

What Can We Learn From the RR Intervals Stored in ICDs?

J.V. OLSEN
Seattle Heart Clinic, Seattle, WA, USA

J. LIAN, D. MÜSSIG, V. LANG
Microsystems Engineering, Inc., Lake Oswego, OR, USA

Summary

Some newer implantable cardiac devices, including implantable cardioverter defibrillators (ICDs), offer extended memory capacity which can record hours of RR interval data. The availability of such long-term RR intervals stored in ICDs may provide more useful diagnostic information regarding the underlying cardiac status of patients than what could be provided by conventional ECG Holters. This article reviews the state-of-the-art techniques for RR interval analysis, with particular emphasis on their potential benefits for risk stratification, arrhythmia prediction, and prevention. The existing technical challenges and possible future research topics are also discussed.

Key Words

RR interval, heart rate variability, implantable cardioverter defibrillator, ectopic beat, ventricular tachyarrhythmia

Introduction

By recording electrocardiograms (ECG) over an extended period of time, conventional Holter monitors can detect heart rhythm abnormalities that are not continuously present, or can help determine if rhythm disturbances are associated with symptoms. Two common approaches have been widely used for Holter ECG analysis: one is based on ECG waveform analysis and the other on RR interval data analysis. The rapid advancement of integrated circuit design enables modern implantable devices to have more embedded functionalities despite smaller size. For example, advanced implantable cardioverter defibrillators (ICDs) provide not only cardiac arrhythmia management, but also a large amount of diagnostic information, including short-term intracardiac electrogram (IEGM) and long-term RR interval recordings. Representative products include Belos and Tachos ICD series (Biotronik, Germany), which offer extended memory capacity for recording 24-hour RR intervals. Unlike conventional ECG Holters, the ICD-based RR interval Holters provide unique opportunities for cardiologists to evaluate

patient's cardiac status based on signals directly recorded from the heart, which may yield more useful diagnostic information.

RR Interval Holter

As an example, Table 1 compares major features between Belos RR interval Holters and conventional ECG Holters. The RR intervals obtained by ECG Holters are derived from the surface ECG, which represents far-field projection of varying cardiac vector over the torso surface. In contrast, the RR intervals obtained by Belos ICDs are based on regional IEGM recordings. Due to the intrinsic advantages of IEGM compared to ECG measurement (higher signal to noise ratio, more stable electrode contact, less sensitive to breath and posture change), ICDs provide more accurate RR intervals than ECG Holters. In addition, Belos ICDs offer some unique features that are not offered by ECG Holters, such as event markers and optional home monitoring [1]. More importantly, Belos ICDs can

	Belos RR interval Holter	ECG Holter
Measurement	Regional signal (mV signal)	Far-field signal (μ V signal)
Signal to noise ratio	High	Low
Electrode contact	Stable	Not stable
Position/breath effect	Little	Modest
Detection accuracy	High	Low
Resolution	10 bits	8 – 12 bits
Sampling rate	512 Hz	128 Hz – 4 kHz
RR intervals	24 hours	24 – 48 hours
Episode recording	Event specific/random	Random
Event markers	Yes	No
Other features	Home Monitoring	-

Table 1. Comparison of a Belos ICD (Biotronik) RR interval Holter and conventional ECG Holter.

record event-specific episodes of RR intervals, particularly those associated with ventricular tachycardia (VT) and ventricular fibrillation (VF). The analysis of RR interval patterns of these episodes may reveal warning "markers" for subsequent episodes of VT/VF.

Heart Rate Variability

The most common approach to analyze RR intervals is to evaluate heart rate variability (HRV). The beat-to-beat variation of RR intervals results from interaction of the sympathetic and parasympathetic systems with the sinus node. The HRV analysis provides a useful means to quantitatively evaluate the fluctuation of the autonomic components [2].

