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Review

Heart rate variability explored in the frequency domain: A tool to investigate the link between heart and behavior☆

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ABSTRACT

The neural regulation of circulatory function is mainly effected through the interplay of the sympathetic and vagal outflows. This interaction can be explored by assessing cardiovascular rhythmicity with appropriate spectral methodologies. Spectral analysis of cardiovascular signal variability, and in particular of RR period (heart rate variability, HRV), is a widely used procedure to investigate autonomic cardiovascular control and/or target function impairment. The oscillatory pattern which characterizes the spectral profile of heart rate and arterial pressure short-term variability consists of two major components, at low (LF, 0.04–0.15 Hz) and high (HF, synchronous with respiratory rate) frequency, respectively, related to vasomotor and respiratory activity. With this procedure the state of sympathovagal balance modulating sinus node pacemaker activity can be quantified in a variety of physiological and pathophysiological conditions. Changes in sympathovagal balance can be often detected in basal conditions, however a reduced responsiveness to an excitatory stimulus is the most common feature that characterizes numerous pathophysiological states. Moreover the attenuation of an oscillatory pattern or its impaired responsiveness to a given stimulus can also reflect an altered target function and thus can furnish interesting prognostic markers. The dynamic assessment of these autonomic changes may provide crucial diagnostic, therapeutic and prognostic information, not only in relation to cardiovascular, but also non-cardiovascular disease. As linear methodologies fail to provide significant information in conditions of extremely reduced variability (e.g. strenuous exercise, heart failure) and in presence of rapid and transients changes or coactivation of the two branches of autonomic nervous system, the development of new non-linear approaches seems to provide a new perspective in investigating neural control of cardiovascular system.

Contents

☆ To the memory of Alberto Malliani, an extraordinary mentor, physician, scientist and friend.

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It is widely accepted that autonomic nervous system (ANS), being not "autonomous" at all, represents an interface between the central nervous system (CNS) and the body. Changes in bodily regulation and function following everyday events, such as emotions, physical and mental stress, sleep, anxiety, social interactions, are mediated by activation of ANS. Moreover, the influence between CNS and ANS is not unidirectional, as for instance, pathological conditions may directly alter ANS activity inducing changes in behavioral states.

It is interesting to note the mounting evidence appearing in the literature providing support to the hypothesis that ANS is involved not only in the regulation of viscera (heart, vessels, gastrointestinal tract, genitourinary system, etc.), but also in the modulation of immune system, inflammation, metabolism, suggesting a comprehensive role of general integration of ANS (Sternberg, 2006; Grassi et al., 2007).

The two branches of the ANS, that is the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) have a reciprocal behavior in most physiological conditions at least in regard to the autonomic tone generated within the CNS. However, coactivation of both autonomic limbs appears to be the rule (Paton et al., 2005) during reflex peripheral activation such as that associated with exercise, cold face immersion or peripheral chemoreflex activation as occurring during apneas or ipovolemic shock (Malliani, 2000; Paton et al., 2005). The activation of SNS represents a predominant response to different physical and psychological coping strategies, allowing surviving performances. However, an excessive and chronic sympathetic activation may represent a continuum between health and disease, being a major risk factor for cardiovascular and non-cardiovascular diseases.

Therefore, the assessment of the state of ANS that has always been considered of utmost importance in the understanding of the pathophysiology of cardiovascular disease has constantly represented a challenging task, and different techniques have been utilized over time. For years, plasma and urinary catecholamines levels provided the only way of assessing sympathetic activity. However, this technique has several limitations whose discussion is beyond the scope of this review. A more specific regional measure of sympathetic activity is provided by cardiac norepinephrine spillover that has the limitation of being a fully invasive technique, thus limited to studies with small number of patients (Esler, 1993). Sympathetic activity may also directly recorded in humans using microneurographic techniques (Vallbo et al., 1979). Measurements of sympathetic nerve activity to skeletal muscle have provided extensive information regarding cardiovascular reflex control in conditions ranging from rest to postural changes, exercise, and mental stress in populations ranging from healthy controls to patients with hypertension and heart failure (Wallin and Charkoudian, 2007). However this approach being minimally invasive is not suitable for large scale clinical studies. Moreover, a limitation pertaining to all the aforementioned techniques is that they do not provide any information on the parasympathetic branch of the ANS.

More than 30 years have elapsed since the pioneering studies by Sayers and his associates (Hyndman et al., 1971; Sayers, 1973) introduced a computationally efficient analysis of heart rate variability (HRV) to unveil both cardiac sympathetic and parasympathetic modulations. The last two decades have witnessed an intensive research in this field (Akselrod et al., 1981; Pagani et al., 1986; Malliani et al., 1991; Malliani, 2000) that has become a florid arena for new findings, interpretations and debates. By now, on the basis of the most relevant observations that appear widely accepted, it is possible to delineate a rather effective conceptual framework which strongly supports the possibility of transforming this methodology into a practical and common preclinical and clinical tool for the study of cardiovascular neural regulation (Malliani et al., 1991; Malliani, 2000).

