Current perspective
Heart rate variability as a clinical tool

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Power spectrum analysis of cardiovascular signal variability, and in particular of the RR period (heart rate variability), is a widely used procedure for the investigation of autonomic cardiovascular control and/or target function impairment. However, a correct methodology is essential to extract the information embedded in the frequency domain. This article has the main purpose of proposing a still wider clinical use of the spectral methodology. Indeed, with this procedure the state of the sympathovagal balance modulating the sinus node pacemaker activity can be quantified in a variety of physiological and pathophysiological conditions. Changes in the 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.

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More than 30 years have elapsed since the pioneering studies by Sayers and his associates[1,2] introduced a computationally efficient analysis of heart rate variability (HRV). The last two decades have witnessed an intensive research in this field[3-5] that has become a florid arena for new findings, interpretations and debates. At present, 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 new methodology into a practical and common clinical tool for the study of cardiovascular neural regulation[5,6].

The growth of such a framework has been repetitively summarized during the last years[5-7] and, quite recently, also in this Journal[8]. In this context, we shall only briefly outline the principles essential to the proposal of a wide clinical application.

Conceptual background

The neural regulation of cardiac function is mainly determined, on its efferent side, by the interaction of sympathetic and vagal mechanisms. In most physiological conditions, the activation of either the 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[5-8]. 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 in cardiac performance required for the various behaviors. The balance oscillates from states of quiescence, 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[5-9].

It has been amply demonstrated that the state of sympathovagal balance can be broadly assessed by quantifying, in the frequency domain, the cardiovascular rhythmicity[4-8] and, in particular, that its blunted responsiveness to an excitatory stimulus characterizes highly variable pathophysiological states[5,6]. The purpose of this article is to indicate how spectral methodology should be used in order to highlight abnormal neural mechanisms that may otherwise remain undetected. In addition, prognostic markers, the clinical relevance of which is being increasingly recognized, can be obtained.

Methodology

Variable phenomena such as the heart period or arterial blood pressure can be described not only as a function of time (i.e. in the *time domain*), but also as 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 address the various approaches for which we refer to previous articles[4-7]. Here, it may suffice to say that the *time domain* analysis, initially based on simple statistics such as the standard deviation 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 the sinusoidal components of different amplitude, frequency and phase values. Various algorithms can be used to evaluate the oscillatory components[10].

The majority of investigators have either relied on the fast Fourier transform algorithm or on autoregressive modeling. The fast Fourier transform is easier to implement and is usually employed with *a priori* selection of the number and frequency range of bands of interest[3,10]. Conversely, autoregressive algorithms can decompose the overall spectrum into single spectral components using the residual theorem, thus automatically providing the number, central frequency, and associated power without the need for *a priori* assumptions[4-6,10]. Furthermore, autoregressive algorithms have 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 spectrum shown in figure 1 contains three components, with frequencies at rest centered at 0.00 Hz (very low frequency-VLF, not written in the figure), 0.11 Hz (low frequency-LF), and 0.29 Hz (high frequency-HF), respectively. The study of the VLF component, which might contain relevant information, requires spe-