The HRV analysis can be generally categorized into three classes: time domain methods, frequency domain methods, and nonlinear methods. Time domain HRV indices are derived either directly from normal RR intervals or from differences between adjacent normal RR intervals. Representative time domain HRV parameters include SDNN (standard deviation of normal RR intervals), SDANN (standard deviation of average normal RR intervals), RMSSD (root mean squared differences of normal RR intervals), pNN50 (percentage of successive normal RR intervals with difference longer than 50 ms), triangle index (a geometric measure derived from the density distribution of normal RR intervals), etc. These indices are straightforward to

derive, but they provide only an overall (statistical) measure of HRV [2]. Frequency domain measures express HRV as a function of frequency, and provide a better representation of the different physiological sources of the heart beat generation. For instance, it is generally accepted that variations in parasympathetic activity contribute to the high frequency component (HF, above 0.15 Hz), whereas low frequency component (LF, 0.04 – 0.15 Hz) is mediated by both sympathetic and parasympathetic activities. Correspondingly, the LF/HF ratio provides a quantitative measure of the sympathovagal balance. Both autoregressive modeling and fast Fourier transform have been applied for HRV spectral analysis [2], while multi-resolution wavelet analysis of HRV has also gained great interests [3,4]. However, these methods are more computationally complex. Moreover, they are not suitable for long-term HRV evaluation [2].

It seems reasonable to postulate that the control of cardiac rhythm on a moment-by-moment basis is nonlinear and dynamic in nature. The range of heart rates is bounded. There is a clear relationship between the n^{th} R-R interval and the immediately preceding one ($n^{\text{th}} - 1$). The inputs to this system are multiple and nested (respiratory drive, temperature, Central Nervous System efferents, etc.), and the geometry of the conducting system appears fractal in nature. Assuming the genesis of HRV as the result of a dynamic system, various nonlinear methods have been proposed for HRV analysis including: 1/f scaling of Fourier spectra [5], symbolic dynamics [6-8], correlation dimension [9,10], Lyapunov exponents [11], entropy analysis [6,12,13], etc. Although these nonlinear methods have the potential to characterize the complex dynamic behavior of the RR series, standards are lacking and the full power of these methods is not sufficiently understood.

As one of the most promising markers to evaluate autonomic activity, HRV has been extensively used in clinical settings to identify patients at risk for an increased cardiac mortality. Depressed HRV, often reflected by diminished vagal activity and corresponding prevalence of sympathetic modulation, has been associated with an increased cardiac mortality in almost all clinical conditions characterized by an autonomic imbalance, such as after myocardial infarction, in patients with congestive heart failure, hypertension, and diabetes [2]. Besides risk stratification, HRV measures may also be used for prediction of ventricular arrhythmia, because growing evidence suggests that

many episodes of spontaneous VT or VF are preceded by changes in HRV parameters [4,7,8,14-21]. Undoubtedly, reliable VT/VF prediction is of significant clinical importance since it will offer unique opportunity to develop preventive strategies, including antiarrhythmic drug and pacing therapies. Unfortunately, the reliability of such an approach has not been established so far due to conflicting data [22,23], retrospective study design, and small patient numbers. Thus, the proposed prediction criteria can not be generalized considering the different pathologies within patient groups, different medications, inter-subject variability, intra-subject circadian patterns, and many other confounding factors such as age, gender, emotion, etc. It is hoped that many of these limitations might be overcome by having patients with ICDs serve as their own controls. To investigate the feasibility of VT/VF prediction, the HAWAI Registry has been recently launched with the primary objective of assessing HRV characteristics prior to the onset of spontaneous VT and VF, by analyzing episode-specific RR intervals recorded in ICDs [24].

Beyond HRV

It should be emphasized that HRV only measures a specific feature, i.e., variability, of the RR intervals. Characterization of other features from different perspectives may offer other useful information embedded in the RR intervals.

