invited review

Spectrum analysis of cardiovascular time series

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Persson, Pontus B. Spectrum analysis of cardiovascular time series. *Am. J. Physiol.* 273 (*Regulatory Integrative Comp. Physiol.* 42): R1201–R1210, 1997.—The demand for noninvasive assessment of cardiovascular control parameters has promoted the use of spectrum analysis. These techniques have been applied on a broad basis; however, because of the abstract mathematical approach, spectrum analysis in physiology is still not fully accepted by some circles in the scientific community. Thus it is the goal of the following review to focus on the rationale for applying spectrum analysis in different fields of circulation research, which range from determining arterial baroreceptor reflex sensitivity to the early detection of heart allograft rejection. Within this scope, major findings regarding the physiological and pathophysiological regulation of the cardiovascular system are discussed. In addition, inherent limitations of these methods are made clear. Toward the end of this survey, a perspective is provided for the general readership.

autonomic nervous system physiology; blood pressure physiology; cardiovascular system physiopathology; heart rate physiology; fast Fourier analysis; chaos

IF SEVERAL SYSTEMS participate in an interaction, as is usually the case in physiological control systems, the resulting data series can become extremely entangled. Ever since the first measurements of arterial blood pressure (AP) by Hales (39), it has become clear that there is considerable variability around the mean blood pressure level. The organism, in general, attempts to buffer excess variability, e.g., via the arterial baroreflex. It would be misleading, however, to assume that these variations in AP are merely random noise. Oscillations may also reflect the action of cardiovascular control mechanisms, in particular, certain feedback loops. This fact formed the basis for attempting to quantify the activity of certain controllers of the cardiovascular system by power spectrum analysis.

Currently, considerable effort is put into the investigation of this complicated structure of cardiovascular regulation by the means of spectrum analysis, which is a phenomenological approach. At first, data are recorded over a certain time span, then the resulting time series is subjected to post hoc analyses, which in the end may provide information concerning the rhythmic characteristics of the underlying control network. Hence, the complex control system is considered to be a black box, and the information provided by this system's analysis occasionally only addresses the crude characterizations of the entity (harmonic oscillators and noise). This form of physiological investigation is in contrast to the general trend in physiological sciences, i.e., to focus on the single elements of control systems.

Power spectrum analysis has the benefit that it requires only an accurate measurement of an appropriate signal, which is then subjected to more or less complex analysis. Thus this technique is currently used to derive noninvasive markers for cardiovascular control. Most attention has been attributed to quantifying sympathovagal activity, determining the magnitude of neurogenic control of local circulation, and several clinical applications, including diabetic neuropathy and hypertension.

Although power spectral analysis has been widely employed for estimating sympathetic tone and vagal activity (see *Assessment of autonomic activity*), another, perhaps even more obvious, purpose for the use of this method is the regulation of AP variability by different buffering systems. By means of spectral analysis it is possible to quantitate the buffering capacity and to determine within which frequency range these buffering systems attenuate AP variability.

This review attempts to outline the most pertinent of these developments and will primarily display various purposes for employing spectrum analysis. It is beyond this scope to shed light on detailed technical features; only a brief survey is presented below, and the following sections referring to the applications of spectrum analysis can be understood without a technical introduction. Excellent reviews that provide a deeper insight into that topic are recommended for technically interested readers (44, 80).

0363-6119/97 $5.00

FAST FOURIER TRANSFORMATIONS AND AUTOREGRESSIVE METHODS

An original recording presents data in a time domain, whereas a power spectrum from this recording constitutes the frequency domain representation of a signal (Fig. 1). Power spectral techniques are among the most fundamental tools for signal processing; they describe the frequency content of a signal by providing the distribution of signal strength, which is technically referred to as power.

Most physiological recordings are contaminated by some noise; thus it is impossible to render a power spectrum without error from a finite time series. Therefore, strictly speaking, these analytic procedures provide power spectral estimates only.

There are two different approaches to obtain power spectral estimates: the discrete Fourier transform and parametric methods often referred to as autoregressive modeling (AR). On most computers, the Fourier transformation is usually implemented in the form of a fast Fourier transform (FFT) algorithm, as originally described by Cooley and Tukey more than 30 years ago (18). The spectrum resulting from the FFT includes all signal variance, regardless of whether the power occurs as a consequence of specific oscillations or if the variance represents forms of noise.