1. Conceptual background

The neural regulation of cardiac function is mainly determined, in its efferent side, by the interaction of sympathetic and vagal mechanisms (Fig. 1). In most physiological conditions, the activation of either sympathetic or vagal outflow is accompanied by the inhibition of the other suggesting the concept of sympathovagal balance, as a horizontal beam pivoted at its center (Malliani, 2000). This reciprocal organization, alluding to a synergistic design, seems instrumental to the fact that sympathetic excitation and simultaneous vagal inhibition, or vice versa, are both presumed to contribute to the increase or decrease of cardiac performance required for various behaviors. The balance oscillates from states of quiet, when homeostatic negative feedback reflexes predominate, to states of excitation, such as those due to emotion or physical exercise, when baroreflex mechanisms are strongly attenuated and central excitatory mechanisms, possibly reinforced by peripheral positive feedback reflexes, are instrumental to the enhanced cardiovascular performance (Malliani et al., 1991; Zucker, 1996; Legramante et al., 1999; Malliani, 2000).

It has been amply demonstrated that the state of sympathovagal balance can be broadly assessed by quantifying in the frequency domain cardiovascular rhythmicity and, in particular, that its blunted responsiveness to an excitatory stimulus characterizes the most various pathophysiological states. The concept of *sympathovagal balance* intends to be neither a simple paradigm nor the proposal that its operation is linear throughout its range. It also does not suggest that the sympathetic and vagal outflows are both homogeneous functional entities. However, given all these limitations, the concept has helped in extracting information that otherwise would have remained embedded in the original records. Thus, the main purpose of this article is to indicate how spectral methodology should be used in order to underscore abnormal neural mechanisms that otherwise may remain undetected. In addition, prognostic markers can be obtained, the clinical relevance of which is increasingly recognized.

2. Methodology

Variable phenomena such as heart period or arterial blood pressure can be described not only as a function of time (i.e. in the *time domain*), but also the sum of elementary oscillatory components, defined by their frequency and amplitude (i.e. in the *frequency domain*).

The analysis of HRV is usually performed off-line with computerized techniques. It is impossible, in this context, to

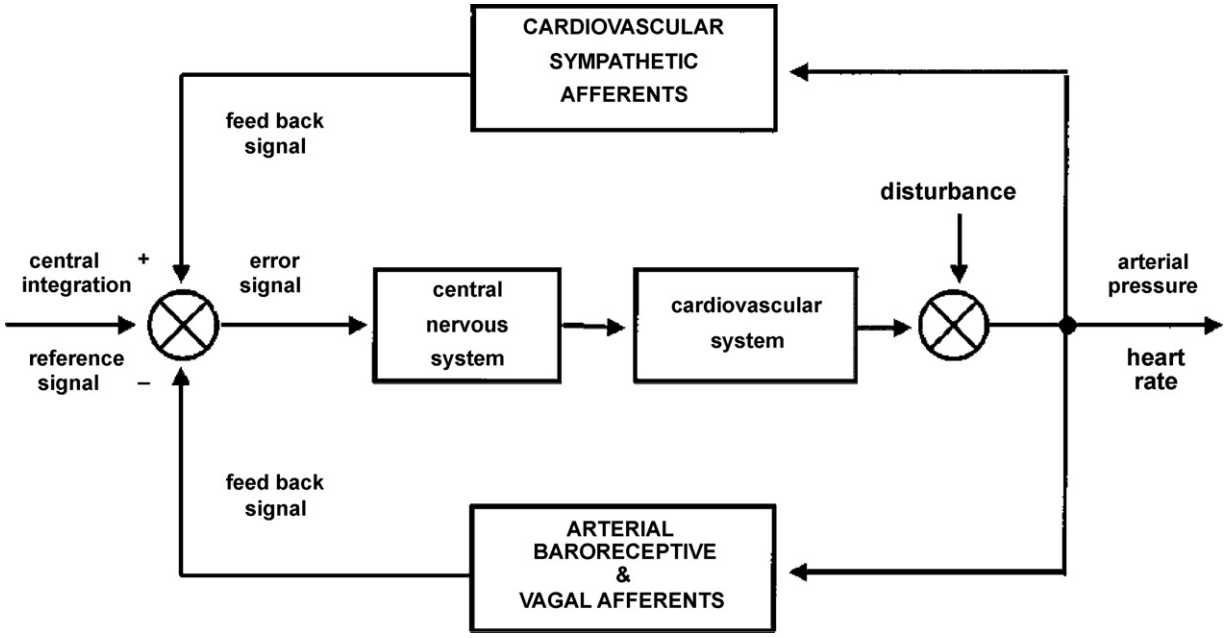

Fig. 1. Representation of opposing feedback mechanisms that, in addition to central integration, subserve the neural control of the cardiovascular system.

address the various approaches for which we refer to previous articles (Pagani et al., 1986; Malliani et al., 1991; Task Force on HRV 1996). Here it may suffice to say that the *time domain* analysis, initially based on simple statistics, such as the standard deviation (S.D.) of RR interval variation, does not provide any information on the time structure or periodicity of the data. Conversely, with the *frequency domain* analysis, the signal series can be represented by the sum of sinusoidal components of different amplitude, frequency and phase values. Various algorithms can be used to evaluate the oscillatory components (Task Force on HRV 1996).