One of the most straightforward features is the trend of RR intervals, or its reciprocal, the trend of heart rate. While decreased HRV may represent the suppression of vagal tone, increased heart rate may indicate a shift toward sympathetic dominance, which is associated with higher risk of ventricular arrhythmias. By analyzing RR intervals stored in ICDs, several studies have described the trend of increase in heart rate before the onset of VT and VF [19-21,23], and similar trend was also noted during our preliminary analysis of the available HAWAI Registry database. Sustained heart rate increase, as manifested by the staircase decrease of RR intervals, was also found to be a potential predictor for the subsequent VF episodes [25]. An interesting finding was recently reported by Meyerfeldt et al. [8], who showed that the trend of heart rate prior to the onset of VT depended on the VT cycle length, in that slow VT was characterized by a significant increase in heart rate, whereas fast VT was triggered during decreased heart rate, compared to the control series.

"Abnormal" RR intervals associated with ectopic beats (EBs) may also provide useful insights into the cardiac status. Conventional HRV analysis is based on normal RR intervals that are free of EBs, including both atrial premature beats and ventricular premature beats. However, these filtered EBs may carry important information that may signal a certain degree of abnormality of the cardiac rhythm control system. For instance, a simple EB counter may serve as a risk factor or predictor since there is evidence that the fre-

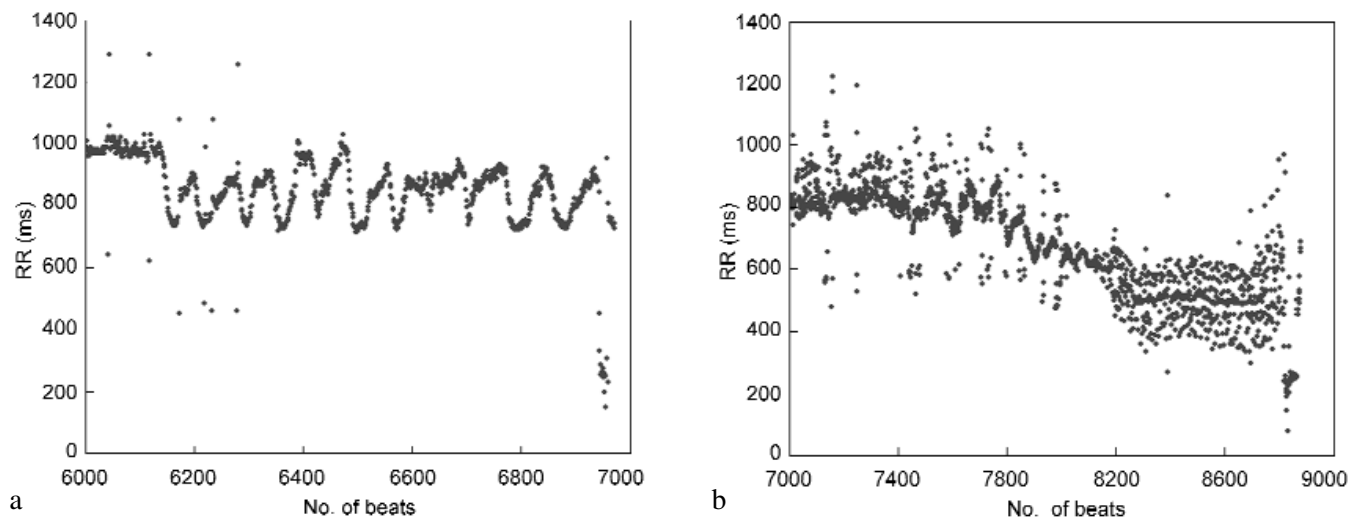


Figure 1. Two typical patterns of RR intervals prior to onset of ventricular tachycardia or ventricular fibrillation.

quency of EBs increases before the onset of the arrhythmic events [23]. Further insights can be gained from the RR intervals associated with the EBs. For example, the prematurity of a ventricular extrasystole (VES) can be assessed by the ratio of VES coupling interval to the preceding normal RR interval. It has been found that late-coupled VESs were the most common triggers of VT [26,27]. Therefore, the prematurity measurement of VESs may help distinguish "risky" VESs from the "non-risky" VESs. Another example is the heart rate turbulence (HRT), which measures the transient dynamics of the RR intervals after single VES [28]. It has been suggested that HRT could serve as a surrogate for baroreflex sensitivity, and may be a potent postinfarction risk stratifier [28,29].