A demand for an improved frequency resolution and retention of spectral shape led to the development of AR techniques. In contrast to FFT, the AR procedures provide best-fitting models that are subsequently used for constructing a final spectrum consisting of a variable amount of peaks and a direct-current component. These techniques are referred to as parametric methods, because a standard estimation equation is fitted to the data and the resulting power spectrum is derived from the parameters of this equation.

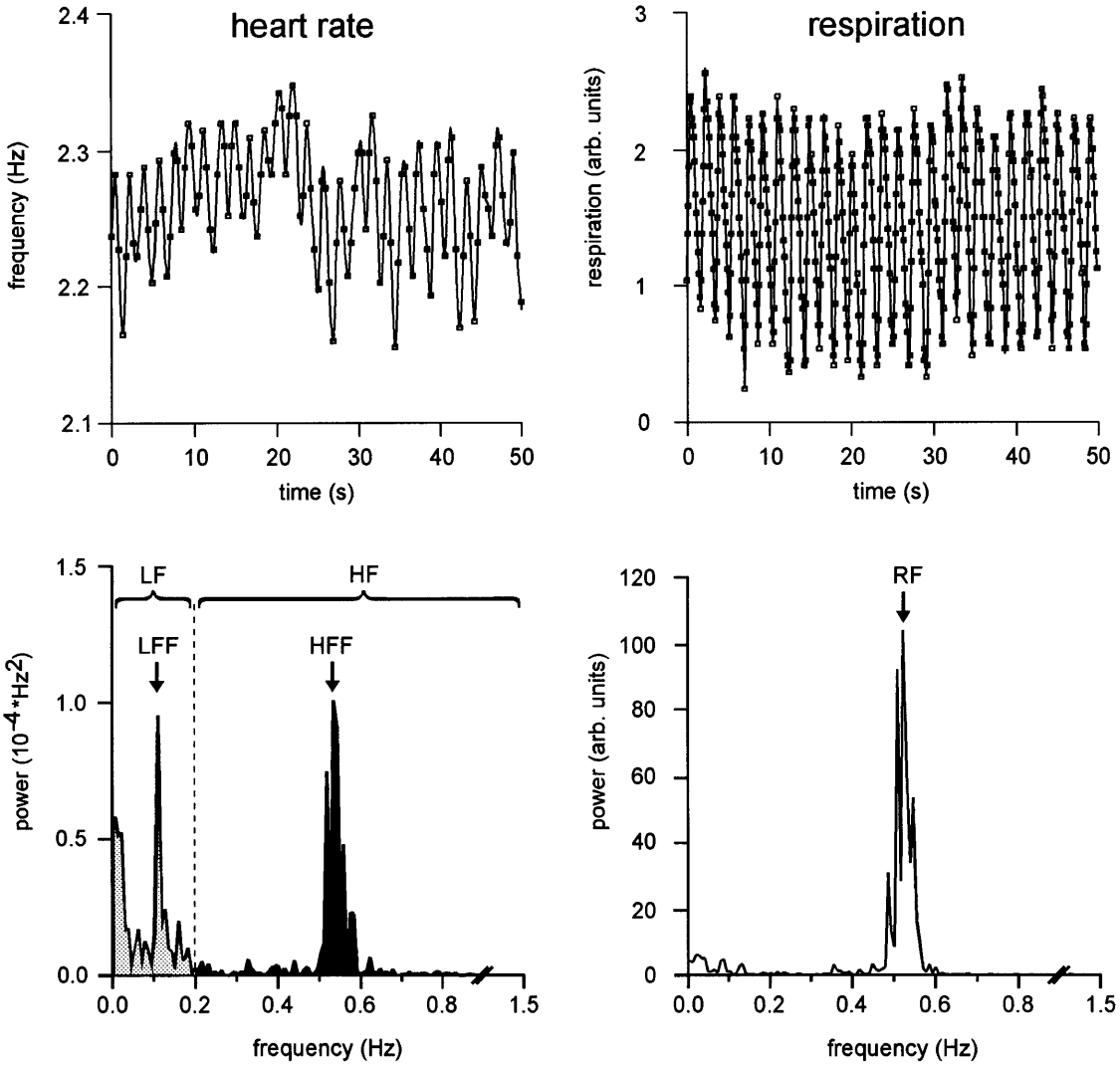

Fig. 1. Heart rate and respiration time series of an infant (*top*) and their corresponding power spectra (*bottom*). Two regions with pronounced power can be discerned, a low-frequency region (LF) with a peak frequency slightly >0.15 Hz (LFF) and a high-frequency range (HF) with maximum power >0.5 Hz (HFF). Latter peak coincides with respiratory rhythm depicted at *right*. Basic characteristics of the power spectrum are the same as for adults; however, the LF and HF ranges are at lower frequencies. [From Patzak et al. (82).]