The majority of investigators have either relied on fast Fourier transform (FFT) algorithm or on autoregressive (AR) modeling. The FFT is easier to implement and is usually employed with *a priori* selection of the number and frequency range of bands of interest (Task Force on HRV 1996). Conversely, AR algorithms can decompose the overall spectrum into single spectral components, using the residual theorem, thus providing automatically the number, central frequency, and associated power without the need for *a priori* assumptions (Task Force on HRV 1996). Furthermore AR algorithm has the additional advantage that even with short segments of data (for instance 200 cycles rather than the more usual 512 cycles) they can provide a reliable and accurate spectral estimation.

The spectral profile of human HRV contains three components, with frequencies at rest centered at 0.00 Hz (VLF = very low frequency), 0.10 Hz (LF = low frequency), and around the respiratory rate (HF = high frequency), respectively. The amplitude of LF and HF components is assessed by the area (i.e. power) of each component and, therefore, squared units are used for its absolute value. In addition, normalized units (nu) are obtained by dividing the power of a given component by the total power (from which VLF has been subtracted) and multiplying by 100 (Fig. 2).

This methodology can be applied also to other signals such as systolic arterial pressure (SAP) (Pagani et al., 1986), respiration rate (Montano et al., 1994) or nerve discharge (Montano et al., 1992; Pagani et al., 1997; Pagani and Malliani, 2000).

A recursive version permits the continuous analysis of recordings over a 24-h period. Like the HF respiratory component, LF does not have a fixed period, and its central frequency can vary from 0.04 to 0.15 Hz (Furlan et al., 1990). However, center frequency of LF (prevalent LF, PLF) seems to be quite stable, around 0.1 Hz, and its change may be related to specific modifications in sympathovagal balance, whose nature is still to be determined. Notably, PLF contains important prognostic information as it can be reported that is a potent predictor of non-sudden cardiac death in post-AMI patients (Wichterle et al., 2004; Kiviniemi et al., 2007).

In general, however, spectral methodology should be applied only to relatively stationary conditions (Task Force on HRV 1996). When time series corresponding to non-stationary states have to be analyzed, specific time-frequency domain algorithms are required such as the smoothed pseudo-Wigner-Ville transformation (Jasson et al., 1997) or a time-variant autoregressive analysis (Furlan et al., 1998), the technical characteristics of which are beyond the scope of this article.

3. Practical aspects

In principle, spectral analysis, used to detect possible rhythmicities hidden in the signal, necessitates stationary conditions that, in strict terms, are unknown to biology.

A crucial procedure to be simultaneously performed is to obtain some measurement of respiratory rate in order to assess its synchronization with HF component (Malliani et al., 1991; Montano et al., 1994) (Fig. 2). Conversely, when the frequency of respiration decreases enough to approach the LF rhythm in such a way that HF and LF merge into one single more powerful oscillation, the so-called *entrainment*, the LF component cannot be interpreted any longer according to the criteria that justify a clinical use. This must be taken into account also in controlled laboratory conditions, since simple tasks such as mental arithmetic test or free talking may greatly affect and shift respiration within the LF band (Bernardi et al., 2000).

Controlled breathing, such as the one following a metronome, can be used in order to maintain the frequency of breathing above the LF range: however one should consider that this is not physiological breathing and that, by increasing the HF synchronization, it can shift the sympathovagal balance towards vagal predominance (Pagani et al., 1986). Alternatively, when the emotional engagement to follow the metronome may become prevalent, the same maneuver may produce a sympathetic excitation.