Furthermore, characterization of RR interval patterns may prove to be useful for VT/VF risk stratification, prediction, and prevention. One well-known pattern is the short-long sequence, which usually consists of a short VES coupling interval and a following long compensatory pause. The pause-dependent ventricular instability leads to enhanced dispersion of ventricular refractoriness and thus to a higher vulnerability predisposing to sustained ventricular arrhythmias [30]. Growing evidence has indicated that both monomorphic and polymorphic ventricular tachyarrhythmias can be triggered by the short-long cycles [26,30-34]. Therefore, suppression of postextrasystolic pauses by rate smoothing may prevent the onset of ventricular tachyarrhythmias [35-37]. On the other hand, our preliminary analysis of the available HAWAI Registry database also revealed several typical patterns of RR intervals prior to the onset of VT/VF. One typical pattern is characterized by an increase in regular and low frequency fluctuation of the RR intervals (Figure 1a). Another pattern can be characterized by a sudden decrease of RR intervals with repeated VESs (Figure 1b). In some patients there appears to be nodal bifurcations in the system prior to events, reminiscent of that seen in classical deterministic chaotic models. Comprehensive analysis of these RR interval patterns will be conducted in future studies.

Challenges and Future Perspectives

By comparison of RR intervals between episodes and control periods in individual patients, several measures of HRV (ectopic beat frequency, short-long sequence, etc.) show statistical differences, suggesting that these

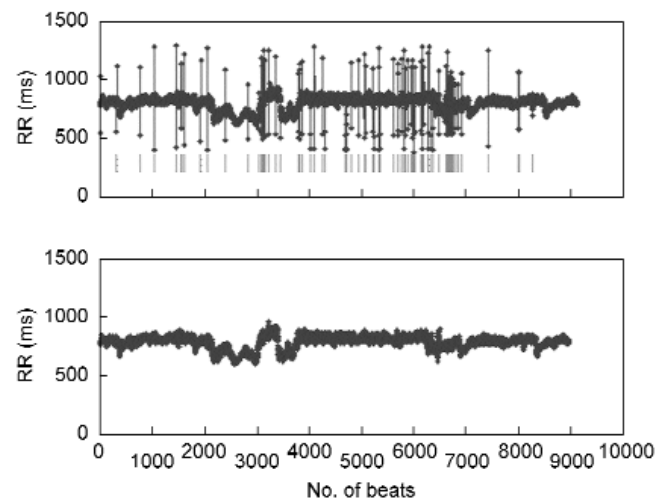


Figure 2. An example of detection of ectopic beats. Top panel shows the original RR intervals with lots of ectopic beats being detected (marked by vertical lines) by the rule-based ectopic beat detector. The bottom panel shows normal RR intervals after ectopic beats have been filtered out.

features can be used for risk stratification. However, little progress has been made in using these features for patient-specific VT/VF prediction. In other words, given a segment of RR interval data, no known method at present can reliably predict the incidence of VT/VF in the short-term.

It was hoped that HRV as a marker of autonomic activity would provide a solution, and they still may. However, the conflicting nature of reports on HRV patterns prior to VT/VF make such feasibility unclear [22,23]. Our initial experience with the HAWAI Registry has also failed initially to give sound prediction based on HRV analysis. Indeed, several technical issues need to be addressed for the purpose of VT/VF prediction: How long prior to onset of VT/VF can HRV parameters give the warning signal? Which HRV analysis method and/or parameter(s) are more robust for VT/VF prediction in terms of both sensitivity and specificity? On the other hand, since different measures of HRV characterize different properties of the RR intervals [9], it is reasonable to believe that combined time domain, frequency domain, and nonlinear HRV methods may provide more promising results.