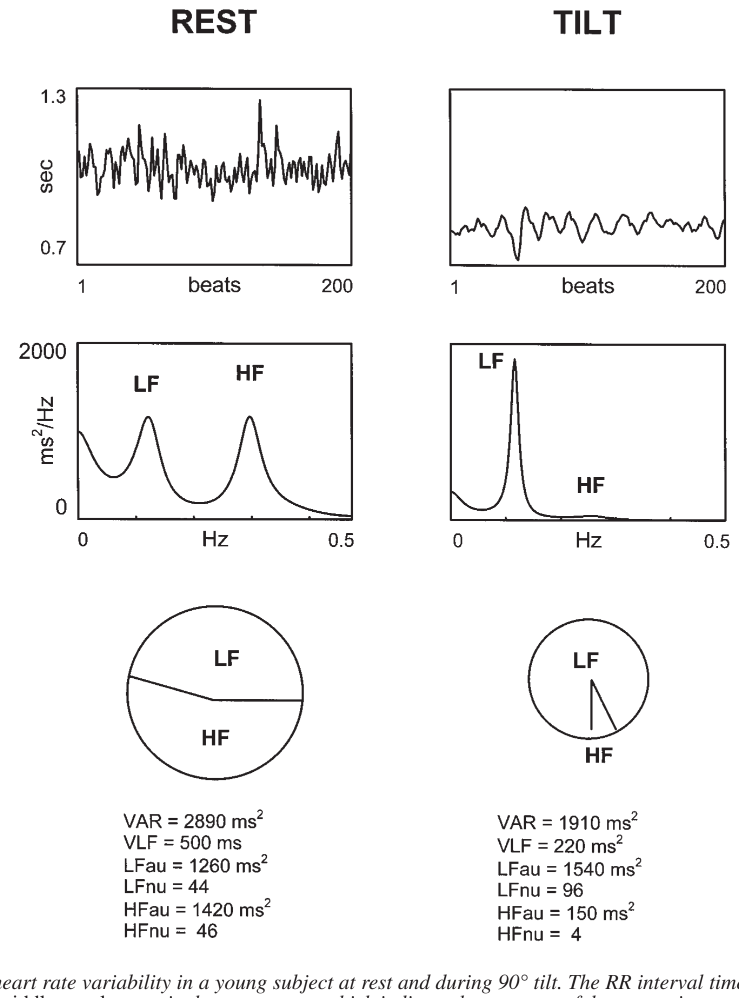

Figure 1. *Spectral analysis of heart rate variability in a young subject at rest and during 90° tilt. The RR interval time series (i.e., tachograms) are illustrated in the* top panels. *The* middle panels *contain the autospectra which indicate the presence of the two major components (low frequency-LF, high frequency-HF). During tilt, the LF component becomes largely predominant. In this example the total power (i.e. variance-VAR) is markedly reduced during tilt and consequently the LF component is only slightly increased when expressed in absolute units (LFau). 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. VLF = very low frequency.*

cific algorithms and long periods of uninterrupted data and is thus not addressed in the present article.

LF and HF components are evaluated in terms of frequency (hertz in the figures) and amplitude. This amplitude is assessed by the area (i.e. power) of each component and, therefore, square units are used for its absolute value (square milliseconds in figure 1). In addition, normalized units (nu) are obtained by dividing the power of a given component by the total power (from which the VLF component has been subtracted) and multiplying by 100 (Fig. 1).

This methodology can also be applied to other signals such as systolic arterial pressure (SAP)[4], respiration rate[4] (Fig. 2) or nerve discharge[5,6,10,11].

A recursive version permits the continuous analysis of recordings over a 24-hour period. Just as the HF respiratory component, the LF component does not have a fixed period, and its central frequency can vary considerably (from 0.04 to 0.15 Hz)[12].

In general, however, spectral methodology should be applied only to relatively stationary conditions[3-6,10]. When time series corresponding to non stationary states have to be analyzed, specific time-frequency domain algorithms such as the smoothed pseudo-Wigner-Ville transformation[13] or a time-variant autoregressive analysis[14] are required. The technical characteristics of these are beyond the scope of this article.

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. Thus, a practical compromise has to be found between the length of the event series (200-500 cycles) and theoretical mathematical requirements[4,5], being shorter segments of data more likely to be stationary.

A crucial procedure, that must be simultaneously performed, is to obtain some measurement of the respiratory rate in order to assess its synchronization with the HF component[4,5,15] (Fig. 2). Conversely, when the frequency of respiration decreases enough to approach the LF rhythm in such a way that the HF and LF components 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 its clinical use[5,6]. This must be taken into account also in controlled laboratory conditions, since simple tasks such as the mental arithmetic test or free talking may greatly affect and shift respiration within the LF band[16].

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[4-6]. Alternatively, when the emotional engagement in following the metronome becomes prevalent, the same maneuver may produce sympathetic excitation.

A final methodological consideration is of fundamental importance. In healthy adolescents or adults, passive tilt or, more simply, standing up is invariably accompanied by a relative increase in the LF component and a decrease in the HF component of RR variability. However, in order to appreciate also numerically the shift of power well evident by simply inspecting the spectral profile, it is necessary to use nu or the LF/HF ratio that provide values that are independent of variance (or total power). In the example shown in figure 1 it is quite clear that during tilt the LF component is only slightly increased in its absolute value, due to the decrease in variance (a fact that may even cause a negative delta in the absolute value of the LF compo-