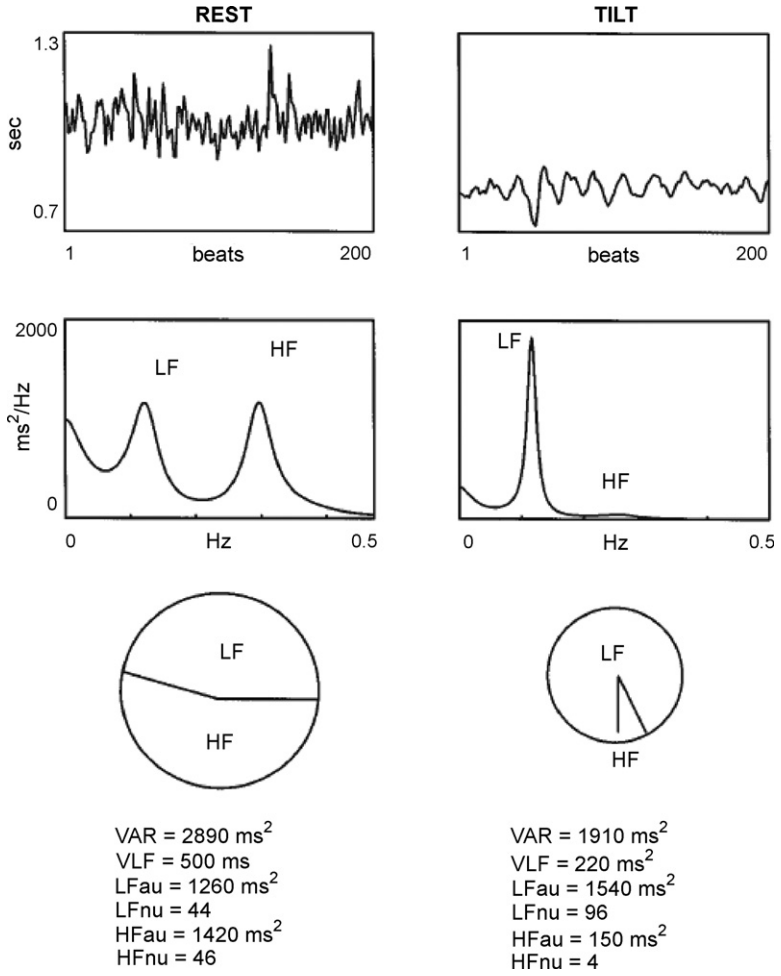

Fig. 2. Spectral analysis of HRV in a young subject at rest and during 90° tilt. The RR interval time series (i.e. tachograms) are illustrated in the top panels. The middle panels contain the autospectra which indicate the presence of two major components (LF = low frequency; HF = high frequency). During tilt, the LF component becomes largely predominant. In this example the total power (i.e. variance) is markedly reduced during tilt and consequently LF and HF powers are both decreased when expressed in absolute units (LFau, HFau). The use of normalized units (nu) clearly indicates the altered relation between LF and HF during tilt as represented by the pie charts which show the relative distribution together with the absolute power of the two components represented by the area. VAR = variance; VLF = very low frequency.

A final methodological consideration is of fundamental importance. Passive tilt or, more simply, standing up is invariably accompanied in healthy adolescents or adults by a relative increase in LF and decrease in HF component of RR variability (Fig. 3). However, in order to appreciate also numerically the shift of power evident from the simple inspection of spectral profile, it is necessary to use the normalized units (nu) or the LF/HF ratio (Montano et al., 1994; Zaza and Lombardi, 2001) that provide values independent of variance (or total power). This procedure had stimulated strong debates in the literature, as the calculation of normalized units has also been considered a mathematical manipulation (Eckberg, 1997). Conversely we have affirmed that this is a simple way to extract part of the information embedded in a frequency code (Malliani et al., 1998; Pagani and Malliani, 2000). In SAP variability spectral analysis, the LF component, marker of sympathetic vasomotor modulation (Pagani et al., 1986), can be instead expressed exclusively in absolute units as SAP variance does not decrease during sympathetic excitations.

4. Physiological studies

The core hypothesis of the proposed approach was that the sympathovagal balance can, on the whole, be explored in the frequency domain. Quite numerous data support the assumptions that (1) the respiratory rhythm of heart period variability, defined as HF spectral component, is a marker o vagal modulation (Akselrod et al., 1981; Pagani et al., 1986; Malliani et al., 1991; Montano et al., 1994); (2) the rhythm defined as LF, present in RR and SAP variabilities and corresponding to vasomotor waves (Mayer, 1876) is a marker of sympathetic modulation; and (3) in physiological conditions, a reciprocal relation exists between the relative amplitude of these two rhythms that is similar to that characterizing the sympathovagal balance (Malliani, 2000).

The above statements are based on numerous experimental studies, some of which are briefly summarized here.

In one study (Montano et al., 1994) we investigated the capability of power spectrum analysis of HRV to assess the changes in sympatho-vagal balance during graded orthostatic tilt. A strong correlation was found between the degree of tilt incline and LF and HF expressed in nu ($\cong$0.78 and $-$0.70, $p < 0.001$, respectively).

Subsequently, in a study carried out on 350 healthy subjects (Malliani et al., 1997), in which data analysis was performed blind, it was found that the information content of three variables (RR, LFnu, HFnu) was sufficient to recognize the individual spectral profiles related to posture, either supine or upright, in about 85% of 175 subjects used as *training set*, and to forecast the posture also in about 85% of the remaining 175 subjects used as *test set*. This study, by applying a complex forecasting linear method, demonstrated

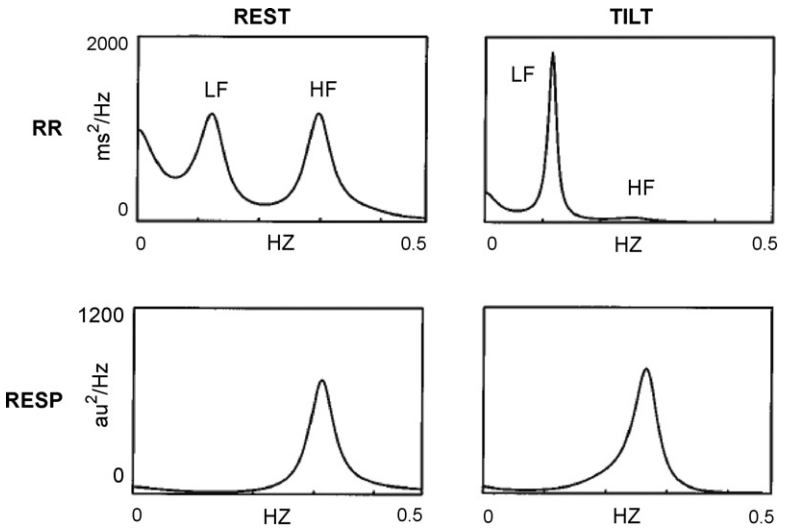

Fig. 3. Same case of Fig. 1. Spectral analysis is displayed of RR variability (upper panels) and of respiration rate (lower panel). Synchronization between HF components of RR and respiration rate variability is quite evident.

the information content of the normalization procedure and of the sympatho-vagal balance hypothesis.

