Can non-invasive parameters of sympatho-vagal modulation derived from Holter monitoring contribute to risk stratification for primary implantable cardiac-defibrillator implantation?

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This editorial refers to ‘Relationship between cardiac autonomic function and sustained ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators’ by I. Battipaglia et al., Europace 2010;12: 1725–31.

Today, we face two major challenges in risk stratification for primary prevention of sudden cardiac death (SCD) to better select patients who really benefit from implantable cardiac-defibrillators (ICDs). First, among patients with impaired left ventricular ejection fraction (LVEF), the reduction in mortality ranged from 23 to 55%, depending on the risk group, in patients treated with ICD therapy compared with optimal medical therapy; thus about half the patients benefit from primary prevention ICD implant.1 – 3 Secondly, among patients with prior myocardial infarction (MI) and with preserved LVEF, although the risk of SCD is lower, the total number of SCD is large;4 thus, it is necessary to identify high-risk subgroups among post-MI patients with preserved LVEF, where primary ICD implantation could prevent sudden unexpected deaths.

Current indications for ICD implantation for primary prevention of SCD are based mainly on a haemodynamic parameter, left ventricular dysfunction (LVEF < 30–40%) both in post-MI and in non-ischaemic cardiomyopathies.1 – 3, 5 – 7 Among electrophysiological parameters, only non-sustained ventricular tachycardia (NSVT), defined as three or more consecutive ventricular beats during Holter monitoring and induction of VT on electrophysiological testing, is recognized in current guidelines as predictors of benefit from ICD implant for primary prevention of SCD.1

Consistent evidence have shown that low heart rate variability (HRV) in combination with reduced LVEF contribute to identification of patients at high risk of SCD.8 – 11 However, according to current guidelines for the prevention of SCD, HRV was useful for risk stratification (Class IIb recommendation), but evidence was not robust enough to include HRV as a predictor in risk stratification for primary ICD implantation.1

Several other parameters, such as baroreflex sensitivity (BRS), heart rate turbulence (HRT), QRS signal averaging (SA), QT variability index (QTVI), QT dyamicsity (QT/RR slope), and microvolt T-wave alternans (mTWA), have been advocated as predictors for SCD, but additional prospective studies are needed to establish their role in risk stratification.1, 10, 12 – 21

Several recent studies attempted to develop new multiparametric approaches to examine the relation between cardiac autonomic modulation (particularly by HRV), to develop electrophysiological properties by non-invasive ECG tests and the occurrence of sustained ventricular arrhythmias, and to improve the prediction of mortality in high-risk patients.14, 22 – 27

Most parameters can easily be derived from standard 24 h digital Holter monitoring that, being inexpensive and noninvasive, can easily be repeated for periodic reassessment of risk, closely following the clinical evolution and the effect of therapies.28

Ventricular arrhythmia burden in risk stratification

Frequent ventricular arrhythmias, defined as > 30 ventricular premature beats per hour during Holter monitoring, have long been associated with increased risk of recurrent coronary events and cardiac death.28 According to Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) study, the detection of frequent and complex arrhythmias on Holter was almost equal, if not superior, to VT inducibility during electrophysiological testing in predicting the long-term efficacy of antiarrhythmic therapies.29 Noteworthy, in Multicenter Automatic Defibrillator

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Heart rate variability in risk stratification

Since 1987, when low HRV was shown to be an independent predictor of mortality in patients after MI, HRV became the most common quantitative index to evaluate sympatho-vagal modulation of the heart. Low HRV is correlated with reduced vagal activity or increased sympathetic activity, both conditions favouring the onset of malignant cardiac arrhythmias. Low HRV is associated with depressed cardiac function, due to heart failure or left ventricular remodelling. In non-cardiac conditions such as diabetes or neurological and neuromuscular disease, low HRV is a sensitive marker of impaired function of the autonomic nervous system. Changes in HRV indexes can evaluate the effect of different interventions on autonomic balance. Impaired HRV progressively recovers with time after acute MI. Drugs such as beta-blockers or angiotensin-converting enzyme inhibitors and non-pharmacological intervention such as exercise training can favourably modify the autonomic balance and improve HRV, increasing indexes of vagal activity and lowering indexes of high sympathetic activity, although complex interactions occur with the substrate.

The time-domain standard deviation of NN intervals (SDNN) is the most established HRV index, following the original study by Kleiger et al., showing that low SDNN, together with frequent VPBs and reduced LVEF, was associated with higher mortality in post-MI patients. A multitude of studies later confirmed those results. Among these, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study showed that reduced HRV (defined as SDNN <70 ms) was a strong predictor of cardiac mortality, together with low BRS, low LVEF, and frequent VPBs, and that most cardiac mortality was due to sudden death (presumably arrhythmic death).

Among frequency-domain spectral variables, two components usually are identified in short-term recordings (5–20 min), a high-frequency component (HF, range 0.15–0.45 Hz), mainly reflecting vagal modulation of heart rate associated with respiration cycles, and a low-frequency component (LF, range 0.04–0.15 Hz), generally associated with sympathetic activity and sympatho-vagal modulation linked to baroreflex control. In addition, in long-term recordings (from 20 min to 24 h), a third component at very-low-frequency (VLF, range 0.01–0.04 Hz) can be identified, mainly representing slow oscillations associated with longer respiratory cycles. The LF/HF ratio is also used to evaluate the relative contribution of sympatho-vagal modulation at cardiac level.