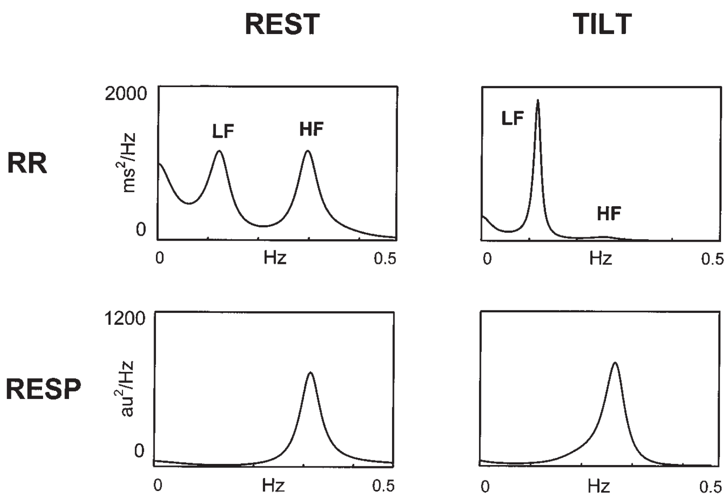

Figure 2. *Same case as figure 1. Spectral analyses of the RR variability* (upper panels) *and of the respiration rate* (lower panels) *are displayed. Synchronization between the high frequency (HF) components of the RR and respiration rate variabilities is quite evident. LF = low frequency.*

nent), but is markedly increased in its relative value (nu). This procedure has stimulated strong debates in the literature, as the calculation of nu has also been considered a mathematical manipulation[17]. Conversely, we have affirmed that this is a simple way of extracting part of the information embedded in a frequency code[11,18]. In SAP variability spectral analysis, the LF component, a marker of sympathetic vasomotor modulation[4-6], can be instead exclusively expressed in absolute units as SAP variance does not decrease during sympathetic excitation.

Physiological studies

The core hypothesis of the proposed approach is 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 the HF spectral component, is a marker of vagal modulation[3-8,10]; 2) the rhythm defined as LF, present in RR and SAP variabilities and corresponding to vasomotor waves[19], is a marker of sympathetic modulation[4-8,10]; and 3) a reciprocal relation that is similar to that characterizing the sympathovagal balance[4-8] exists between the relative amplitude of these two rhythms.

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

In one study[15] we investigated the capability of power spectrum analysis of HRV to assess the changes in the sympathovagal balance during graded orthostatic tilt. A strong correlation was found between the degree of tilt inclination and the LF and HF components expressed in nu (~ = 0.78 and -0.70, $p < 0.001$, respectively).

Subsequently, in a study including 350 healthy subjects[20], 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 the training set, and to forecast the posture also in about 85% of the remaining 175 subjects used as the test set. This study, by applying a complex forecasting linear method, demonstrated the information content of the normalization procedure and of the sympathovagal balance hypothesis.

In addition, a high coherence was found between the LF and HF components present in RR and SAP variability spectra and similar components present in the discharge variability of cardiac[21,22] or muscle sympathetic nerve activity (MSNA)[23,24]. Accordingly, during sympathetic activation induced by tilt[24] or by the vasodilatory effects of nitroprusside[23], a similar highly coherent oscillatory pattern, consisting of an increased LF rhythmicity, characterized MSNA, RR and SAP variabilities.

Finally, in healthy human subjects[25] high doses of atropine, leading to a muscarinic blockade, abolished the HF component of RR variability, as already described[3,26], and, as a consequence, the remaining power in RR variability was restricted to the VLF and LF regions. However, the HF component of the MSNA was enhanced underscoring the central vagotonic effect of atropine. Hence, the detection of LF and HF rhythms in the autonomic neural outflows[5,11] offers a window on the central pattern organization in which the prevalence of the LF component seems to reflect a state of excitation and the prevalence of the HF component a state of quiescence[6,23].

Autonomic changes induced by mental and physical activity can also be easily investigated by means of spectral analysis of HRV. Thus, it has been possible to evaluate the changes in neural control accompanying different levels of exercise[27] and hence the contribution of metaboreflexes[28,29] to cardiovascular adjustment.

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

The clinical use

General considerations. In spite of an ever more widespread use of the spectral methodology and of a Task Force attempt[10], true standard values[30] 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 influenced by a great variety of factors such as age, gender, lifestyle, physical fitness, and, in addition, by highly variable 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 was the reduced responsiveness of neural modulation to an excitatory stimulus, such as passive tilt or active standing.

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.