In addition, a high coherence was found between LF and HF present in RR and SAP variability spectra and similar components present in the discharge variability of cardiac sympathetic fibers (Montano et al., 1992, 2000) or muscle sympathetic nerve activity (MSNA) (Pagani et al., 1997; Furlan et al., 2000). Accordingly, during sympathetic activation induced by tilt (Furlan et al., 2000) or by the vasodilatory effects of nitroprusside (Pagani et al., 1997), a similar highly coherent oscillatory pattern, consisting in an increased LF rhythmicity, characterized MSNA, RR and SAP variability.

Finally, in healthy human subjects (Hayano et al., 1991; Montano et al., 1998) high doses of atropine, leading to a muscarinic blockade, abolished the HF component of RR variability, as already described in dogs (Akselrod et al., 1981; Rimoldi et al., 1990), and, as a consequence, the remaining power in RR variability was restricted to the VLF and LF regions. However the HF component of MSNA was enhanced underscoring the central vagotonic effect of atropine. Hence the detection of LF and HF rhythms in the autonomic neural outflows (Pagani and Malliani, 2000) offers a window on the central pattern organization in which the prevalence of LF component seems to reflect a state of excitation and a prevalence of HF a state of quiet (Pagani et al., 1997; Montano et al., 1998). Similarly, Cogliati et al. (2004) described that the intravenous administration of atenolol is associated with the expected bradycardia and shift of the sympathovagal balance towards a parasympathetic predominance in the HRV (Cogliati et al., 2004). However, MSNA was surprisingly increased by atenolol while the spectral profiles was similar to that of HRV, showing a predominance of the HF component and not of the LF as expected due to the increased neural activity. Coherence between respiration and HF oscillation of MSNA was significantly increased, thus suggesting that atenolol might increase the respiratory coupling, maybe via the brainstem, as recently suggested (Gourine et al., 2008).

Results from the study by Cogliati et al. (2004) stimulate at least to major consideration: one is that the oscillatory pattern and the average gross neural activity convey complimentary, and not redundant information; the second, and even more important, is that the central repiratory-sympathetic coupling, whose mechanisms are still largely unknown, seems to play a crucial role in protecting target organs by detrimental effect of excessive sympathetic excitation. This inhibitory mechanism could be altered in cardiovascular disease and provide a target for therapeutical interventions. Moreover, the neural oscillatory pattern was detected at the level of the cardiac sympathetic outflow (Montano et al., 1992), of the spinal sympathetic network (Montano et al., 2000), of single brainstem neurons (Montano et al., 1996) and also of thalamic somatosensory neurons (Massimini et al., 2000), suggesting that it represents a widespread neural code.

Autonomic changes induced by mental stress (Lucini et al., 2005, 2007) and physical activity can also be easily investigated by mean of spectral analysis of HRV. Thus, it has been possible to evaluate the changes in neural control accompanying different levels of exercise (Furlan et al., 1993) and hence the contribution of metaboreflexes (Piepoli et al., 1995; Iellamo et al., 1999) to cardiovascular adjustment.

In conclusion, this methodology, without artificially separating the influence of either sympathetic or vagal outflows, can reveal with unprecedented efficacy some aspects of their interaction which is at the basis of neural regulation.

5. Physical exercise: the complex simplicity of cardiovascular neural control

Spectral analysis of short-term HRV has been shown to be capable to detect and track the complex adaptational changes in sympatho-vagal balance attending regular physical training, a core component of primary and secondary cardiovascular prevention and of an optimal care management in cardiovascular diseases. This has been demonstrated from patients to high-performance world class athletes, implying relevant clinical information and practical applications.

