Review Article

Arrhythmic Sudden Cardiac Death: Substrate, Mechanisms and Current Risk Stratification Strategies for the Post-Myocardial Infarction Patient

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For practical reasons, and to overcome potential ambiguities in the existing previous definitions, it was proposed that the term "sudden cardiac death" (SCD) should signify a natural death from cardiac causes, heralded by an abrupt loss of consciousness within one hour of the onset of acute symptoms.[1] Because fatal ventricular tachycardia and fibrillation (VT/VF) do cause SCD, this entity has emerged as a tachyarrhythmia surrogate and is used as a classification endpoint in relevant clinical studies.[2] However, many other pathophysiological conditions that evolve rapidly can also lead to unexpected death, and in fact the clinical diagnosis of SCD is not synonymous with VT/VF in every case.[3] Additionally, recent studies of patients with implanted cardiac defibrillators (ICDs) indicate that many of the deaths defined as sudden were not due to tachyarrhythmia.[4] Therefore, the following limitation should be taken into consideration: although SCD usually comes as a consequence of malignant tachyarrhythmia, this is not always the rule. This article presents, in a comprehensive way, the issue of SCD of arrhythmic aetiology in patients suffering from coronary artery disease (CAD). The potential arrhythmogenic substrate, the mechanisms for arrhythmia initiation and current strategies for SCD risk stratification are described, with emphasis on their clinical applicability.

Epidemiology of coronary artery disease and SCD

The annual incidence of SCD in Europe and North America is estimated to be approximately 1 episode per 1000 persons.[5] SCD is significantly associated with CAD and almost 50% of deaths occurring in myocardial infarction (MI) survivors are of sudden origin.[5,6] The risk of arrhythmic death in post-MI survivors has a temporal trend, with the highest death rate observed in the first 6 months after MI and remaining high for the next 2 years.[7]

Prevention of SCD

Previous studies established the role of the ICD for protection against ventricular tachyarrhythmias,[8-10] and the current guidelines recommend the ICD for the primary prevention of SCD in post-MI pa-

tients with left ventricular ejection fraction (LVEF) <35%.[11] Implanting an ICD in all patients with low LVEF does not guarantee that all these devices are going to be activated, as it is well known that 11 high-risk CAD patients need to be treated over a 3-year period for one life to be saved.[12] Selecting patients for ICD implantation with screening based on the LVEF criterion leads to a high-cost health policy.[13] Concurrently, among patients presenting with preserved left ventricular systolic function (LVEF>35%), there is a high-risk subgroup that is not protected by the current guidelines.[14] Moreover, as the magnitude of the population of patients with LVEF>40% is very high, the absolute number of SCD victims within this population is also high.[15,16] These patients should be detected. For these reasons the improvement of current SCD risk stratification methods is of paramount importance.

Prerequisites and mechanisms for arrhythmogenesis

During the acute phase of MI, VF or polymorphic VT is triggered by the *presence of ischemia*.[17] During the period after MI, SCD may be caused by different mechanisms: post-infarction areas, including regional and intramural fibrotic zones and scars, remain electrically unexcitable and may form local conditions for *re-entry* leading to sustained monomorphic VT.[18,19] The gradual deterioration in left ventricular systolic function leads eventually to clinically overt heart failure, with subsequent activation of the sympathetic limb of the autonomic nervous system and activation of the renin–angiotensin–aldosterone system.[20] *Enhanced sympathetic activity* predisposes to electrical instability and arrhythmogenesis.[21] The dilatation of the left ventricle contributes to the appearance of *electrical heterogeneity* and *temporal dispersion of repolarisation*.[22,23] These conditions may be arrhythmogenic. The electrophysiological feature that is responsible for the initiation of VF appears to be the *electrical heterogeneity*. Alterations predisposing to VF can be introduced by anatomic/functional substrates and by transient initiating events that can modulate the basic arrhythmia mechanisms of *re-entry*, *automaticity* and *triggered activity*.[24] *Re-entry* constitutes the major mechanism responsible for ventricular arrhythmias appearing in acute and chronic CAD and is significantly related to *heterogeneity*. Transient factors initiating arrhythmias include electrolytic disturbances, acidosis, ischaemia, haemodynamic instability, volume overload and a rapid increase in intraventricular pressure, proarrhythmic action of cardiovascular or other medications, and ion channel abnormalities.[24,25] Holter recordings reveal that 80% of SCD episodes are due to tachyarrhythmias and 20% to bradyarrythmia.[26]

Prognostic markers and their association with the pathophysiological substrate of SCD

Risk stratification schemes are based on markers that, by identifying the arrhythmic substrate and the severity of the arrhythmia mechanisms present, are also considered to quantify the risk of SCD.[27] Briefly, such markers (Table 1) reflect: 1) myocardial substrate lesions and post-infarction fibrosis; 2) abnormal repolarization; 3) impaired autonomic nervous system function; and 4) inducibility.

Current SCD risk stratification strategies and methods

LVEF

The impaired left ventricular systolic function is the consequence of post-infarction fibrosis. The deterioration in systolic function is accompanied by oth-

Table 1. Current matching of prognostic markers to pathophysiological substrate.

1. Myocardial substrate lesions and post-infarction fibrosis	3. Impaired autonomic nervous system function
LVEF	HR
QRS & LBBB	HRV
SAECG	HRT
fragmented QRS	DC
MRI	BRS
PVBs & NSVT	HR recovery after exercise
NYHA class	
2. Abnormal repolarisation	**4. Inducibility**
QT	EPT
QTd	
T wave alternans	
QT/RR	
QTVI	
TWV	

LVEF – left ventricular ejection fraction; QRS – QRS interval; LBBB – left bundle branch block; SAECG – signal averaged electrocardiogram; MRI – magnetic resonance imaging; PVBs – premature ventricular beats; NSVT – non-sustained ventricular tachycardia; NYHA – New York Heart Association functional class of heart failure; QT – QT interval; QTd – QT dispersion; QT/RR – QT dynamics; QTVI – QT variability index; TWV – T-wave variability; HR – heart rate; HRV – heart rate variability; HRT – heart rate turbulence; DC – deceleration capacity; BRS – baroreflex sensitivity; EPT – electrophysiological testing.