The resulting AR and FFT spectra are often similar, especially when the order of the AR model comes close to the data set size and when an FFT spectrum is smoothed or windowed. Nevertheless, there are certain cases in which one model is superior to the other: when only a limited amount of measurements are available, the AR model bears the advantage that it still can provide a spectrum with a satisfactory frequency resolution. On the other hand, as recently pointed out by Parati et al. (80), an FFT has the benefit that it does not rely on the expertise of the investigator to determine a reasonable model order.

ANALYZING THE POTENCY AND FREQUENCY CHARACTERISTICS OF AP BUFFERING SYSTEMS

The standard deviation of blood pressure frequency distributions is the traditionally employed index for quantifying blood pressure variability (for review see Ref. 66). The use of the standard deviation as a measure for blood pressure variability is quantitative and robust, but unfortunately, the standard deviation does not allow analysis as to in which frequency domain variability occurs. One can overcome this restriction via spectrum analysis, which accordingly has been performed to quantify the effects of baroreceptor denervation (8, 10, 11, 23, 55, 86, 91, 112) (see *Arterial baroreceptor reflex sensitivity*). Recently, a novel AP buffering mechanism was discovered by fast Fourier analysis, i.e., nitric oxide (NO; see *Identifications of NO as a physiological blood pressure buffer*) (33, 57, 71, 84).

Arterial baroreceptor reflex sensitivity. Assessment of baroreflex characteristics has gained interest since the discovery that alterations in baroreflex control have a diagnostic as well as a prognostic value in several forms of disease, including myocardial infarction and heart failure (63). Two issues regarding baroreceptor function have been clarified by application of spectrum analysis: *1*) how hemodynamic variations are affected by the baroreflex (e.g., respiratory sinus arrhythmia) and the frequency characteristics of the baroreflex (8, 10, 22, 25, 51, 55–57, 86, 91, 106, 107, 112, 121) and *2*) the influence of anesthesia on the baroreflex frequency characteristics (104). There have also been various efforts regarding the quantification of baroreflex sensitivity by spectral techniques (12, 22, 49, 75, 92, 114).

Hitherto, the most commonly used approaches to estimate the baroreflex sensitivity have been either invasive, injecting vasoactive drugs (99), or technically arduous, e.g., use of a neck chamber device (24). Newer developments in this field involve blood pressure and R-R interval signal analysis in the time domain as well as in the frequency domain. The time domain procedure consists of identifying episodes of three beats in which systolic blood pressure and R-R interval either increase or decrease (49, 77, 79, 81). These sequences are assumed to mirror baroreflex activity to the heart if the correlation coefficient exceeds 0.85 and the slope of these sequences, accordingly, correspond to the sensitivity of the cardiac baroreflex. Recently, Cerutti and colleagues described a novel statistical procedure to obtain baroreflex sensitivity (11).

There are also approaches for determining baroreflex sensitivity in the frequency domain, which have been described recently (22). They all rely on the assumption that baroreceptors can only modulate heart rate within a certain frequency range. This frequency range was empirically assumed to lie between 0.25 and 0.35 Hz in the first descriptions by de Boer and colleagues (20). The coherence (which is a measure for the magnitude of agreement between two dynamic signals) of blood pressure and pulse interval signals can be taken as a quantitative measure for the range of expected baroreceptor interactions. For statistical reasons, the coherence should be >0.5.

Because the cardiac branch of the baroreflex seems to operate within a defined frequency span, the modulus in this frequency band can provide a quantitative measure for baroreflex sensitivity (47, 92, 108). The modulus, or gain, of a transfer function is comparable to the regression coefficient in the time domain. It is defined as the ratio between changes in pulse interval and changes in systolic pressure (ms/mmHg) in a defined frequency band.