In hypertensive patients who feature clear signs of elevated sympathetic activity (Mancia et al., 1999; Esler et al., 2006), moderate exercise training decreased the LF component of HRV while simultaneously increasing the HF component, concomitantly with an increased arterial baroreflex gain, to indicate an overall improvement in cardiac vagal control and a reduced sympathetic activation (Pagani et al., 1988a,b). The same effects on HRV have consistently been reported in patients with ischemic heart disease (Lucini et al., 2002b; Malfatto et al., 1998; Iellamo et al., 2000) and chronic heart failure (Coats et al., 1992; Piepoli et al., 1996) in which restoring a better sympatho-vagal balance in

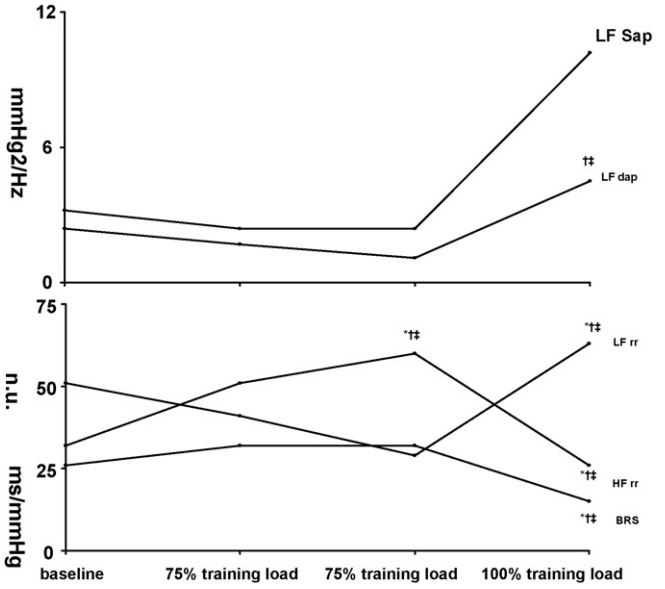

Fig. 4. Changes in spectral parameters with increasing training load. Sap, systolic arterial pressure; Dap, diastolic arterial pressure; RR, R–R interval; BRS, baroreflex sensitivity; LF, low-frequency component; HF, high-frequency component; nu, normalized units.

a direction towards an enhanced parasympathetic and a decreased sympathetic cardiac control is of paramount prognostic relevance. The mechanisms responsible for this shift in parasympathetic activity are not clear. However it could be hypothesized that constant exercise may increase the central coupling between respiration and autonomic outflows, increasing the inhibitory effect of respiration on sympathetic activity.

Spectral analysis of HRV did find application also in sports medicine, to obtain information on adaptational changes in cardiovascular neural regulation in response to very intensive exercise training, such that experienced by world class athletes, as well as non-invasive indicators of their training status (Iellamo et al., 2002).

In this context, Iellamo et al. (2002) provided evidence that, at variance with what occurs in response to moderate exercise training such that currently prescribed for prevention purposes, strenuous exercise training in high-performance world class athletes is associated with a switch from vagal to sympathetic predominance in autonomic cardiovascular modulation, as indicated by the marked increase in the LF component of both HR and blood pressure variability and the decrease in the HF component of HRV and BRS on going from sub-maximal to maximal training load (Fig. 4). These findings, subsequently confirmed by the same group (Iellamo et al., 2004), led to the hypothesis that the sympathetic activation represents the neurovegetative counterpart of an optimal training status, as suggested by the excellent sports results obtained by the athletes at nearing high-level competitions and to the conclusion that spectral analysis of HRV could be employed as a simple and valuable tool to assess the time course of neurovegetative adaptations to competitive training, further expanding the use of this new approach for practical purposes.

6. The clinical use

6.1. General considerations

In spite of an always more diffuse use of spectral methodology and of a Task Force attempt (1996), true standard values (Fagard et al., 1999) corresponding to normal or abnormal conditions are not yet available. This is not surprising and, in a sense, is only partly detrimental. Indeed, what is to be measured is the dynamic equilibrium of the sympathovagal balance and the range of its excursions that can be extremely wide. Quite obviously this complex ensemble of properties is affected by a great variety of factors such as age, gender, style of life, physical fitness, and, in addition, by very different pathophysiological conditions. Thus a wide range of values is to be expected. Nonetheless in most of the clinical studies performed with an adequate methodology during the last 15 years, the feature common to numerous and different pathophysiological conditions consists in a reduced responsiveness of neural modulation to an excitatory stimulus, such as passive tilt or active standing. However, the concept of *sympathovagal balance* intends to be neither a simple paradigm nor the proposal that its operation is linear throughout its range. It also does not suggest that the sympathetic and vagal outflows are both homogeneous functional entities. However, given all these limitations, the concept has helped in extracting an information that otherwise would have remained embedded in the original records.

The following are some of the abnormal conditions that have been investigated with spectral methodology. It is out of the scope of this article to attempt a complete summary.

6.2. Essential arterial hypertension

Since the first study (Guzzetti et al., 1988) it was found that a slight but significant positive correlation was present at rest between the LF nu component and the severity of hypertension as expressed by diastolic blood pressure levels ($r = 0.30$, $p < 0.01$). Moreover it was also found that passive tilt produced smaller increases in LF nu in hypertensive patients than in normotensive controls (ΔLF = 6.3 ± 2.7 versus 26 ± 2.7 nu). The altered effects of tilt were significantly correlated with the degree of the hypertensive state, suggesting a continuum distribution ($\cong -0.38$, $p < 0.001$). These findings are likely to be influenced by numerous factors among which the stage of hypertension, the gender, the previous pharmacological treatment. Such a reduced sympathovagal responsiveness to tilt or to an upright position has been confirmed by subsequent studies (Radaelli et al., 1994; Yo et al., 1994; Huikuri et al., 1996).