er disturbances, such as action potential prolongation, changes in intracellular calcium homeostasis, an increase in the dispersion of repolarisation, accumulation of connective tissue into the cellular gap junctions, and neurohormonal activation. Therefore, the presence of a low LVEF reflects not only the anatomical dysfunction, but also the electrical instability predisposing to VT/VF.[27] The annual arrhythmic mortality increases as LVEF decreases: in patients with LVEF >30% it was 3.2%; in patients with a diminished LVEF between 21-30% it rose to 7.7%; and when the LVEF was <20% the annual arrhythmic mortality climbed to 9.4%.[28] A meta-analysis of 20 studies showed that the critical zone of LVEF<30-40% was correlated with a 4.3 hazard ratio for major arrhythmic events, with a sensitivity of 59% and a specificity of 77%.[29] The association of left ventricular systolic dysfunction with death due to pump failure and ventricular tachyarrhythmia in the post-MI population is well established.[30] Moreover, LVEF preserves its prognostic value in the modern therapeutic era of thrombolysis and b-blockers.[31] However the prognostic ability of LVEF has several limitations: 1) LVEF measurements show intra-and inter-observer variability; 2) systolic function may present temporal variability depending on interventions such as coronary artery bypass, percutaneous coronary intervention, and pharmacological treatment, as well as the natural evolution of the disease; 3) LVEF is correlated more with total mortality than with SCD; and 4) LVEF has low sensitivity, as two thirds of SCDs occur in patients with an LVEF>35%.

QRS

The QRS segment quantifies the duration of ventricular depolarisation. The more prolonged the QRS interval, the more extensive the underlying myocardial ischaemia and/or fibrosis.[32] Therefore, a prolonged QRS interval is correlated with reduced survival. The presence of left bundle branch block (BBB) was an independent prognostic factor for cardiovascular mortality caused by SCD,[33] and a QRS cut-off point >120 ms was reported to be a significant prognostic marker among ICD recipients, predicting those who would benefit from appropriate ICD activation.[34] Furthermore, patients with an intraventricular conduction delay or left (but not right) BBB exhibited a 50% increase in both SCD and total mortality, independently of LVEF and the results of electrophysiological testing.[35]

Signal-averaged ECG (SAECG) and the presence of late potentials

Abnormal electric activity due to depolarization delay may develop in areas of fibrosis and scars around the infarcted myocardial zones. Such areas favour the development of re-entrant circuits and the initiation of monomorphic ventricular tachycardia. Low-amplitude, high-frequency currents located in the late segment of the QRS complex (late potentials) can be revealed and quantified with the SAECG signal-processing method after the application of specific criteria.[36] The SAECG improves the signal-to-noise ratio, facilitating the detection of low-amplitude potentials. After repeated processing, ectopic or premature complexes are eliminated by comparing incoming QRS complexes against a previously established QRS template. According to the established criteria, the presence of an electrical current can be accepted as real late potentials (LP) when the following three criteria are fulfilled: 1) a filtered QRS complex >114 ms (fQRS>114 ms); 2) a low-amplitude signal voltage <40 μV in the terminal QRS complex that lasts >38 ms (LAS>38 ms); and 3) a signal <20 μV in the last 40 ms of the filtered QRS complex (RMS<20 μV).[37] It has been suggested that these SAECG criteria should not be applied in patients with BBB and a wide QRS (≥120 ms), based on the hypothesis that endogenous intraventricular delayed conduction can either mask or mimic such abnormal currents. Therefore, clinicians mainly use the SAECG in patients without BBB and with a normal QRS duration (<120 ms). However, there is evidence supporting the efficacy of the SAECG, even in patients with intraventricular conduction delay or BBB, through modification of the LP criteria.[38] The first SAECG studies evaluating the arrhythmic risk in post-MI patients were applied in the pre-thrombolytic era, and suggested a low positive, but *a high negative predictive value for arrhythmic events*,[16,39] independently of the presence of other well established risk stratifiers.[39-44] It was also shown that the presence of LP distinguishes the electrical from the anatomical arrhythmia substrate,[41] while demonstrating widespread variability during the first 60 days after MI.[42] These studies reported that the presence of LP had a sensitivity of 30-76% in the prediction of SCD or major arrhythmic events, with a specificity of 63-96%. The introduction of effective reperfusion therapies that alter the evolution of post-infarction scar formation also

affected the presence of LP. A reduced presence and prognostic power for LP were reported from recent post-MI studies after thrombolysis[45] and percutaneous coronary intervention,[46,47] questioning the utility of the SAECG for arrhythmia risk stratification.[48] In summary, the existing data indicate that early revascularization during an evolving MI limits not only the fibrotic scar, but also the LP. In contrast, in patients with extended ischaemia and a well formed post-infarction scar, LP are frequently present, and can detect patients at risk for SCD.[43,44] The SAECG is currently recommended as a Class IIb, Level of Evidence B, risk stratification tool among post-MI patients.[49]

Ventricular premature beats and non-sustained ventricular tachycardia

Ventricular premature beats (VPBs) and non-sustained ventricular tachycardia (NSVT) originate from tissue areas with enhanced automaticity. Automaticity is influenced by autonomic nervous system tone, ischaemia/reperfusion, electrolyte disturbances, and cardio-toxic factors.[6,50] The presence of polymorphic VPBs and NSVT increases the risk of the development of polymorphic VT or VF. While frequent VPBs may be manifested in a normal heart without carrying any prognostic significance, they are of prognostic importance when they are manifested in patients with CAD, especially in the presence of ischaemia and/or left ventricular dysfunction. Most of the studies in this field conclude that the relative risk for SCD increases when the cut-off point of 10 VPBs/hour is exceeded in post-MI patients.[30,51-53] While the positive predictive accuracy of VPBs for arrhythmia prediction is low (5-15%), *the negative predictive accuracy is high (>90%)*.[54] Furthermore, if VPBs are combined with other prognostic markers, their prognostic power increases.[55] NSVT is defined as a sequence of at least 3 ventricular premature beats at a rate >100 beats/minute that is self-terminated in less than 30 s. In post-infarction patients, the presence of NSVT episodes, with further inducibility of sustained VT during programmed ventricular stimulation, is associated with an increased risk of SCD.[8,9] NSVT preserves its prognostic significance even in the modern era of b-blockers, and it was proved to be a significant predictor of SCD in post-MI patients with a preserved ejection fraction (LVEF>35%), independently of diabetes mellitus, age, and LVEF.[56]