Other related approaches have been made to assess baroreflex sensitivity. In these studies (75, 79), an index, referred to as "alpha coefficient," was obtained by calculating the square root of the quotient between pulse interval spectral powers (P_{PI}) and the systolic blood pressure spectral powers (P_{SBP}): $\sqrt{(P_{PI}/P_{SBP})}$

All the methods of estimating baroreflex sensitivity have been validated by comparison with more traditional methods, e.g., the "Oxford method" of injecting vasoactive substances and subsequent measurement of heart rate and the neck chamber device. They seem to agree very well; the correlation coefficient is usually very high (75, 92, 114). In other studies, the new procedures for determining baroreflex sensitivity were successfully tested by baroreceptor denervation (7, 10, 11, 79) or by unloading arterial baroreceptors by suddenly reopening the vascular bed of both lower extremities, which had been occluded for 5 min (47, 108). In the latter studies, occluding cuffs were placed around the lower extremities. The release of pressure in the occluding cuffs decreased blood pressure, which was followed by a baroreceptor-mediated increase of heart rate. Finally, a large magnitude of agreement between the sequence method in the time domain with the spectral analysis approach has been verified by Hughson et al. (49) and, over 24 h, by Parati et al. (78).

Identification of NO as a physiological blood pressure buffer. Spectrum analysis of blood pressure was recently used to identify a novel blood pressure buffering system, i.e., NO. In a series of recent papers by Elghozi and colleagues and our group (33, 57, 71, 84), it was possible to demonstrate a buffering influence of NO on arterial pressure variability. The following chain of events formed the basis for assuming that NO exerts an arterial pressure buffering action (for review see Ref. 83). An acute change of arterial pressure alters shear stress, thus modifying NO generation and release.

Subsequent vasodilatation or vasoconstriction occurs in response to the varying NO levels, which in turn readjust vascular resistance to reduce arterial pressure variability. NO acts rapidly; it diffuses out of the endothelium to the subjacent vascular smooth muscle cells, where it causes vasorelaxation within seconds. Hence, NO can affect the regulation of blood pressure more rapidly than the arterial baroreflex.

To detect this rapid action of NO on changes in arterial pressure, a power spectral analysis was performed. Indeed, as would be expected when a blood pressure buffering system is abolished, there was a marked increase in blood pressure variability. As can be seen in Fig. 2, NO buffers variability in a higher frequency range than arterial baroreceptors. After baroreceptor denervation, there is a continuous increase in the blood pressure power spectrum at lower frequencies (23, 112). Above this frequency range, power actually decreases, indicating that the baroreceptor activity itself elicits well-defined blood pressure oscillations. This frequency span coincides with the blood pressure buffering action of NO (57).

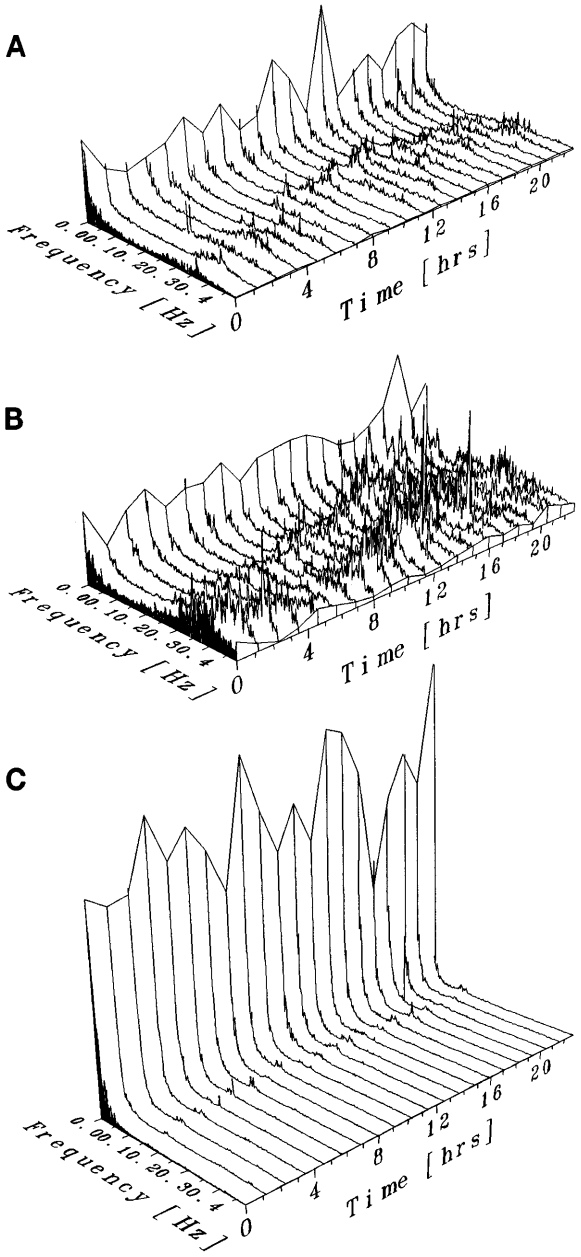

Fig. 2. Analysis of blood pressure variability during control (*A*; $n = 5$), after inhibition of NO formation (*B*; $n = 5$), and after denervation of arterial baroreceptors (*C*; $n = 5$). After NO inhibition, power in the range >0.2 Hz increases significantly, indicating that NO buffers blood pressure variability at these frequencies (*B*). Effect of baroreceptor denervation is more pronounced; however, the increase in power is limited to very slow frequency oscillations (*C*). [From Just et al. (57).]

