Physiological rhythms are central to life. Some rhythms are maintained throughout life, and even a brief interruption leads to death. Glass and Mackey1

Since the original report by Wolf et al,2 analysis of spontaneous variations of beat-to-beat intervals has become a valuable tool, familiar to clinical cardiologists. In 1987, Kleiger and coworkers3 published a pioneering work demonstrating that a reduced heart rate variability (HRV) was capable of identifying a subgroup of subjects with increased cardiac mortality after myocardial infarction (MI) and that its predictive value was independent of traditional clinical risk-stratifying factors. It was originally proposed that reduction in HRV might reflect, at the sinus node level, an autonomic imbalance characterized by increased sympathetic and reduced vagal activity. This interpretation was also supported by indirect findings, such as a tendency toward faster heart rates and a smaller day-night heart rate difference observed in these patients.

This initial observation was followed by several reports4 in which time-domain parameters or geometric indices of HRV, measured on Holter recordings, were found to be effective in identifying post-MI patients with increased cardiac mortality. Unfortunately, when sensitivity and specificity were determined, their value was less than expected, with a positive predictive value <30%. The confounding effect of the variety of computation methodologies present in commercial instrumentation also contributed to the limited application of this methodology in routine clinical practice.4

In 1987, spectral analysis of HRV was applied to post-MI patients.4–8 The complexity of computation was partially compensated for by the capability of spectral methodology to recognize and quantify the power of the principal rhythmic components hidden in the HRV signal. When it was shown4–8 that autonomic modulation and, in particular, sympathetic and parasympathetic influences were largely responsible for the low-frequency (LF; ≈0.1 Hz) and high-frequency (HF; ≈0.25 Hz) components of HRV, it was possible to evaluate alteration in autonomic control in a variety of cardiovascular diseases4 and, in particular, after MI. When short-term recordings were analyzed,4,5,9 2 distinct spectral patterns were identifiable: the first, in uncomplicated MI, was characterized by a predominant LF and a smaller HF component, with an LF/HF ratio >2, indicating a sympathetic activation and reduced vagal tone; the second, occurring in complicated MI, was instead distinguished by a significant reduction in total power, a small or absent LF component, and a relatively predominant HF component, with >60% to 70% of power in the VLF range. The autospectrum of these patients did not reflect the clinical picture of neurohumoral sympathetic activation and was similar to that subsequently reported in congestive heart failure patients in the most advanced phases of the disease.4,10

When spectral analysis was instead applied to 24-hour recordings, ≈90% of the power was present in the ultralow-frequency (ULF; <0.0033 Hz) and very-low-frequency (VLF; 0.0033 to 0.04 Hz) range, whereas the LF and HF components accounted for <10% of spectral energy.4,11 Moreover, a significant reduction in total as well as fractional power distinguished patients with increased cardiac mortality from those with a better prognosis. Nevertheless, the sensitivity, specificity, and positive predictive value of spectral parameters were similar to those of the SD of the normal R-R interval (SDNN) or triangular index.4,11,12

What was unexpected was the capability of time- and frequency-domain measures of HRV to predict total cardiac and arrhythmic mortality to a substantially similar extent, particularly when the amount of clinical and experimental evidence on the proarrhythmic role of sympathetic activation and reduced vagal tone was taken into account. Moreover, the interpretation of a markedly reduced LF in high-risk patients was difficult to explain. These and other unanswered questions have generated a new interest in the analysis of original R-R interval time series and in a more comprehensive appraisal of the central and peripheral mechanisms responsible for beat-to-beat fluctuations.

**Nonlinear Dynamics**

A 24-hour tachogram indicates that heart period fluctuates not only in response to environmental factors, such as posture or physical activity, but also during stationary conditions. This rhythmicity, which may have multiple interactions with other physiological rhythms, such as respiration, may also be affected by small perturbations (eg, premature ventricular contractions, atrioventricular block). As a result, the time series is not constant on time, does not show regular periodicity, and cannot be completely explained by a linear approach.
A nonlinear deterministic approach appears to be more appropriate to describe more complex phenomena, showing that apparently erratic behavior can be generated even by a simple deterministic system with nonlinear structure.\textsuperscript{13,14} It is therefore not surprising that a specific subtype of nonlinear dynamics, chaos theory and fractals, has recently been applied to the study of HRV signal. Initially it was assumed that chaotic fluctuations could explain cardiac electrical activity during atrial or ventricular fibrillation. Later, it was proposed that the fluctuations of heartbeats during normal sinus rhythm could be partially attributed to deterministic chaos and that a decrease in this type of nonlinear variability could be observed in different cardiovascular diseases and before ventricular fibrillation.\textsuperscript{4,13,14}