Real-time automatic EB detection may also represent a challenging technical problem. Such an EB detector is important because real-time HRV analysis requires real-time EB filters to obtain normal RR intervals. Although dual-chamber-sensing ICDs (e.g., DDD,

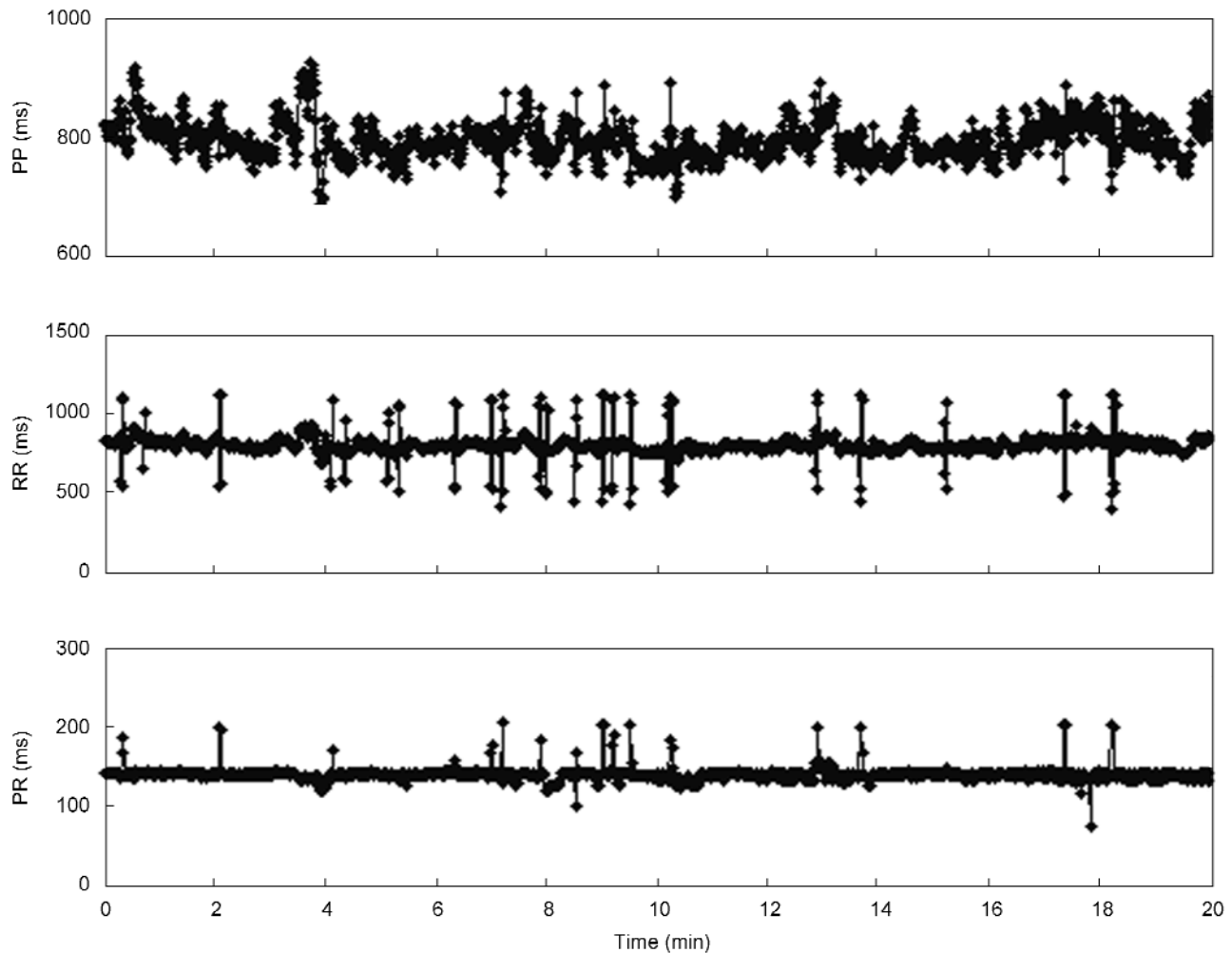


Figure 3. The first 20-min segment of 24-hour PP, RR, and PR intervals recorded by an implanted Belos DR dual chamber ICD (Biotronik).