Low frequency and HF components cannot be univocally related to sympathetic or vagal activity, and time-domain and frequency-domain variables cannot be considered fully equivalent. As an example, in severe heart failure, with evident high sympathetic basal activity, SDNN is generally reduced, but LF component is not increased, but often paradoxically reduced or abolished, while VLF and HF components are also reduced.

Several studies showed that in post-MI, spectral HRV indexes were significant predictors for mortality, but the results were not uniform among different studies. The ATRAMI study indicated that low LF was a significant predictor in depressed LVEF, while other studies indicated that low LF and low VLF were significant predictors only in preserved LVEF. In the recent Cardiac Arrhythmias and Risk Stratification after acute Myocardial infArction (CARISMA) study, both low VLF and low HF (but not low LF) was significant predictors of events. Such differences may be due in part to the duration of recording (short- vs. long-term) and to the time of assessment after MI. Thus, more studies are needed to fully clarify the relevance of spectral HRV indexes as predictors of cardiac events.

A specific analysis of the ATRAMI database showed that patients with very reduced cardiac function (EF <30%, MADIT II-like patients) but with preserved sympatho-vagal balance (SDNN >105 ms) had a lower risk of events, when compared with patients with depressed HRV, identifying a lower risk group despite very low LVEF, less likely to benefit from ICD implantation. Consistent with these data, the study by Battipaglia et al. indicates that among patients with primary prevention ICD and depressed LVEF, low SDNN, low LF, and low VLF were associated with appropriate ICD shocks, confirming that depressed HRV, even if measured on shorter recordings (2 h rather than 24 h recording), was able to identify a higher risk group, where low HRV was associated with the occurrence of sustained ventricular arrhythmias.

Several non-linear methods have been proposed to better characterize the complex interaction between haemodynamic, electrophysiological, and neurohumoral parameters. However, none of these methods has so far been conclusively associated with a higher probability of cardiac events in large prospective studies. In summary, despite lack of conclusive evidence, an increasing number of studies support the idea that a simple and inexpensive measure of HRV from Holter monitoring, in combination with depressed LVEF, can help to select the patients more likely to benefit from ICD. Yet, even if HRV analysis is nowadays easily available from standard Holter equipments, its
application remains confined to research studies, while its use in routine clinical evaluation and risk stratification of cardiac patients remains regrettably limited.

Methods combining multiple non-invasive tests in risk stratification

A wide range of non-invasive electrophysiological tests have been proposed to better characterize the arrhythogenic properties of the myocardial substrate and their interaction with the autonomic modulation. Among them, the most promising tests derived from digital Holter monitoring are HRT,\textsuperscript{12,14} QRS SA,\textsuperscript{15} QT dynamicty (QT/RR slope),\textsuperscript{16–18} QTVI,\textsuperscript{19} and mTWA.\textsuperscript{20,21}

Although each method has potential interest and specific areas of application, none of them alone has proved its efficacy as a single predictor of adverse cardiac events. Several recent studies have attempted to develop new multiparametric methods using multiple indexes from different areas, to better identify subgroups of patients at higher risk.

Among them, the Risk Estimation Following Infarction Noninvasive Evaluation (REFINE) study included HRT, exercise TWA, LVEF, BRS and HRV, and showed that HRT, TWA, and EF <50% (but not HRV) were associated with adverse events in the late phase after MI.\textsuperscript{25} These results were consistent with ISAR-Risk (Improved Stratification of Autonomic Regulation) study, where in post-MI severe autonomic failure (abnormal HRT plus depressed deceleration capacity) identified a high-risk group among patients with preserved LVEF, with mortality similar to depressed LVEF.\textsuperscript{14}

In the CARISMA study, which considered LVEF, HRV, HRT, QT duration and dispersion, SA electrocardiogram (ECG), NSVT and VPB number, VT/VF inducibility, and exercise ECG, the significant predictors were HRV indexes (low VLF, low HF, low SDNN) together with sustained VT, QT dispersion, and turbulence slope.\textsuperscript{26}

In the MUtura Subita en Insuficiencia Cardiaca (MUSIC) score, which considered including LVEF, HRV, HRT, Holter and exercise TWA, QRS duration, and several clinical variables, the best predictors for late adverse events were both Holter and exercise TWA, BRS and HRT, low LVEF, and diabetes, while HRV was only borderline significant.\textsuperscript{27}

Multiparametric scores based on non-invasive variables derived by Holter monitoring, associated with LVEF and other clinical variables, are likely to improve risk stratification of patients at risk of cardiac arrhythmic death. Thus, the widely available inexpensive and non-invasive Holter monitoring maintains an important role in a cost-saving stepwise approach to risk stratification of cardiac patients. Advancements in digital Holter technology have improved the quality of ECG signals and new dedicated algorithms have expanded the clinical application allowing a comprehensive evaluation of cardiac risk profile. Other indexes such as Holter-derived respiration to monitor sleep apnoea should soon be available.\textsuperscript{13}

By a global approach, Holter analysis can become a true comprehensive non-invasive electrophysiological test, able to characterize the three components of the triangle of factors that lead to electrical instability and sudden death; the electrophysiological substrate, the autonomic nervous system modulation, and the trigger for life-threatening cardiac arrhythmias.\textsuperscript{3,24}

A new scenario is foreseen by the use of implantable recorders that can record rhythm disturbances by patient activation or by automatic autotrigger functions. Although these devices require surgical implantation, they have been shown to be useful in diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life-threatening symptoms.\textsuperscript{1–30} In a more distant future implantable long-term ECG, recorders will probably include non-invasive electrophysiological tests, such as HRV, HRT, or even TWA, more accurately identifying risk factors for SCD.

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References