Different approaches have been used to show nonlinear dynamic mechanisms either by describing system trajectory in the space, by computing fractal dimensions, or by determining self-similarity properties.\textsuperscript{13} Of particular interest is the approach based on the assessment of the long-term correlation of R-R interval time series by determination of the long-range power-law correlation. When the power and frequency of HRV are plotted on a bilogarithmic scale, the plot within the $10^{-4}$ to $10^{-2}$-Hz frequency range, which corresponds to VLF, is described by a straight line with a slope of $-1.15$. This broadband spectrum indicates a fractal-like process with a long-term dependence, suggesting that fluctuations in R-R interval are related to variations that occurred hundreds of beats earlier and, at least in experimental animals, are dependent on the functional integrity of baroreflex mechanisms.\textsuperscript{16}

In patients after MI,\textsuperscript{17} the presence of left ventricular dysfunction was associated with a significantly more negative slope of the power-frequency relationship. The exponent of 1/f slope was significantly correlated with extent of left ventricular dysfunction but not with total power. Another index of fractal dimension, $D_2$, was smaller in patients with depressed ejection fraction than in control subjects. Both findings were consistent with the hypothesis that the altered HRV pattern observed in these patients, initially indicated by a marked reduction in total power, was also associated with a loss of complexity of the variability signal. The ability of power-law regression to predict death after MI was first reported by Bigger and coworkers.\textsuperscript{18} These authors demonstrated that a power-law regression parameter below $-1.372$ was significantly associated with total cardiac and arrhythmic mortality, with a predictive value similar to that of ULF and VLF power when considered individually but significantly greater when combined with zero correlation power.\textsuperscript{18}

In the present issue of Circulation, Huikuri and coworkers\textsuperscript{19} report the results of a new application of nonlinear dynamics to the study of HRV signal in post-MI patients enrolled in the DIAMOND study. In addition to 1/f slope, the authors also analyzed short-range correlation of interbeat intervals by means of detrended fluctuation analysis,\textsuperscript{20} which allows us to compute 2 indices of the fractal scaling properties of short ($<11$ beats) and intermediate ($>11$ beats) R-R interval time series.

During a 2-year follow-up period, 114 deaths occurred; 75 were classified as arrhythmic. Traditional time- and frequency-domain parameters of HRV as well as indices of nonlinear dynamics differed significantly between survivors and nonsurvivors. However, among all R-R interval variability measures, the reduced short-term scaling $\alpha_1$ had the best overall independent accuracy in predicting all-cause mortality after adjustment for other variables. In addition, this index was the only parameter that independently predicted arrhythmic death as well.

These results, which stimulate new interest in the study of HRV, deserve a few considerations.

First, they indicate that the amount of information hidden in the variability signal cannot be completely extracted with a single approach. It is certain that not only the duration of recordings but also the specific pattern of fluctuations present in the variability signal might deserve different modalities of study. When HRV is depressed, as in high-risk post-MI patients, linear components of the variability signal are almost undetectable, as indicated by the absence or marked attenuation of the LF component and by the steeper slope of the power-frequency relation within the VLF range. The present results are in agreement with this hypothesis: lower values of the short scaling exponent ($<11$ beats) indicate a loss of short-term correlation properties of the R-R interval in the same time scale that corresponds to LF oscillation periodicity. Thus, the alteration of autonomic control mechanisms that characterize acute MI may span from a small reduction in HRV with a relative predominance of LF over HF to a marked attenuation of rhythmic oscillations with a loss of short- and long-term correlation of interbeat intervals.

In addition, the data of Huikuri and coworkers\textsuperscript{19} suggest that a loss of short-term correlation can predict not only total cardiac but also arrhythmic mortality. It is therefore possible that in high-risk patients, a persistent sympathetic activation and a reduced vagal tone may determine a marked reduction in dynamic complexity of heart rate fluctuations that would make heart period less adaptable and less able to cope with the requirements of a continuously changing environment.\textsuperscript{14,18}

An additional advantage of this methodology is the possibility of performing analysis on raw data without the necessity of time-consuming and often disputable editing. Unfortunately, the model proposed by Huikuri and coworkers\textsuperscript{19,20} does not appear to be easily exported to clinical practice, in which frequency domain is still almost unconsidered. Nevertheless, only an approach based on an integrated analysis of linear and nonlinear dynamics of interbeat fluctuations seems to be adequate to properly evaluate the HRV signal and to better identify patients at risk. In this context, the short-term scaling exponent stands as one of the most promising new parameters.

**Conclusions**

Time- and frequency-domain analysis of HRV has been proved effective in evaluating autonomic modulation of the sinus node and in stratifying patients after MI. The marked reduction in HRV observed in high-risk patients seems to be associated with a significant attenuation of the linear and rhythmic components of HRV; thus, a nonlinear approach based on the evaluation of long- and short-term correlation of interbeat intervals seems to be more efficient in detecting the
abnormal pattern of R-R fluctuations present in these patients and likely to reflect an abnormal autonomic modulation.

References

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