Recent Advances in Heart Rate Variability Signal Processing and Interpretation

OVER the past 30 years, heart rate variability (HRV) has become a central topic in physiological signal analysis, serving as a vital noninvasive indicator of cardiovascular and autonomic system function, with direct connections to respiratory, central nervous and metabolic dynamics. A Medline search reveals more than 8000 papers on different aspects of HRV during this period, covering physiological modeling and interpretation, diagnostic tools in major pathological states such as ischemia and myocardial infarction, heart failure, hypertension, diabetes and other pathologies involving autonomic and central nervous systems, in ambulatory patient monitoring, in intensive care unit and anesthesia level measurement, in sports and space medicine, as well as for the detection of stress level and environmental effects.

Nearly a decade ago, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology took the initiative of supporting a Task Force which issued a seminal paper: "Heart rate variability: standards of measurement, physiological interpretation and clinical use" (*Circulation* 1996;93:1043–1065). The fact that this paper is the third most cited in *Circulation* suggests that HRV is not only an interesting and reliable quantitative approach to physiological analysis, but also a widely used clinical tool. In fact, practically all 24h-Holter elctrocardiogram (ECG) recording systems have their own modules for the calculation of long and short-term HRV parameters both in time and in frequency domains. The same is true for the surveillance of critical patients in intensive and coronary care units where objective indicators of HRV may contribute to a better treatment. Applications to ECG diagnostic equipment are increasing in recent years for cardiovascular diagnosis, as well as for assessing therapeutic effects. Further, fetal ECG monitoring systems are incorporating HRV as a measure of fetal distress for better surveillance in the perinatal period. Various applications are also being proposed in the post-partum period, as well as for monitoring ECG and heart rate characteristics in the early months of life, especially in those considered at risk for sudden infant death syndrome (SIDS). Autonomic parameters are also considered clinically useful in many neurological disorders such as in dementias, in Parkinson's disease, in multiple sclerosis, as well as for a better detection of sleep stages and sleep disordered breathing. There is increasing interest in using HRV during renal dialysis for the prevention of hypotensive episodes. However, a major challenge is to demonstrate the utility and clinical implications of specific measures of HRV in diagnosis and monitoring so that such measures become part of routine patient care.

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Furthermore, much effort remains to be done for elucidating the mechanisms underlying complex heart rate dynamics and cardiovascular control. A diverse application of signal processing and modeling efforts in this context has yielded substantial enhancements in our understanding but also underscores the need for further investigations. For example, a key question concerns the basic and clinical significance of the growing number of nonlinear and complexity-related measures. A stronger integration between physiological modeling and HRV signal processing should help to construct fundamental links between more speculative research and real-world clinical impact. Perhaps it is even time to consider another task force initiative on HRV with appropriate updating, critical review and suggestions for new directions, taking into account the important results obtained in the last 10 years.

This special issue will focus on many of these advanced and innovative methods of HRV signal processing. Furthermore, new models to better describe various physiological and clinical behaviors using HRV are considered. Emphasis is given on the concept of a bridge between HRV signal processing and physiologic modeling to open up aspects of the complex multi-system dynamics, thus providing new avenues for innovative interpretations and explorations.

The issue is divided into the following five sections.

1) Heart Rate Variability Signal Processing and Interpretation: includes six contributions that draw attention to very efficient methods of processing and interpreting HRV data. Barbieri *et al.* propose an adaptive filtering procedure for obtaining a reliable HRV time series. The method has been verified on healthy subjects as well as on heart failure patients during sleep and is proposed as a novel approach to characterize heart beat dynamics. Solem *et al.* approach the problem of dealing with the presence of ectopic beats by suggesting a new method based upon the integral pulse frequency modulation (IPFM) model. Lake introduces the stochastic Renyi entropy rate as a measure of heart rate gaussianity to discriminate between different physiological and clinical conditions. Such a method may provide an alternative to the nonlinear deterministic approach with particular applications in newborns. Togo *et al.* suggest an original way of interpreting the spectral information in the so-called very-low-frequency (VLF) range during sleep in humans. Their claim is that this activity is related to endogenous rhythmic events generated during sleep and their method, based upon the continuous wavelet transform, may capture these slow rhythmic components more effectively than the more traditional spectral estimates. Goren *et al.* propose a time-frequency approach for analyzing HRV patterns: such a method may facilitate investigating the role of autonomic system control even in non steady-state data. In particular, this technique may enhance detection of the time-varying boundaries of the frequency bands, especially during autonomic provocative tests. Merati *et al.* seek to expand the vistas of HRV data analysis by considering various estimators of nonlinear parameters: the basic issue is that a nonlinear model seems in many instances more suitable to explain the complexity of the physiological control mechanisms of heart rate and the changes involved in various pathologies.