Prolongation of QT interval and QTc

The repolarisation duration is influenced by the action potential (AP) duration. Prolongation of the AP also induces prolongation of repolarisation. In the case of a prolonged AP, early afterdepolarisations may potentially develop and may further trigger arrhythmias.[57] Enhanced AP transmural heterogeneity also reduces the threshold for transmural re-entry.[58] All these underlying arrhythmia-facilitating disturbances are reflected by the prolongation of repolarisation, which may be quantified with a simple 12-lead surface ECG marker: the QT interval. Various methods for the measurement of the QT interval have been described, including fully automatic methods for QT calculation. The main disadvantage of this marker is the high inter-observer variability of the measurements, ranging from 25-42%.[59,60] The more the heart rate increases, the more the QT interval shortens. For this reason, and to facilitate the comparison of QT intervals among different patients (with different basic heart rates), heart-rate correction of the QT interval has been proposed. The main correction formulas used are Bazett's ($QTc=QT/\sqrt{RR}$) and Fridericia's ($QTc=QT/\sqrt[3]{RR}$). When heart rate is particularly fast or slow, Bazett's formula may either overcorrect or undercorrect. Fridericia's cube-root formula has the same limitations at slow heart rates, but is considered to be more accurate in subjects with tachycardia. Post-infarction patients with QTc>450 ms have a hazard ratio of 2-3 for SCD.[61,62] Other techniques estimating different aspects of repolarisation are QT dispersion,[63] QT dynamics,[64] T-wave amplitude variability,[65] QT variability index,[66] and spatial QRS-T angle.[67,68]

T-wave alternans calculated from exercise and ambulatory ECG recordings

T-wave alternans (TWA) can result from changes in membrane voltage due to steep APD restitution. It has also been proposed that alterations in intracellular calcium cycling are an important basis for repolarisation alternans. Such alternans can occur whenever the heart rate is elevated. Discordant alternans is thought to be highly arrhythmogenic, because it establishes steep, heterogeneous repolarisation gradients and is conducive to re-entry and VT/VF.[69] TWA reflects the spatiotemporal heterogeneity of repolarisation and serves as a mechanism of arrhythmogenesis by amplifying repolarisation hetero-

geneity.[70] Two techniques have been established for TWA detection. The spectral method analyses fluctuations in the T wave by computerised techniques, using a Fast Fourier Transform. A progressive exercise protocol for increasing the heart rate, with simultaneous use of specific electrodes and a high-accuracy recording process, is necessary for detecting TWA on a μV scale. A bicycle or a treadmill exercise test is used for achieving the optimum heart rate. The typical definition for an abnormal TWA test is the occurrence of >1.9 μV of alternans starting at a heart rate of <110 beats per minute.[70] The modified moving average (MMA) method streams odd and even bins and creates median complexes for each bin. The advantage of this method is that it can be applied to a routine 24-h ambulatory ECG recording. A TWA value ≥53 μV at maximum heart rate derived from ambulatory ECG monitoring has been reported as a cut-off point indicating a high risk for SCD and cardiovascular mortality.[71] During the first TWA examination, 83 patients underwent atrial pacing for revealing TWA during electrophysiological testing.[72] Subsequently, an ergometer-exercise methodology was applied to disclose the presence of TWA after an increase in heart rate in 290 patients referred for electrophysiological testing. The prognostic value of TWA proved to be better than that of the SAECG, while a combination of the two methods improved the predictive accuracy.[73] Previous studies have also shown that, among patients with heart disease and LVEF<40%, TWA identified not only a high risk group, but also a low risk group unlikely to benefit from ICD prophylaxis.[74] Furthermore, for the guidance of ICD insertion, non-invasive TWA is comparable to electrophysiological testing in predicting the risk of ventricular tachyarrhythmias or SCD in patients with CAD, LVEF≤40%, and NSVT.[75] In addition, exercise-induced TWA and Holter repolarisation alternans calculated by the MMA method presented similar hazard ratios (2.75 vs. 2.94) for the primary endpoint of cardiac death or resuscitated cardiac arrest,[76] while TWA was predictive of serious arrhythmic events in post-MI patients with preserved LVEF (>40%).[77] TWA magnitude calculated by the MMA method from 24-hour Holter recordings was also predictive of VF or arrhythmic death.[71,78] In contrast to these positive studies, several others reported negative results concerning the use of TWA for arrhythmia risk assessment.[79-81] TWA is said to have a very high negative predictive accuracy for serious ventricular arrhythmias and SCD.[82] Current guidelines recommend ambulatory TWA as a Class I, Level of Evidence A, and electrocardiographic TWA as a Class IIa, Level of evidence A, test for the evaluation of patients with ventricular arrhythmias.[49]

Autonomic nervous system indices

Mean heart rate

Automaticity in the sinus node generates the intrinsic heart rate (HR). Beyond the intrinsic, the resting HR is also determined by the simultaneous influence of the extrinsic mechanism for HR regulation at the level of the sinus node, which includes the two limbs of the autonomic nervous system (ANS). The sympathetic limb releases norepinephrine and accelerates HR, whereas the parasympathetic limb releases acetylcholine and decelerates HR.[83] In this way, HR may represent a simple marker reflecting the final interactions[84] of the external interplay of the sympathetic and parasympathetic with the intrinsic rate at the level of the sinus node. These interactions are reflected by the formula: $HR = m \times n \times HRo$.[85] MI, ischaemia, and heart failure provoke functional changes in the ANS. These changes may influence HR and indices such as heart rate variability,[86] heart rate turbulence,[87] baroreceptor sensitivity,[88] and deceleration capacity.[89] Mean 24-hour HR is strongly correlated with HRV markers, and an increased HR is an independent predictor of SCD in the general population, as well as in ischemic patients.[90,91] Previous studies have reported a 5-fold increase in SCD incidence in a patient subgroup with HR>90 bpm in comparison to the subgroup with HR<60 bpm,[92] 14.3% mortality for patients with HR>100 bpm versus 0.6% mortality for patients with HR<60 bpm,[93] and a 4-fold risk of SCD for participants with HR>75 bpm in comparison to the subgroup with HR<60 bpm.[94] The cut-off point of 70 bpm predicted total mortality rather than SCD in a post-MI patient population with depressed left ventricular systolic function in our prospectively ongoing long term APRET observational study.[95] Figure 1 presents HR diagrams of two different post-MI APRET patients and their correlation with the follow up.