Similarly it was also reported (Guzzetti et al., 1991a), by means of 24-h Holter recordings, that the normal circadian rhythmicity of LF nu (Furlan et al., 1990) was undiscernible in hypertensive patients (ΔLF in normal subjects = 17 ± 4 nu; in hypertensive patients = 1 ± 4 nu, $p < 0.01$). This finding, that has also been confirmed (Chakko et al., 1993; Guzzetti et al., 1994a,b), indicates another possibility of assessing the spontaneous fluctuations of the autonomic modulation. Moreover, quite recently, Lucini et al. (2002a,b), studying prehypertensive subjects demonstrated that RR-variability parameters might prove useful to assess, with longitudinal studies, the mechanistic role of autonomic impairment in the increased risk of prehypertensive conditions. It is important to note that there is no correlation between increase in LF component and severity of hypertension. A possible hypothesis is that while sympathetic hyperactivation play a fundamental etiopathogenic role at the beginning of the hypertensive state, subsequently other structural and functional mechanisms contribute to maintain the high levels of arterial pressure.

6.3. Myocardial infarction

Important research in this area has attempted to obtain prognostic indexes in patients after myocardial infarction, using time domain measures such as SD (Kleiger et al., 1987), FFT algorithm applied to a single 24-h power spectrum (Bigger et al.,

1992), or baroreflex sensitivity and time domain analysis of HRV (La Rovere et al., 1998).

An abnormal spectral profile has been reported in patients in the early phase of myocardial infarction (Lombardi et al., 1996a,b). A shift towards sympathetic predominance was present in the case of anterior infarction. Moreover, even in patients with inferior infarctions, a condition that should be associated with a clear vagal predominance (Pantridge et al., 1981), this could not be detected. This may indicate that parasympathetic overactivity associated with inferior myocardial infarctions may be short-lasting and, simultaneously, this observation may open the door to the early use of β-blockers after an acute myocardial infarction independently from its localization.

A sympathetic predominance was consistently found also 2 weeks after myocardial infarction and at this time a tilting maneuver was incapable of further increasing the LF component (Lombardi et al., 1987). On the other hand, a disappearance of an LF component from RR variability power spectrum suggests an unfavorable outcome (Lombardi et al., 1996a,b): accordingly it was also found that on the second day after myocardial infarction the LF/HF ratio was significantly lower in patients who died within 30 days (Singh et al., 1996).

6.4. Transient myocardial ischemia

The assessment of autonomic profile would be of paramount importance for our understanding of the complexity and of the complications of this cardiac event (Malliani, 2000). However while a satisfactory spectral profile is easy to obtain in experimental conditions, e.g. in conscious dogs (Rimoldi et al., 1990), the difficulties arising in human pathophysiological studies are quite numerous (Lanza et al., 1996). Due to the presence of numerous transients, specific algorithms are often necessary. A stimulating study by Joho et al. (2002), using a *wavelet analysis* of RR variability, i.e. a time-frequency approach, has however proven its feasibility. These authors found clear signs of sympathetic excitation (273%) during myocardial ischemia produced by balloon coronary occlusion. Conversely, in patients with cardiac denervation, assessed with scintigraphy, the sympathetic excitation was markedly blunted (34%).

6.5. Congestive heart failure

In controlled laboratory conditions, patients with congestive heart failure were studied (Guzzetti et al., 1995) and classified according to their New York Heart Association functional class. In NYHA class II patients, LF nu of RR variability was greater than in control subjects, but remained unchanged during tilt. Patients in class III presented, at rest, a pseudonormalization of the spectral pattern expressed in normalized units, but not in absolute units that were reduced as consequence of the concomitant decrease in variance. Finally patients in class IV were characterized by a very small LF component which was almost absent during tilting. Interestingly in a later study (Van de Borne et al., 1997) it was observed that LF component of MSNA was also absent in patients with severe heart failure, suggesting that part of the alteration in the oscillatory pattern might also depend on central autonomic mechanisms (Fig. 5).

In addition, patients who present a reduced or undetectable LF component in RR (Mortara et al., 1994; Guzzetti et al., 1995; Galinier et al., 2000) or MSNA (Van de Borne et al., 1997) variability seem to have the worst clinical state and prognosis. Later, a longitudinal study on heart failure patients by La Rovere et al. (2003) confirmed that short term HRV changes (namely a reduction in LF values $<13\ ms^2$) was able to strongly predict mortality in these patients.