CONTROL OF REGIONAL BLOOD FLOW

Time series analyses in the frequency domain constitute powerful tools for state-of-the-art investigations on regional blood flow regulation. The fundamental principles used are closely related to the procedures of estimating baroreflex sensitivity. In analogy to calculating the dependence of heart rate oscillations on blood pressure variability, the impact of perfusion pressure, or nervous activity, on blood flow is derived. A transfer function between renal arterial pressure and renal blood flow, for instance, provides a measure as to the extent and at which frequencies changes in pressure will alter blood flow to the kidney. Accordingly, the transfer function characterizes renal autoregulation in the frequency domain (Fig. 3; Refs. 3, 4, 13, 16, 41, 43, 45, 46, 93, 119). A low gain of the transfer function means that there is only a weak relationship between blood flow and perfusion pressure, thus indicating potent autoregulation. The gain is calculated by dividing the cross-spectral estimates by the corresponding autospectral values. The entire transfer function is then obtained by plotting each gain over the respective frequency.

A conventional autoregulation diagram plots blood flow versus perfusion pressure, which in a certain range reveals little or no pressure dependency of flow. The advantage of a frequency domain analysis of autoregulation is that the investigator obtains the exact frequency characteristics of autoregulation (44, 119). This can be of particular benefit for autoregulation studies of renal blood flow, because the kidney has two potent autoregulatory mechanisms: the myogenic response and the tubuloglomerular feedback. As these two autoregulatory instruments operate in different frequency ranges (the myogenic response is more rapid than the tubuloglomerular feedback), it is possible to discern the individual autoregulatory potencies (Fig. 3) (45, 119). Thus it becomes possible to quantify the individual effects of both autoregulatory mechanisms.

NEUROGENIC CONTROL OF CIRCULATION

Neurogenic control of circulation is another field for the application of frequency domain analysis (21, 51, 52, 87). It is possible, for instance, to determine the extent of the neurogenic control of organ blood flow by comparing the frequency characteristics between the specific nerve activity and blood flow (101). In this

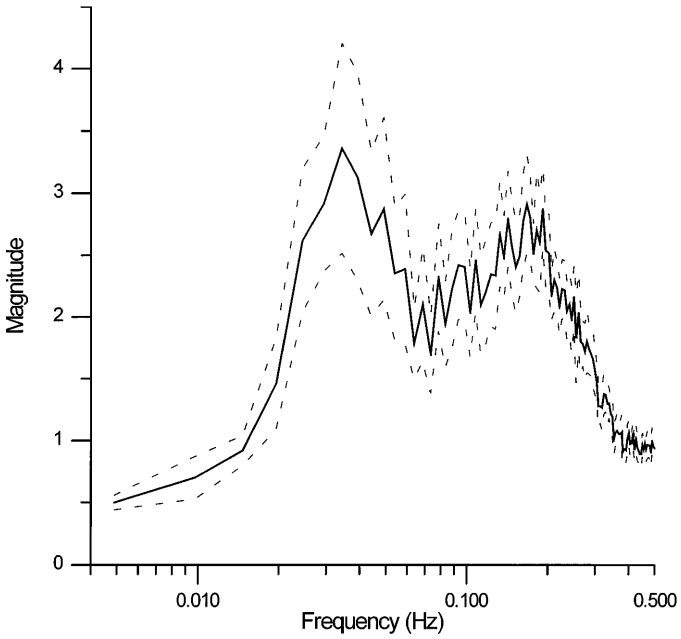

Fig. 3. Transfer function indicating frequencies at which renal autoregulation occurs. Magnitude declines markedly below 0.02 Hz, reflecting potent attenuation of renal blood flow oscillations. Resonance is observed at two ranges, at 0.03 Hz and at roughly 0.2 Hz. This results in consequence of the rapid myogenic component and the sluggish tubuloglomerular feedback mechanism. [From N.-H. Holstein-Rathlou (unpublished observation).]

study, the splanchnic nerve was stimulated at different frequencies to examine which frequency range is conveyed to the mesenteric vascular bed. The mesenteric vascular bed responded to stimulation frequencies <0.5 Hz. This is a fundamental issue for the feasibility of using power spectral analysis as a marker for sympathetic tone (see *Assessment of autonomic activity*).