VDD, DDI modes) may solve this problem easily based on sequence of signals in the chambers of the heart, an automatic EB detector is desired for real-time processing of RR intervals recorded by single-chamber ICDs (e.g., VVI mode). Existing EB detection algorithms are either based on oversimplified interval filters [25,38], or based on computation-demanding morphological analysis [39]. To achieve fast and accurate EB detection, a rule-based EB detector incorporating expert knowledge is being developed and appears promising in helping to make this discrimination. A representative example is illustrated in Figure 2.

Although accurate VT/VF prediction is an attractive idea, considering the limitations of available techniques, a more realistic immediate goal would be real-

time risk evaluation. By monitoring RR intervals recorded by ICD, a composite risk score may be updated continuously based on real-time analysis of HRV, EB statistics, RR interval trend and/or patterns. Preventive therapies, including overdrive pacing or rate smoothing, may be initiated when the risk score reaches a predetermined threshold. As a trade-off to its lower specificity (a high risk score only signals a warning flag of a possible arrhythmic event) such a strategy may achieve a sufficiently high sensitivity that most potential VT/VF episodes could be prevented by the triggered therapy.

In addition to RR intervals, PP intervals and PR intervals may also provide important information regarding cardiac conduction properties and autonomic modula-

tions of the heart [40-43]. Such measurements are difficult for conventional ECG Holters because of the difficulty in identifying characteristics of the P-wave. However, reliable PP interval and PR interval measurement can be easily achieved by latest dual-chamber ICDs such as Belos DR series. It is expected that these advanced PP, PR, and RR interval recordings will offer more diagnostic information and allow more systematic evaluation of the cardiac rhythm. As an example, Figure 3 shows a segment of PP, RR, and PR intervals recorded by a Belos DR device that was recently implanted in a patient.

Conclusion

The variation of RR intervals reflects the complicated dynamics of the heart rhythm control system. Various methods have been proposed to extract the information embedded in the RR intervals. Both challenges and potential exist in extending this work. Newer ICDs with extended Holter function not only record episode-specific RR intervals, but can also record PP intervals and PR intervals. The availability of such ICD Holters together with advanced techniques for dynamic rhythm analysis, may potentially lead to better risk stratification and arrhythmia prediction, and may facilitate future preventive therapies.