Essential arterial hypertension. Since the first study[31], it was found that a slight but significant positive correlation was present at rest between the LFnu 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 the LFnu component in hypertensive patients than in normotensive controls ($\Delta LF = 6.3 \pm 2.7$ vs 26 ± 2.7 nu). The altered effects of tilt were significantly correlated with the severity of hypertension, suggesting a *continuum* distribution (~ = -0.38, $p < 0.001$). These findings are likely to be influenced by numerous factors among which the stage of hypertension, gender and previous pharmacological treatment. Such a reduced sympathovagal responsiveness to tilt or to an upright position has been confirmed by subsequent studies[32-34].

Similarly, it was also reported[35], by means of 24-hour Holter recordings, that in hypertensive patients the normal circadian rhythmicity of the LFnu component[12] was indiscernible (ΔLF in normal subjects 17 ± 4 nu; ΔLF in hypertensive patients 1 ± 4 nu, $p < 0.01$). This finding, that has also been confirmed in other studies[36,37], indicates another means of assessing the spontaneous fluctuations in autonomic modulation.

Myocardial infarction. Important research in this area has attempted to obtain prognostic indexes in patients after myocardial infarction, using time domain measures such as the standard deviation[38], the fast Fourier transform algorithm applied to a single 24-hour power spectrum[39], or the baroreflex sensitivity and time domain analysis of HRV[40].

An abnormal spectral profile has been reported in patients in the early phases of myocardial infarction[41]. A shift towards sympathetic predominance was present in case of anterior infarction. However, in patients with inferior infarctions a clear vagal predominance, as clinically described by Pantridge's team[42], could not be detected. This may indicate that parasympathetic overactivity may be short-lasting and, simultaneously, this observation may open the door to the early use of β-blockers that are usually prescribed in the absence of a true quantification of the autonomic disturbance.

A sympathetic predominance was also consistently found 2 weeks after myocardial infarction and at this time a tilting maneuver was incapable of further increasing the LF component[43]. On the other hand, the disappearance of the LF component from the RR variability power spectrum suggests an unfavorable outcome[44]: similarly, 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[45].

Transient myocardial ischemia. The assessment of the autonomic profile would be of paramount importance for our understanding of the complexity and of the complications of this cardiac event[6,46]. However, while a satisfactory spectral profile is easy to obtain in experimental conditions, e.g. in conscious dogs[26], the difficulties arising in human pathophysiological studies are quite numerous. Due to the presence of numerous transients, specific algorithms are often necessary[6]. A recent and stimulating study by Joho et al.[47] who used *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 at scintigraphy, the sympathetic excitation was markedly blunted (34%).

Sudden cardiac death. It is foreseeable that in the near future the combined use of implanted defibrillators storing the recordings before cardiac arrest and of adequate algorithms may provide a picture of the autonomic disturbances preceding the episode. Such findings may play an extremely important role in the prevention and treatment of this condition.

Congestive heart failure. In controlled laboratory conditions, patients with congestive heart failure were studied[48] and classified according to their NYHA functional class. In NYHA class II patients, the LFnu component of RR variability was greater than in control subjects, but remained unchanged during tilt. Patients in NYHA class III presented, at rest, a pseudonormalization of the spectral pattern expressed in nu, but not when expressed in absolute units that were reduced as a consequence of the concomitant decrease in variance. Finally patients in NYHA class IV were characterized by a very small LF component which was almost absent during tilting. Interestingly, in a later study it was observed that the LF component of the 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[49].

In addition, patients who present a reduced or undetectable LF component in RR[48,50,51] or MSNA[49] variability seem to have the worst clinical state and prognosis.

Other conditions. These are quite numerous and include atrial fibrillation[52], cardiac transplantation[53-56], Chagas' disease[57], hypertrophic cardiomyopathy[58], ventricular aneurysms[59], vasovagal syncope[14], obstructive sleep apnea[60], diabetic neuropathy[61,62], and various neurological alterations including spinal lesions producing tetraplegia[63,64], just to mention a few.

In all these cases the use of spectral methodology has provided new information.

Conclusions

This new clinical tool has the merits of being totally non invasive and of providing a global, although indirect, evaluation of the autonomic modulation of the heart period. In several instances the assessment of the sympathovagal balance obtained with this procedure seems to reflect an even more general equilibrium ranging from quiescence to excitation. This approach, together with other methods, pertains to the perspective of capturing the whole information content embedded in the time series of biological signals.

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