Heart rate variability (HRV)

In healthy individuals the duration of the cardiac cycles shows a normal variation, due to the influence of the ANS on sinus node function and the dynam-

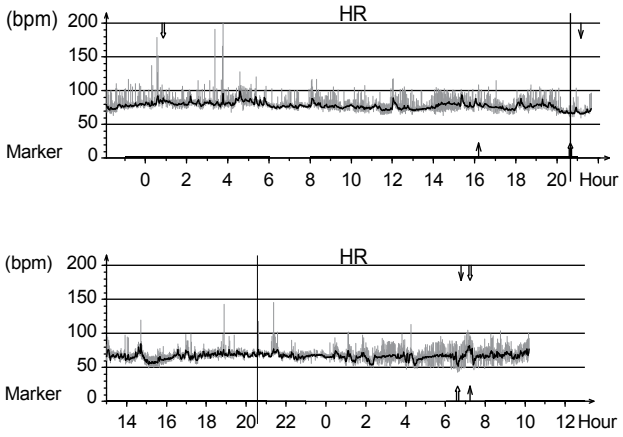

Figure 1. Upper diagram: Mean heart rate (HR) 77 bpm. From 24-hour Holter of a patient with coronary artery disease (CAD; 3 vessels), New York Heart Association (NYHA) class III, left ventricular ejection fraction (LVEF) 25%, and heart rate variability (HRV) SDNN index 60 ms. Lower diagram: Mean HR 66 bpm. From 24-hour Holter of a CAD patient (2 vessels), NYHA II class, LVEF 25% and HRV SDNN 77 ms. During 14 months of follow up, the first patient died (pump failure), whereas the second remained alive. From the APRET 2011 database.

ic balance between its sympathetic and parasympathetic limbs. However in cardiovascular diseases, the ANS is impaired and this normal variation may be lost. Enhanced sympathetic tone, loss of parasympathetic activity, or both, are consequences of cardiovascular diseases, leading to an autonomic imbalance that can further predispose to ventricular arrhythmias and increased mortality.[84,96-98] HRV, by quantifying this variation, reflects the ANS status. A Holter recording can be considered as a heartbeat time series. Hidden information with predictive ability may be extracted from this time series after analysis using specific methods. Conventional methods of HRV analysis include time domain analysis (Figure 2 AII, 2 BII),[86,99] and frequency domain analysis (Figure 2 AIII, 2 BIII).[86,100] In addition, approximate entropy,[101] detrended fluctuation analysis,[102-105] and analysis in the time-frequency domain with wavelet transform[106,107] have also been used. Recommendations for HRV measurement and interpretation have been published previously.[86]

Methods of analysis of HRV

Time-domain analysis

Statistical methods were first used for HRV analysis, extracting simple statistical indices directly computed from RR intervals (with the final results expressed in time units, ms), or extracting the differences between successive RR intervals (with the final results expressed as a percentage).[86,99]

SDNN

Standard deviation of the normal-to-normal RR intervals, usually computed for 24-hour continuous recording,

$$SDNN = \sqrt{\sum_{i=1}^{N} \frac{(NN_i - \overline{NN})^2}{N}}$$

where NN_i is a normal RR interval, N is the total number of such intervals, and $\overline{NN}$ is the mean value of all these intervals. This is a simple metric, which mainly describes long term correlations such as those of the circadian rhythm. It is expressed in ms (Figure 2 AII, 2 BII).

SDANN

Standard deviation of 5-minute averaged NN intervals, usually computed for 24-hour continuous recording. It is expressed in ms.

SDNN index

Mean of the standard deviations of all NN intervals for all 5-minute segments, usually computed for 24-hour continuous recording. It is expressed in ms.

RMSSD

Root mean square of the successive NN interval differences, usually computed for 24-hour continuous recording. It is expressed in ms.

PNN50

The ratio between the number of NN intervals that differ by more than 50 ms from their preceding interval extracted from the total number of NN intervals. No units, expressed as a percentage.

Since the two last indices are extracted by using differences of successive intervals, they are considered as indices that quantify the influence of the parasympathetic limb on the sinus node. Thus, RMSSD and PNN50 are strongly correlated with the high frequencies of the spectrum of the signal.[108] Changes