Arterial baroreflex. Methods for determining baroreflex sensitivity are discussed in the section concerning AP buffering systems (*Arterial baroreceptor reflex sensitivity*). This has been the main application of spectral analysis. Imaizumi and associates (51) have used transfer function analysis to investigate the central baroreflex arc. Aortic nerve activity and renal nerve activity were simultaneously recorded while arterial pressure was randomly perturbed. The magnitude of squared coherence, between 0.02 and 0.3 Hz, was large and the phase was close to $-180°$. This indicates that changes in renal nerve activity were linearly and instantaneously, albeit inversely, related to changes in aortic nerve activity. Above 0.3 Hz, the coherence was low, suggesting weak association between both signals in this frequency range. Earlier, the same group had used frequency analysis to determine the contribution of wall mechanics to the dynamic properties of aortic baroreceptors (52). This study did not provide strong evidence for the importance of wall mechanics on the dynamic properties of arterial baroreflex.

Assessment of autonomic activity. To the inexperienced observer, patterns of blood pressure time series can mainly appear as random noise. After construction of the power spectrum, however, more or less distinct peaks can often be identified (Fig. 1). The most obvious one reflects the blood pressure cycles caused by the beat of the heart. In addition to these pulse pressure variations, there are two slower oscillating components that have attracted much attention. The first is widely referred to as the high-frequency (HF) oscillations, the second as the low-frequency (LF) component. In humans, the HF waves usually have a frequency between 0.2 and 0.4 Hz and are linked to respiration (2, 37, 40, 72, 80, 117). The LF waves, having an average frequency of ~0.1 Hz, do not correspond to any obvious cardiorespiratory event. These oscillations may be related to thermoregulatory mechanisms, the baroreflex, and other neurogenic processes.

Unfortunately, the ranges for HF and LF are chosen differently throughout literature. Several groups also define an intermediate "midfrequency" range (23, 29, 30, 53, 90), and because all frequency bands also reveal species specificity, nomenclature becomes difficult. In several studies and in the present review, only two components, HF and LF, are used.

Throughout the past years, several attempts have been made to use the power of HF and LF as markers for the activity of the different autonomic nervous components regulating blood pressure and heart rate (1, 2, 5, 19, 27, 35, 40, 54, 69, 72, 74, 76, 87, 89, 96, 105, 115–117). Although the generation of these oscillations is still not totally resolved, it is currently held that vagal nervous control of circulation is reflected by rapid as well as the slower oscillations of heart rate and blood pressure. Sympathetic nervous control of circulation, on the other hand, may only have an effect on the slow cardiovascular lability because it is too sluggish to mediate HF oscillations. In the face of the different response times, the vagosympathetic activity in cardiovascular control might be derived from the relationship of power between the HF and LF range, as initially proposed by Malliani and colleagues and later confirmed by others (1, 12, 34, 35, 54, 72, 74, 91).

Despite the clear rationale behind the approach for quantifying the sympathovagal activity by means of spectrum analysis, the various studies do not provide unequivocal evidence totally in favor of this approach. Oscillations linked to respiratory rate have been observed in the activity of the splanchnic nerve (87). This nerve contains mainly sympathetic efferents, thus this finding appears counterintuitive; these oscillations are generally assumed to be too rapid to be mediated by the sympathetic nervous system. This seeming contradiction would be resolved if the neuroeffector junction (i.e., transmitter action, second messengers, etc.) were the reason for slow sympathetic transmission. In this case, the rapid oscillations seen in the direct recordings would be filtered out by the sluggish neurotransmission. Stauss and Kregel (101) recently stimulated the splanchnic nerve to clarify this issue. Stimulation frequencies up to 0.5 Hz were conveyed to mesenteric vascular resistance of the rat. Higher frequency oscillations, however, yielded only an attenuated or no response in vascular resistance. Therefore, it does appear to be the neuroeffector junction that accounts for the

slow sympathetic transmission. These results do not preclude the use of the LF power as a marker for sympathetic activity: oscillations of sympathetic origin are indeed slower than parasympathetic variability, which is due to the delayed signal transmission of sympathetic nerve endings or postjunctional transduction processes (102).

