 2007).
(3) Although individual values for the log of LF power do not correlate with cardiac sympathetic outflow, as indicated by cardiac noradrenaline spillover, they do correlate positively with the log of baroreflex-cardiovagal gain (Moak *et al.* 2007; Rahman *et al.* 2011).
(4) Patients who are status post bilateral thoracic sympathectomies have normal baroreflex function and normal LF power, even though they have evidence for partial cardiac sympathetic denervation (Moak *et al.* 2005; Fig. 1).
(5) Evaluation of patient groups with chronic autonomic failure provides a powerful means to determine whether LF power is related to cardiac sympathetic innervation, baroreflex function or both, because chronic autonomic failure syndromes vary greatly in terms of cardiac sympathetic innervation. Three well-studied forms are pure autonomic failure, multiple system atrophy and Parkinson's disease with orthostatic hypotension. Patients with pure autonomic failure and Parkinson's disease with orthostatic hypotension have neuroimaging, neurochemical and postmortem neuropathological evidence of cardiac sympathetic denervation (Goldstein *et al.* 2000; Goldstein & Orimo, 2009), whereas most patients with multiple system atrophy have intact cardiac sympathetic innervation (Orimo *et al.* 2002) and normal cardiac noradrenaline spillover (Goldstein *et al.* 2000). All three diseases are associated with baroreflex-cardiovagal failure (Goldstein *et al.* 2003), and all three are associated with low LF power (Rahman *et al.* 2011). In our series, across all subjects the log of LF power has shown a strong positive correlation with the log of HF power ($r = 0.74$, $P < 0.0001$). As a result of this, we cannot separate baroreflex modulation of sympathetic outflow from baroreflex modulation of parasympathetic outflow.
(6) Although most patients with cardiac sympathetic denervation also have baroreflex failure, there are rare exceptions. Among subjects in our series with cardiac sympathetic denervation (less than 5000 nCi-kg cc-mCi^{-1} of septal ^{18}F-fluorodopamine-derived radioactivity) and normal baroreflex-cardiovagal gain (more than 2 ms mmHg^{-1}), LF power is approximately normal (Moak *et al.* 2007). Mean values for this important group ($n = 5$) are depicted by the yellow circle with brown rim in Fig. 1).
(7) A recent study showed that in conscious mice, carotid sinus, aortic and combined sino-aortic baroreceptor denervation decreases both LF and HF power (Rodrigues *et al.* 2011).

Conclusion

With or without adjustment for HF power, total power or respiration, LF power seems to provide an index not of cardiac sympathetic tone but of baroreflex function. Manipulations and drugs that change LF power or LF:HF may do so not by affecting cardiac autonomic outflows directly but by affecting modulation of those outflows by baroreflexes.

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