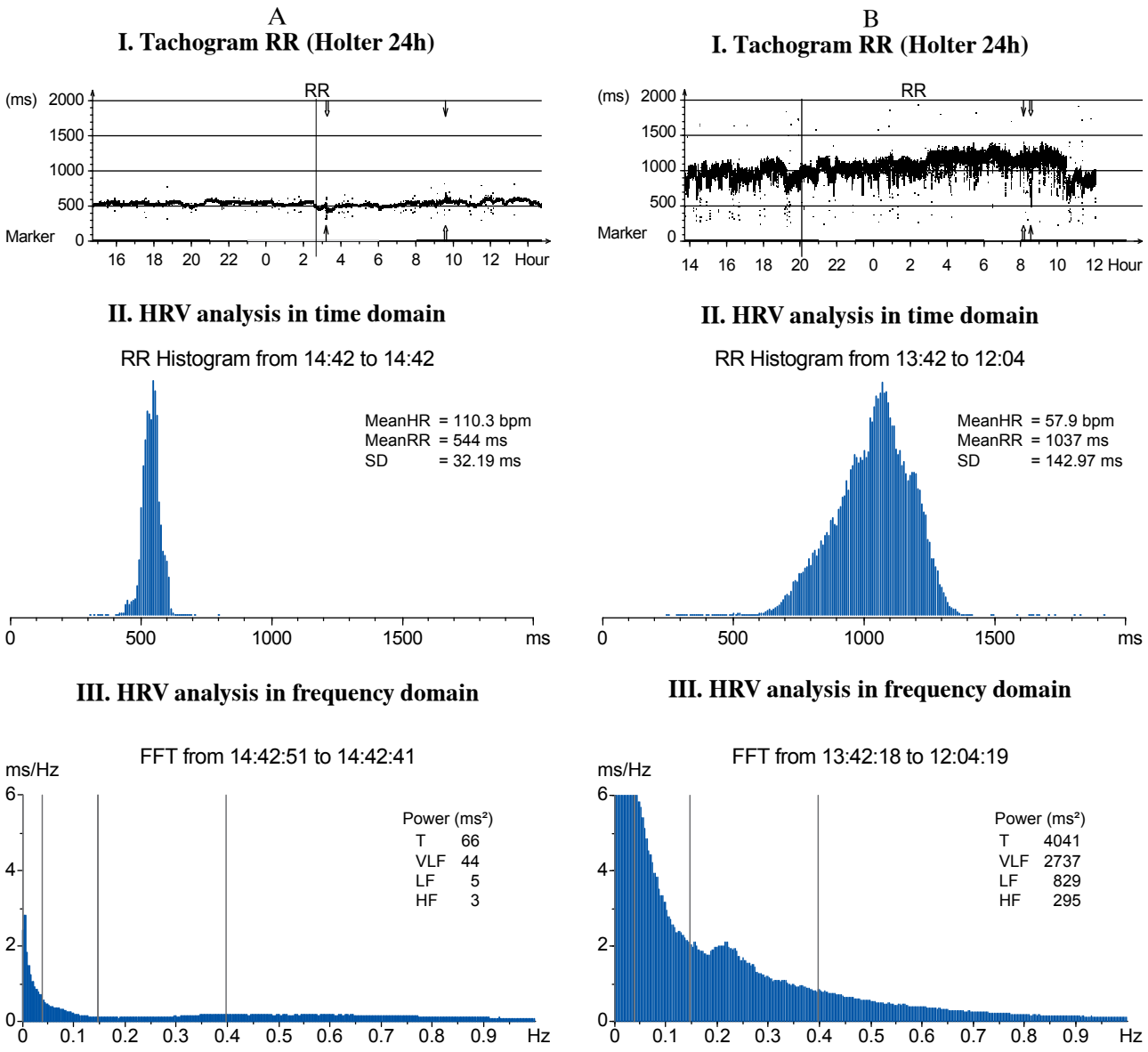

Figure 2. HRV analysis in two patients with different prognosis and survival. The patient in the subfigures of column A was a 55-year-old male hospitalised with an acute myocardial infarction (MI) in the coronary care unit (CCU), who presents very low HRV compared to the patient of column B. From the tachogram (A I) of RR intervals in a 24-hour recording, mean RR duration is 544 ms, which corresponds to a high mean HR of 110 bpm. The variability of RR intervals is minimal. Analysing HRV in the time domain (A II), we obtain a very low value for SDNN (32 ms). In frequency analysis (A III), all bands show low values. This patient experienced electrical storm and finally died in the CCU. Column B shows the corresponding analysis of a 43-year-old patient with an old ST-elevation MI and percutaneous coronary intervention (1 vessel), LVEF 30%, and NYHA II. The patient is still alive without life-threatening ventricular arrhythmias in the follow up. Tachogram (B I): mean RR is 1037 ms, mean HR is 57 bpm. Analysis of HRV in the time domain (B II) with SDNN 142 ms. Analysis of HRV in the frequency domain (B III) gives satisfactory values for all frequency bands. From the APRET 2011 database. Abbreviations as in Figure 1.

in the duration between successive RR intervals are due to the rapid effect of the vagus on the sinus node, something that takes less than 400 ms. In contrast, the effect of the sympathetic stimulation on the heart rate starts with a latency of approximately 5 s, with the maximum response within 20-30 s.[109]

Frequency domain analysis (spectral analysis)

Spectral methods have been used for the analysis of HRV for many years now.[110] These methods calculate how the power of the heart rate signal is distributed among the different frequency bands. The most

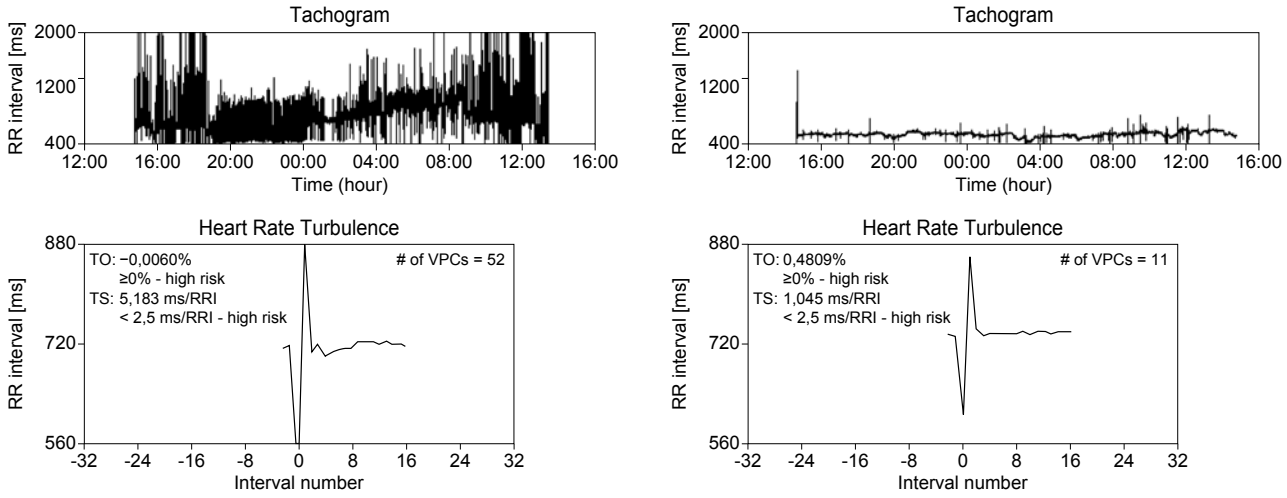

Figure 3. Tachograms (top) and turbulograms (bottom) for two different patients. On the left, a patient with previous MI and LVEF 35% without arrhythmias in the follow up. Please note that in the right tachogram there is limited variability present and the turbulence is almost absent, with values of turbulence onset (TO) 0.480 ms and turbulence slope (TS) 1.04 ms. This is the same high risk patient as in Figure 2, who suffered electrical storm and death. From the APRET 2011 database. Abbreviations as in Figures 1 & 2.