References

- [1] Brugada P. Home monitoring technology for improved patient management in ICD therapy (abstract). *PACE*. 2003; 26 (Part 2): 32.
- [2] Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996; 93: 1043-1065.
- [3] Pichot V, Gaspoz JM, Molliex S, et al. Wavelet transform to quantify heart rate variability and to assess its instantaneous changes. *J Appl Physiol*. 1999; 86: 1081-1091.
- [4] Chen SW. A wavelet-based heart rate variability analysis for the study of nonsustained ventricular tachycardia. *IEEE Trans Biomed Eng*. 2002; 49: 736-742.
- [5] Kobayashi M, Musha T. 1/f fluctuation of heartbeat period. *IEEE Trans Biomed Eng*. 1982; 29: 456-457.
- [6] Voss A, Kurths J, Kleiner HJ, et al. The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovasc Res*. 1996; 31: 419-433.
- [7] Wessel N, Ziehmann C, Kurths J, et al. Short-term forecasting of life-threatening cardiac arrhythmias based on symbolic dynamics and finite-time growth rates. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics*. 2000; 61: 733-739.
- [8] Meyerfeldt U, Wessel N, Schutt H, et al. Heart rate variability before the onset of ventricular tachycardia: differences between slow and fast arrhythmias. *Int J Cardiol*. 2002; 84: 141-151.
- [9] Kanters JK, Hojgaard MV, Agner E, et al. Short- and long-term variations in non-linear dynamics of heart rate variability. *Cardiovasc Res*. 1996; 31: 400-409.
- [10] Carvajal R, Zebrowski JJ, Vallverdu M, et al. Dimensional analysis of HRV in hypertrophic cardiomyopathy patients. *IEEE Eng Med Biol Mag*. 2002; 21: 71-78.
- [11] Casaleggio A, Cerutti S, Signorini MG. Study of the Lyapunov exponents in heart rate variability signals. *Methods Inf Med*. 1997; 36: 274-277.
- [12] Hogue CW Jr, Domitrovich PP, Stein PK, et al. RR interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. *Circulation*. 1998; 98: 429-434.
- [13] Wessel N, Voss A, Kurths J, et al. Evaluation of renormalised entropy for risk stratification using heart rate variability data. *Med Biol Eng Comput*. 2000; 38: 680-685.
- [14] Huikuri HV, Valkama JO, Airaksinen KE, et al. Frequency domain measures of heart rate variability before the onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. *Circulation*. 1993; 87: 1220-1228.
- [15] Valkama JO, Huikuri HV, Airaksinen KE, et al. Changes in frequency domain measures of heart rate variability in relation to the onset of ventricular tachycardia in acute myocardial infarction. *Int J Cardiol*. 1993; 38: 177-182.
- [16] Fei L, Statters DJ, Hnatkova K, et al. Change of autonomic influence on the heart immediately before the onset of spontaneous idiopathic ventricular tachycardia. *J Am Coll Cardiol*. 1994; 24: 1515-1522.
- [17] Makikallio TH, Koistinen J, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. *Am J Cardiol*. 1999; 83: 880-884.
- [18] Mani V, Wu X, Wood MA, et al. Variation of spectral power immediately prior to spontaneous onset of ventricular tachycardia/ventricular fibrillation in implantable cardioverter defibrillator patients. *J Cardiovasc Electrophysiol*. 1999; 10: 1586-1596.
- [19] Shusterman V, Aysin B, Weiss R, et al. Dynamics of low-frequency R-R interval oscillations preceding spontaneous ventricular tachycardia. *Am Heart J*. 2000; 139: 126-133.
- [20] Lombardi F, Porta A, Marzeggalli M, et al. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. *Am J Cardiol*. 2000; 86: 959-963.
- [21] Pruvot E, Thonet G, Vesin JM, et al. Heart rate dynamics at the onset of ventricular tachyarrhythmias as retrieved from implantable cardioverter-defibrillators in patients with coronary artery disease. *Circulation*. 2000; 101: 2398-2404.
- [22] Vybiral T, Glaeser DH, Goldberger AL, et al. Conventional heart rate variability analysis of ambulatory electrocardiographic recordings fails to predict imminent ventricular fibrillation. *J Am Coll Cardiol*. 1993; 22: 557-565.
- [23] Nemeč J, Hammill SC, Shen WK. Increase in heart rate precedes episodes of ventricular tachycardia and ventricular fibrillation in patients with implantable cardioverter defibrillators: analysis of spontaneous ventricular tachycardia database. *PACE*. 1999; 22: 1729-1738.