Nevertheless, the feasibility of using spectral power as a marker for sympathetic tone remains controversial. Direct comparison of LF with either neural activity (97) or epinephrine/norepinephrine levels (97, 100) has yielded conflicting results. Furthermore, direct nerve and blood flow recordings by Julien and coworkers (55) have shown that LF waves in arterial pressure are mostly secondary to rhythmic fluctuations in the vasomotor sympathetic tone. In part, these oscillations originate from the synchronizing influence of the baroreceptor reflex. Furthermore, as suggested by this study, HF oscillations of arterial pressure appear to be of pure mechanical origin.

Finally, it should be pointed out that oscillations induced by physiological control systems may not provide as much information toward the long-term activity of the generating network, but may rather indicate acute changes. Most mechanisms in cardiovascular control reset to maintain optimum sensitivity. Thus chronic changes in sympathetic tone may have little impact on cardiovascular rhythms. In accord with this interpretation, an influence of short-term sympathetic blockade on LF power is well documented (26, 30, 38, 87); however, a chronic increase in sympathetic nerve activity, as documented in the spontaneously hypertensive rat strain, is not reflected by an increased LF power (1, 42, 87). Thus, taken together, spectral analysis may provide some information about the acute modulation of the cardiovascular system without providing a reliable quantitative estimate of autonomic tone.

Below the HF and LF range, a continuous increase in power is found (38, 42, 60, 65, 67, 68, 85, 95, 112). This exponential power increase relies only partly on very slow frequency oscillations, such as those in the range of 20 min (86), or even slower waves that occur at a cycle length between 1 and 2 h (9, 98). The main source of this strong, very low frequency power is due to nonharmonic (fractal) noise reflecting the combined action and interaction of different oscillating control mechanisms. The increasing power at lower frequencies is generally referred to as a $1/f$ characteristic. Attempts have been made to use this feature of blood pressure and heart rate spectra as a marker for vagal and sympathetic tone, e.g., in conscious dogs (112) and cats (23) baroreceptor denervation does change the $1/f$ slope significantly. Nevertheless, the results hitherto have not been encouraging because blockade of α- and β-receptors or atropine does not modify the $1/f$ slope (38, 112).

EXAMPLES OF CLINICAL APPLICATION

Use of spectral analysis as a clinical tool has been the aim of several previous efforts. The clinical applications range from diabetic neuropathy (28, 62, 64, 73, 116, 118) to the prognosis of heart transplant recipients (6, 17, 27, 61, 94, 122). The rationale behind the use of spectral analysis for testing reinnervation of the transplanted heart (27) is clear: the reoccurrence of HF and LF oscillations reflects the established connection between the donor allograft and the recipient's central nervous system. Heart rate spectra of the noninnervated heart reveals a marked decline in the HF and LF powers, which is especially pronounced for the HF band (only 5% of control) (6). Allograft rejection, as well, might be associated with a change in heart rate spectral powers; thus heart rate time series may provide a valuable predictive index. Unfortunately, however, there is a discrepancy between studies addressing this topic; some show an increase of spectral powers related to graft rejection (94), whereas others have found no change (61) or a decrease in power (122).

There is more agreement among the reports regarding the use of power spectral techniques in diabetic neuropathy (Fig. 4). These patients typically exhibit