widely used method is Fast Fourier Transform. The heart-rate signal is transformed from one represented in the time domain, into a signal represented in the frequency domain, i.e. the signal is decomposed into several frequencies (sinusoid functions). These frequencies are grouped into several bands and the total power in each of these bands is used for the quantification of HRV.111 Results may be expressed in ms^2 (Figure 2, AIII, 2 BIII).

The frequency bands defined for this purpose are as follows.

HF: 0.15- 0.4 Hz (high frequencies)

Describes cyclic variations of the signal for periods of 2.5-6.6 s, which are due to the discharging of the vagus nerve on the sinus node, and reflects the influence of breathing on the cardiac cycle.[110,112] Atropine and bilateral vagotomy as well as vagal cooling may result in minimisation of the effects.[110,112,113] HF has been proposed as a non-invasive index for vagal efferent activity in both experimental and clinical studies.[111]

LF: 0.04-0.15 Hz (low frequencies)

Describes cyclic variations of the signal for periods 6.6-25 s, mediated by both the sympathetic and the parasympathetic limbs of the ANS. LF variations have been related to cardiac sympathetic control. LF variations in HR correlate positively with variations in thoracic preganglionic sympathetic nerve activity in decerebrate cats[114] and with variations in the muscle sympathetic nerve activity in humans.[115] In conditions with enhanced sympathetic tone, triggered by various factors such as hypotension, transient experimental coronary obstruction for ischaemia induction, and physical exercise, LF is increased.[113,116] Although LF can be considered a measure of the control of the cardiovascular system by the sympathetic nervous system,[117] existing data show that both limbs of the autonomic nervous system influence the LF component. Vagal activity also produces fluctuations in the LF. A reduction in the parasympathetic input may also reduce the power of LF.[109] An index proposed as representative of the dynamic balance between the sympathetic and the parasympathetic limbs is the ratio LF/HF.[113] Although this index has been used extensively, the interpretation of the associations reflected by the simple ratio LF/HF has been questioned.[118]

VLF: 0.0033-0.04 Hz (very low frequencies)

Approximately 12% of the total power of the signal originates from variations in the sequences of RR intervals that present a periodicity varying between 20 s and 5 min. The precise mechanism that causes these variations is not completely known. However, VLF can be eliminated with the use of atropine, suggesting that VLF are related to a parasympathetic efferent limb.[119,120] At least in part, those frequencies re-

flect the activity of the renin–aldosterone system.[121] It has also been proposed that VLF power reflects thermoregulation or vasomotor activity.[122] Physical exercise[123] and sleep-disordered breathing can also influence VLF.[124]

ULF: 0-0.0033Hz (ultra low frequencies)

This is the band with the lowest frequencies in the spectrum, which in a 24-hour recording can detect and quantify variations of RR intervals with a periodicity of 5 min to 24 hours. The underlying mechanisms of ULF are still unknown. Their relatively large periodicity allow us to consider that they are mediated by mechanisms reflecting the long-term equilibrium of the ANS, also reflecting circadian and hormonal activity. A reduction in the power in this frequency band has been clinically proved to be a powerful prognostic index for cardiovascular diseases.[100] ULF power is strongly associated with SDANN.[125] HRV is influenced by several clinical parameters, such as hypertension, diabetes and CAD. Reduced HRV has been related with increased mortality in subjects who survived after an MI.[99,100]

In the b-blocker era, modern treatment modifies the influence of the sympathetic nervous system on the heart, also affecting HRV. For this reason, the prognostic value of HRV has been questioned.[31] However, HRV is widely used for the risk stratification of post-MI patients. In the first fundamental study in such patients, it was shown that the patient subgroup with SDNN<50 ms presented a 5.3 fold higher mortality in comparison to the subgroup with SDNN>100 ms.[99] Similar results have been demonstrated for the prognostic cut off value of SDNN<70 ms.[88,126] With multi-resolution wavelet analysis in the time-frequency domain, the dynamic nature of changes in HRV may be studied[127,128] and high SCD risk subjects may be detected among post-MI heart failure patients.[107]

Heart rate turbulence (HRT)

The premature ventricular ectopic beats in healthy persons are followed by a normal biphasic response of the sinus rhythm. Each ectopic beat is followed by a small period when the rhythm is accelerated and a small period when the rhythm is decelerated. This phenomenon is mediated through the baroreceptor reflex of the ANS and the vagus nerve. When the ANS is working normally, there is clear turbulence appearing in the heartbeat series, but when the ANS does not work as expected (e.g. in post-MI patients), then this turbulence is reduced or even disappears. HRT is considered to be an index that quantifies mainly the reflex vagal activity.[129,130] As vagal reflexes have a cardioprotective effect, a diminished HRT indicates the inability of vagal nerves to achieve such an effect.[130,131] The method was described in 1999.[132] The two phases of HRT, the early sinus rate acceleration and late deceleration, are quantified by 2 parameters: turbulence onset and turbulence slope (Figure 3). A visual representation of the phenomenon and detailed references can be found on line (www.h-r-t.com). As a measure of the autonomic response to perturbations of arterial blood pressure after single ventricular complexes, HRT correlates significantly with baroreflex sensitivity[130] and is simple to measure from Holter recordings.[133] The analysis requires an adequate number of ectopic beats in the recording. Low turbulence has been proved to be a powerful prognostic marker of total mortality after MI, independently of other widely accepted risk stratification indices.[132,134,135] A reduced turbulence slope predicted SCD in MI survivors, as well as in patients with preserved left ventricular systolic function (LVEF>35%).[56]