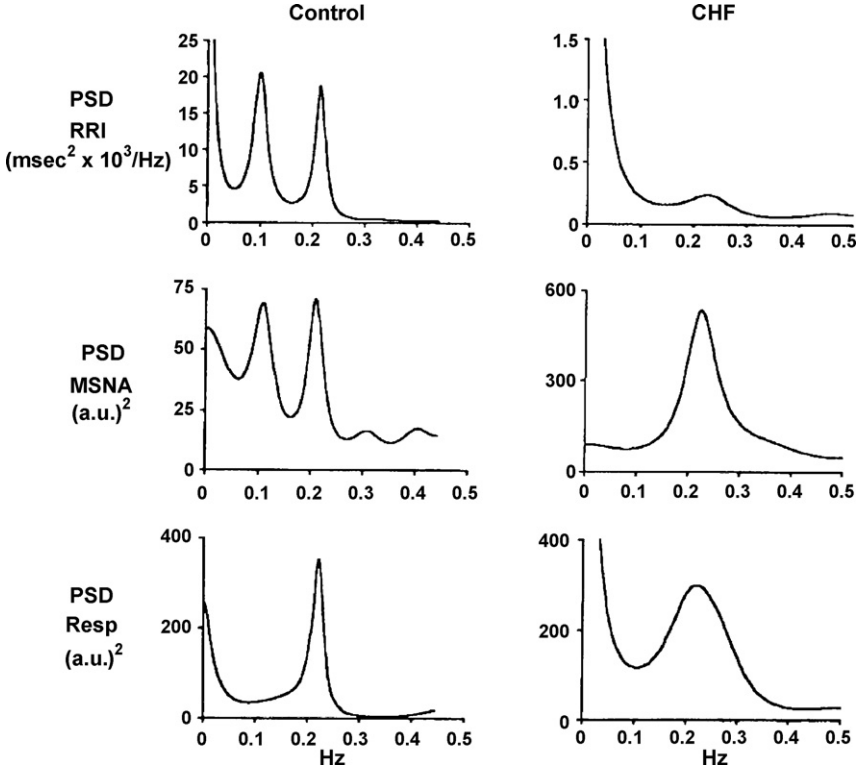

Fig. 5. Spectral analysis of RR interval (upper panels), muscle sympathetic nerve activity (MSNA; middle panels) and respiration (lower panels) in a control subject and in a patient with severe heart failure (CHF). Notice that the LF component, notwithstanding the well-known increase in sympathetic activity present in CHF, was absent in spectral profiles of both MSNA and RRI (Reprinted with permission from Ref. 52).

6.6. Other conditions

They are quite numerous and include atrial fibrillation (Lombardi et al., 2001), cardiac transplantation (Bernardi et al., 1989; Guzzetti et al., 1996; Van de Borne et al., 1999, 2001), Chagas' disease (Guzzetti et al., 1991b), hypertrophic cardiomyopathy (Ajiki et al., 1993), ventricular aneurysms (Dalla Vecchia et al., 1998), vaso-vagal syncope (Furlan et al., 1998), obstructive sleep apnea (Narkiewicz et al., 1998), diabetic neuropathy (Pagani et al., 1988a; Bernardi et al., 1992), ulcerative colitis (Furlan et al., 2006), various neurological alterations including spinal lesions producing tetraplegia (Guzzetti et al., 1994a,b; Koh et al., 1994; Iellamo et al., 2001) and Parkinson's disease (Barbic et al., 2007), just to mention some of them. In all these cases the use of spectral methodology has provided new information. For instance, as most recent example, Barbic et al. (2007), assessing autonomic modulation by means of HRV and BPV in patients with Parkinson's disease, were able to detect initial alterations in both cardiac and vascular sympathetic modulatory activity in these patients, revealed by spectral modifications to a gravitational stimulus. The early recognition of sympathetic abnormalities might result in timely therapeutic intervention.

7. Future perspectives

Linear analysis of HRV can therefore furnish non-invasive indexes of cardiac autonomic modulation in the presence of rhythmic variability. On the other hand, in settings characterized by rapid and non-repetitive changes, like the periods preceding cardiac events, or in conditions characterized by co-activation of the two branches of the ANS, non-invasive standard measurements of these control systems give less reliable information than during more stable periods (Porta et al., 2000).

We have recently proposed a new non-linear tool based on symbolic analysis of 3-beats sequences to distinguish sympathetic and parasympathetic cardiac modulation (Guzzetti et al., 2005; Porta et al., 2007a,b). The symbolic analysis method adopted consists mainly of the transformation of a time series (RR intervals) into short patterns (3 beats long), their classification, and the evaluation of their rates of occurrence. This type of non-linear analysis takes into account short patterns distributed in the RR series and would seem appropriate for studying the short HRV instabilities that precede sudden cardiac events such as major arrhythmias (Guzzetti et al., 2005) or conditions associated with an extremely altered HRV, such as heart failure (Porta et al., 2007a,b; Cysarz et al., 2007).

Although previous studies proposed other non-linear algorithms to stratify arrhythmic risk in cardiac patients (Makikallio et al., 1999; Weiss et al., 1999; Huikuri et al., 2003) our method provides new interpretative insights into the role played by autonomic modulation in triggering major arrhythmic events.

8. Conclusions

Frequency domain analysis of heart rate variability is a physiological and clinical tool having the merit of being totally non-invasive and of providing a global, although indirect, evaluation of autonomic modulation of heart period. In several instances the assessment of sympathovagal balance obtained with this procedure seems to reflect an even more general equilibrium ranging from quiet to excitation.

This approach, together with other methods based on non-linear dynamics, pertains to the perspective of capturing the whole information content embedded in the time series of biological signals.

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