2) Heart Rate Variability and Cardiovascular Modeling: emphasizes an important connection between cardiovascular modeling and HRV signal processing. Doing modeling is useful for HRV signal interpretation and conversely, values obtained from HRV signals present precise correlates with physiological parameters. Three contributions deal with this topical approach. Baselli *et al.* aim to investigate the role of low-frequency (LF) oscillations in cardiovascular system regulation. Through a simple dynamical model, consisting of active peripheral vascular districts fed by a compliant/resistant arterial tree, they evaluate the relationship between local arterial pressure and flow and systemic arterial pressure waves. The conclusion is that the complexity of the underlying physiological mechanisms may be explained by the concurrence of microvascular dynamics with the contribution of multiple neural controls. Faes *et al.* suggest a way to complement the traditional approach of multivariate signal analysis and to apply a method for the measurement of causal relationships between systolic arterial pressure and RR intervals. They analyze cases of vaso-vagal syncope and present evidence for depressed baroreflex gain in resting patients at baseline and a further drop of baroreflex coupling just before syncope. Blasi *et al.* introduce a time-varying closed-loop model to investigate the cardiorespiratory variability in arousal phenomena during sleep: the resolution algorithms are a combination of recursive least squares and the Laguerre expansion that allow obtaining robust parameter estimation. This investigation may provide an objective index of the severity of autonomic dysfunction in sleep apneas and related pathologies.

3) Multiscale and Fractal Heart Rate Variability: demonstrates the substantial efforts in research dedicated to determine scale-invariant parameters, with the possibility that they may more accurately quantify the complex nature of cardiovascular interactions with respect to the traditional second-order approach (based on power spectral density and autocorrelation function). Four contributions investigate a variety of algorithms for measuring fractal dimension or related measures. Nakamura *et al.* study fractal and multifractal characteristics of the HRV signal by employing local Hölder exponents after wavelet decomposition. Through this approach a novel method is suggested to detect occurrences of life-threatening singular events, such as apnea episodes in preterm infants. Further, some interpretations are provided about the relationships between autonomic nervous system development and the values of the global scaling exponent, as well as the variance of the local Hölder exponent histogram. Kiyono *et al.* also report on multiscale analysis of HRV signals, mainly considering the deformation process of probability density function when going from fine to coarse scales. Human heart rate presents robust scale invariance even in non-Gaussian fluctuations: such an invariant parameter may provide better understanding of the physiological origins of HRV. Struzik *et al.* introduce multiscale long-term analysis for describing the effects of aging on HRV parameters. Their approach suggests that age-induced changes from 1/f temporal scaling are similar to those of primary autonomic failure associated with sympathetic depression. Sassi *et al.* demonstrate that a scaling exponent calculated over the entire 24 h HRV data sample may have direct clinical applications in identifying postmyocardial infarction patients who might benefit from prophylactic treatment with the antiarrhythmic drug, amiodarone, to avert life-threatening tachycardias.

4) Fetal and Neonatal Heart Rate Variability: considers a very important clinical application of HRV analysis. Indeed, the first observations of beat-to-beat HR changes were made in this setting. Cao *et al.* demonstrate that a multivariate regression model, which employs various measures of RR variability in time and frequency domains, as well as acceleration-deceleration and entropies correlates well with clinical diagnosis, thus suggesting a comprehensive set of quantitative parameters to be used for bedside monitoring. Ferrario *et al.* introduce a multiscale entropy approach for estimating the regularity of RR series in fetal ECG. The use of both sample entropy and approximate entropy may reliably indicate fetal distress through a joint combination of short-and longer-term analysis. Moorman *et al.* suggest the use of heart rate characteristics for neonatal patient management: after appropriate validation, they demonstrate that continuous monitoring of selected heart rate characteristics is a major aid in the early diagnosis of sepsis in premature infants in neonatal intensive care units. Such an approach may lead to more precise and timelier diagnosis, prior to the appearance of symptoms of severe illness and often irreversible sepsis.

5) Classification: reports two different methods that make use of HRV signal parameters. Chan *et al.* employ a multi-layer fuzzy clustering algorithm to extract the relationships between HRV and physical activity through the measurement of body accelerations. Discrete wavelet transforms are also incorporated to detect time-varying characteristics of heart rate in order to obtain reliable estimates. Baier *et al.* employ a discrete hidden Markov model to classify pregnancy disorders on the basis of beat-to-beat RR and systolic blood pressure series using symbolic dynamics. Different patterns are obtained in different pathological conditions during pregnancy, thus suggesting different blood pressure regulatory mechanisms.

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