Deceleration capacity (DC)

HR deceleration is achieved through vagal function. There exists experimental evidence for the parasympathetic nervous system offering protection to the heart from malignant arrhythmias.[136] DC is computed from the series of RR intervals in a 24-hour Holter recording (Figure 4).[89] It is believed that the DC method extracts from the cardiac time-series information relevant to the parasympathetic influences taking place at the sinus node level.[89] Reduced DC has been proved to be a powerful prognostic index of mortality in post-MI patients.[89] The index also has prognostic value for patients with preserved left ventricular systolic function (LVEF>35%).[137] Combined HRT and DC identified a subgroup of patients with severe autonomic failure among a post-MI patient population with LVEF>30% who had a high mortality risk.[138] Specifically, the subset of patients presenting with impaired HRT and DC, characterised as patients with severe autonomic failure, had greater mortality (38.6% vs. 6.1%, p<0.001) during a 5-year follow-up period compared to the patients with normal indexes.[139]

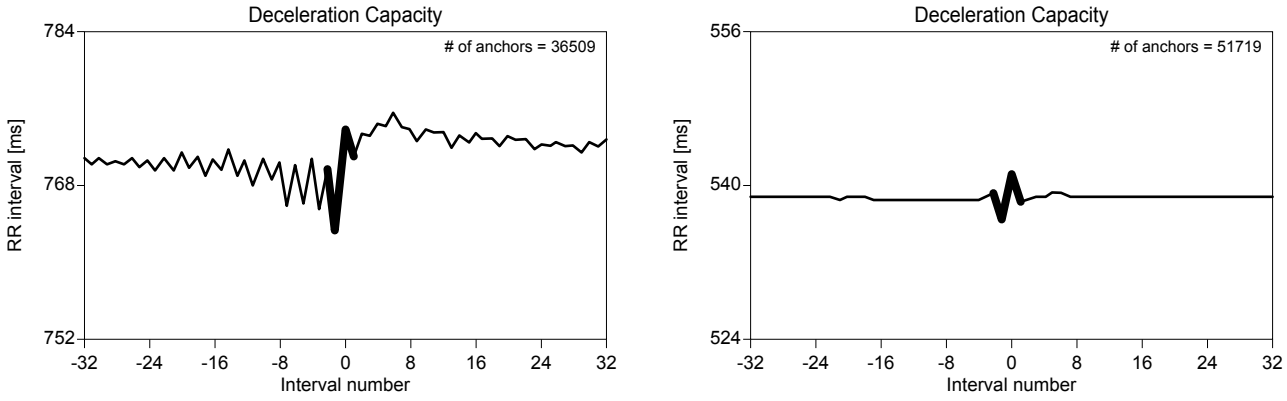

Figure 4. Left: decelerogram of a low-risk post-MI patient (LVEF>35% without ventricular arrhythmias). Right: decelerogram of a high-risk patient who died (see also Figures 2 and 3). Values for the surviving patient: DC 4,010 ms, AC -6,897 ms. Values for the dead patient: DC 1,346 ms, AC -1,461 ms. From the APRET 2011 database. Abbreviations as in Figure 1.

Vulnerability in electrophysiological testing

As the myocardial infarction heals a scar remains. This fibrotic area constitutes the anatomical substrate for the initiation and maintenance of an electrical re-entry circuit that may establish a dangerous VT. Programmed ventricular stimulation evaluates the arrhythmia inducibility in the electrophysiology laboratory.[140] The performance of electrophysiological testing (EPT) depends on the stimulation protocol used (number and degree of prematurity of programmed extrastimuli) as well as the sites of stimulation and the underlying severity of left ventricular dysfunction, and/or the other previously mentioned non-invasive high-risk indices of an abnormal substrate and repolarisation phase.[82,140] The value of EPT in the risk stratification process has been well documented by previous studies.[141-143] EPT was used successfully to select patients for ICD implantation in the MADIT I and MUSTT trials,[8,9] whereas a MADIT II sub-analysis reported that EPT predicted VT but not VF.[144] Following this report, the value of the method for risk stratification of the post-MI patient was partly questioned. Regardless of this, EPT is a powerful prognostic tool for the assessment of high-risk patients, and this has been further confirmed by recent studies.[145-147]

Future trends

Innovative research is evolving in the field of complex cardiac, respiratory and brain biosignals. Open signal databases and downloadable programs will facilitate international interdisciplinary research. Such important e-sites and groups include: 1) Physionet, with the MIT-BIH Arrhythmia Database (www.physionet.org); 2) The Working Group of Biological Signal Analyses of TUM (www.h-r-t.org); 3) The Academic Working Group of Eberhard-Karls-Universität Tübingen (www.thebiosignals.com); 4) The Working Group on in e-Cardiology of the European Society of Cardiology (www.escardio.org/communities/Working-Groups/e-cardiology); 5) The International Scientific Conference, Computing in Cardiology (www.cinc.org); 6) The International Society of Holter and Non-invasive Electrocardiology (www.ishne.org).