- [24] Fetsch T, Podstufka T, Rieger G. Analysis of heart rate variability from RR-interval recordings of implantable cardioverter-defibrillators. *Prog Biomed Res.* 2000; 5: 254-258.
- [25] Thong T, Goldstein B. Prediction of tachyarrhythmia episodes. Proceedings of the 2nd Joint Meeting of the IEEE Engineering in Medicine and Biology Society (EMBS) and the Biomedical Engineering Society (BMES). 2002 Oct 23-26; Houston Tx, USA. 2002; 2: 1445-1446.
- [26] Roelke M, Garan H, McGovern BA, et al. Analysis of the initiation of spontaneous monomorphic ventricular tachycardia by stored intracardiac electrograms. *J Am Coll Cardiol.* 1994; 23: 117-122.
- [27] Saeed M, Link MS, Mahapatra S, et al. Analysis of intracardiac electrograms showing monomorphic ventricular tachycardia in patients with implantable cardioverter-defibrillators. *Am J Cardiol.* 2000; 85: 580-587.
- [28] Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet.* 1999; 353: 1390-1396.
- [29] Wichterle D, Melenovsky V, Malik M. Mechanisms involved in heart rate turbulence. *Card Electrophysiol Rev.* 2002; 6: 262-266.
- [30] Cranefield PF, Aronson RS. Torsade de pointes and other pause-induced ventricular tachycardias: the short-long-short sequence and early afterdepolarizations. *PACE.* 1988; 11: 670-678.
- [31] Denker S, Lehmann M, Mahmud R, et al. Facilitation of ventricular tachycardia induction with abrupt changes in ventricular cycle length. *Am J Cardiol.* 1984; 53: 508-515.
- [32] Gomes JA, Alexopoulos D, Winters SL, et al. The role of silent ischemia, the arrhythmic substrate and the short-long sequence in the genesis of sudden cardiac death. *J Am Coll Cardiol.* 1989; 14: 1618-1625.
- [33] Meyerfeldt U, Schirdewan A, Wiedemann M, et al. The mode of onset of ventricular tachycardia. A patient-specific phenomenon. *Eur Heart J.* 1997; 18: 1956-1965.
- [34] El-Sherif N, Turitto G. The long QT syndrome and torsade de pointes. *PACE.* 1999; 22: 91-110.
- [35] Fromer M, Wietholt D. Algorithm for the prevention of ventricular tachycardia onset: the Prevent Study. *Am J Cardiol.* 1999; 83 (Suppl 5B): 45D-47D.
- [36] Viskin S, Fish R, Roth A, et al. Prevention of torsade de pointes in the congenital long QT syndrome: use of a pause prevention pacing algorithm. *Heart.* 1998; 79: 417-419.
- [37] Viskin S, Glikson M, Fish R, et al. Rate smoothing with cardiac pacing for preventing torsade de pointes. *Am J Cardiol.* 2000; 86 (Suppl 1): K111-K115.
- [38] Malik M, Cripps T, Farrell T, et al. Prognostic value of heart rate variability after myocardial infarction. A comparison of different data-processing methods. *Med Biol Eng Comput.* 1989; 27: 603-611.
- [39] Acar B, Savelieva I, Hemingway H, et al. Automatic ectopic beat elimination in short-term heart rate variability measurement. *Comput Methods Programs Biomed.* 2000; 63: 123-131.
- [40] Leffler CT, Saul JP, Cohen RJ. Rate-related and autonomic effects on atrioventricular conduction assessed through beat-to-beat PR interval and cycle length variability. *J Cardiovasc Electrophysiol.* 1994; 5: 2-15.
- [41] Kowallik P, Gilmour RF Jr, Fleischer S, et al. Different vagal modulation of the sinoatrial node and AV node in patients with congestive heart failure. *Clin Sci (Lond).* 1996; 91 (Suppl): 58-61.
- [42] Dilaveris PE, Farbom P, Batchvarov V, et al. Circadian behavior of P-wave duration, P-wave area, and PR interval in healthy subjects. *Ann Noninvasive Electrocardiol.* 2001; 6: 92-97.
- [43] Shouldice R, Heneghan C, Nolan P, et al. Modulating effect of respiration on atrioventricular conduction time assessed using PR interval variation. *Med Biol Eng Comput.* 2002; 40: 609-617.

Contact

Dr. John V. Olsen
Swedish Medical Center
801 Broadway Suite 808
Seattle, WA 98122
USA
Phone: +1 206 292 7990
Fax: +1 206 292 4882
E-mail: John.Olsen@swedish.org