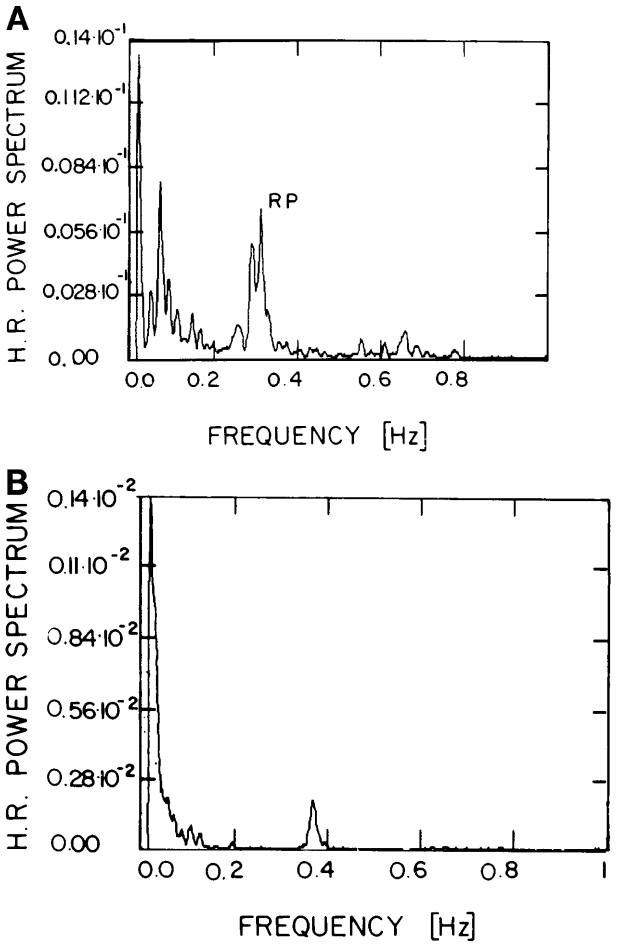

Fig. 4. Heart rate power spectrum from a control subject (*A*) and a patient suffering from diabetic neuropathy (*B*). Frequency peaks are clearly blunted in the latter (note different power scaling). RP, respiratory peak. [Reprinted from *J. Auton. Nerv. Syst.* 19 (Lishner, M., S. Akselrod, V. M. Avi, O. Oz, M. Divon, and M. Ravid. Spectral analysis of heart rate fluctuations. A noninvasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus, 119–125, 1987) with kind permission of Elsevier Science–NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.]

reduced heart rate and blood pressure spectral powers; the response to physical stress, e.g., tilt or orthostatic challenge, is likewise attenuated (62, 64, 116, 118).

Conversely, the more complex nature of the mechanisms behind sudden infant death syndrome is not mirrored by profound changes in heart rate or respiratory power spectra. Although subtle changes have been detected between healthy infants and those at risk for sudden infant death (31, 59), these alterations are not sufficiently large to justify spectrum analysis as a screening method (32).

Human hypertension has been the main focus of clinical studies employing spectrum analysis over the past years (26, 30, 35, 50, 75, 76, 105). The major goal of these studies was to recognize hypertension-prone subjects at an early stage, thereby allowing proper treatment before secondary pathophysiological manifestations. In accord with investigations proposing the use of LF-to-HF ratio for quantifying vagosympathetic activity, a greater LF power was observed in hypertensives compared with normotensive controls (35, 105). The opposite observation, however, has also been made (50), and Parati and colleagues (76) did not detect any difference between normotensive and hypertensive subjects over a 24-h time scale. Thus, at present, time series analysis does not seem applicable as a tool for screening patients at risk for hypertension.

FUTURE PERSPECTIVES

Prompted by the wide application of linear analysis, nonlinear techniques are being tested as further, perhaps superior, markers for cardiovascular derangement (14, 15, 48, 58, 65, 109, 111). As in spectral analytic procedures, nonlinear dynamic analysis is performed by measuring only a single, or very few, variables over a certain period of time, rendering a time series that is then characterized phenomenologically. It is generally not the aim of these studies to obtain any information regarding the individual contribution of each single control element. Instead, these new techniques provide crude insight into the underlying dynamics (i.e., the temporal development; for review see Ref. 88). This development in cardiovascular physiology is based on rapidly developing techniques derived from the "chaos theory"; thus at present it is not possible to make conclusive evaluations. Among the most often employed tools for nonlinear techniques are the determination of the Lyapunov exponent and the correlation dimension. A hallmark of chaotic dynamics is the extreme sensitivity to minute perturbations. The "butterfly effect" is a popular example for demonstrating the characteristic sensitive dependence on initial conditions, which is quantified by the largest Lyapunov exponent. This measure refers to the divergence of nearby trajectories in phase space. A phase space is a coordinate system in which axes are defined by the independent variables of the system. Unfortunately, in biological systems we have almost infinite degrees of freedom that must be overcome to allow the general description of the overall system behavior. In this reconstructed phase space, the largest Lyapunov exponent indicates the magnitude of divergence of two nearby trajectories. Thus this is a quantitative measure for chaotic behavior; a positive exponent indicates a chaotic (or stochastic) system. The correlation dimension provides an estimate for the fractal dimension.

The first steps made to introduce nonlinear dynamics into the wide field of circulatory physiology concluded that "chaotic" behavior arises during pathological situations such as hypertension (120). In contrast to this initial view, newer studies indicate that indeed healthy systems may be characterized as being chaotic (36, 38, 70, 82, 103, 110, 113).

The constructive review of the manuscript and the valuable suggestions by Dr. H. Ehmke (Ruprecht-Karls Universität Heidelberg) are gratefully acknowledged.

This work was supported by the German Research Foundation and the European Union.

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