The evolution of technology is leading to the incorporation of all the non-invasive markers in Holter software. Risk stratification will be simplified, and a massive collection and analysis of prognostic information from just a simple daily heart signal recording will be routine. As the arrhythmic substrate is dynamic and evolves, the question arises as to what is the appropriate moment for risk estimation using each technique. Regardless of the technique used, non-invasive stratification methods should be subjected to randomised definitive trials to prove that patients identified as being at risk in fact derive benefit from a prophylactic ICD.[148] In the coming years, the SCD risk stratification for post-MI patients is expected to be expanded to populations with a preserved ejection fraction.[14,149] Considering that the overall risk of SCD is currently <1% per year in this group, clinical trials in this field will need to incorporate at least 10 to 20 times as many patients as studied in previous studies in order to identify the small subgroup of patients who have sufficient risk to justify an ICD. This requires the screening of >10,000–20,000 patients per trial. Such a sample size forms a financial barrier that must be overcome in order to organise such trials.[149]

Current trends are leading to prognostic scores that, by summarising the indices reflecting different arrhythmia mechanisms and electrical instability parameters (anatomical substrate, autonomic imbalance, repolarisation prolongation, inducibility), promise better predictive accuracy for future malignant ventricular arrhythmias. The previous studies, REFINE, MUSIC and CHARISMA, moved in this direction and developed multi-parametric global prognostic scores, improving on the prediction of the individual markers.[150] To achieve this target, the prospective observational clinical study Arrhythmia Prevention Trial (APRET) has been ongoing during the last 6 years, clinically assessing all the previously described non-invasive markers. APRET is being performed at the First Department of Cardiology and EP Lab, Medical School, National and Kapodistrian University of Athens; once the study results are complete, the respective arrhythmic SCD prognostic score will be formed.

References

1. Myerburg RJ, Castellanos A. Cardiac Arrest and Sudden Cardiac Death. In: Braunwald's Heart Disease, 7th edition. Philadelphia Pennsylvania: Elsevier Saunders; 2005. p 866.
2. Goldberger JJ. Evidence-based analysis of risk factors for sudden cardiac death. Heart Rhythm. 2009; 6: S2-7.
3. Huikuri HV, Mäkikallio TH, Raatikainen MJ, Perkiömäki J, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. Circulation. 2003; 108: 110-115.
4. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. Circulation. 1996; 93: 519-524.
5. Priori SG, Aliot E, Blømstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death, European Society of Cardiology. Europace. 2002; 4: 3-18.
6. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. Ann Intern Med. 1993; 119: 1187-1197.
7. Yap YG, Duong T, Bland M, et al. Temporal trends on the risk of arrhythmic vs. non-arrhythmic deaths in high-risk patients after myocardial infarction: a combined analysis from multicentre trials. Eur Heart J. 2005; 26: 1385-1393.
8. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996; 335: 1933-1940.
9. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999; 341: 1882-1890.
10. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002; 346: 877-883.
11. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008; 51: e1-62.
12. Moss AJ. MADIT-II and its implications. Eur Heart J. 2003; 24: 16-18
13. Al-Khatib SM, Anstrom KJ, Eisenstein EL, et al. Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. Ann Intern Med. 2005; 142: 593-600.
14. Gatzoulis KA, Tsiachris D, Archontakis S, et al. Implantable cardioverter defibrillator therapy activation for high risk patients with relatively well preserved left ventricular ejection fraction. Does it really work? In press. http://dx.doi.org/10.1016/j.ijcard.2012.04.005
15. Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol. 2001; 12: 369-381.
16. Goldberger JJ, Cain ME, Hohnloser SH, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. J Am Coll Cardiol. 2008; 52: 1179-1199.
17. Gatzoulis KA, Archontakis S, Dilaveris P, et al. Ventricular arrhythmias: from the electrophysiology laboratory to clinical practice. Part I: malignant ventricular arrhythmias. Hellenic J Cardiol. 2011; 52: 525-535.
18. Gatzoulis KA, Archontakis S, Dilaveris P, et al. Ventricular arrhythmias: from the electrophysiology laboratory to clinical practice. Part II: potentially malignant and benign ventricular arrhythmias. Hellenic J Cardiol. 2012; 53: 217-233.
19. Stevenson WG, Khan H, Sager P, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. Circulation. 1993; 88: 1647-1670.
20. Struthers AD. Pathophysiology of heart failure following myocardial infarction. Heart. 2005; 91 Suppl 2: ii14-ii16.
21. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. Circulation. 1984; 69: 790-800.
22. Eckardt L, Haverkamp W, Johna R, et al. Arrhythmias in heart failure: current concepts of mechanisms and therapy. J Cardiovasc Electrophysiol. 2000; 11: 106-117.
23. de Groot JR, Schumacher CA, Verkerk AO, Baartscheer A, Fiolet JW, Coronel R. Intrinsic heterogeneity in repolarization is increased in isolated failing rabbit cardiomyocytes during simulated ischemia. Cardiovasc Res. 2003; 59: 705-714.
24. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation.

1998; 98: 2334-2351.
25. Gatzoulis KA, Tsiachris D, Mamarelis I, et al. Effect of transient myocardial ischemia on QT interval dispersion among patients with unstable angina. Hospital Chronicles. 2012; 7: 96-101.
26. Bayés de Luna A, Coumel P, Leclercq JF. Ambulatory sudden death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J. 1989; 117: 151-159.
27. Arsenos P, Trikas A, Gatzoulis K, Stefanadis C. Risk stratification for sudden cardiac death in heart failure. Heart Failure 2006; 2: 99-119. [Greek]
28. Priori S, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J. 2001; 22: 1374-1450.
29. Bailey JJ, Berson AS, Handelsman H, Hodges M. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. J Am Coll Cardiol. 2001; 38: 1902-1911.
30. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation. 1984; 69: 250-258.
31. Huikuri HV, Tapanainen JM, Lindgren K, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol. 2003; 42: 652-658.
32. Lev M, Unger PN, Rosen KM, Bharati S. The anatomic substrate of complete left bundle branch block. Circulation. 1974; 50: 479-486.
33. Freedman RA, Alderman EL, Sheffield LT, Saporito M, Fisher LD. Bundle branch block in patients with chronic coronary artery disease: angiographic correlates and prognostic significance. J Am Coll Cardiol. 1987; 10: 73-80.
34. Centers for Medicare and Medicaid Services. National coverage determination on implantable defibrillators: http://www.cms.hhs.gov/coverage/download/id39-5.pdf
35. Zimetbaum PJ, Buxton AE, Batsford W, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. Circulation. 2004; 110: 766-769.
36. Gatzoulis K. Late Potentials. In: Toutouzas P, Stefanadis C, Boudoulas C (Editors). Heart Diseases. Athens: Parisianos editions; 2001. pp 1063-1073
37. Breithardt G, Cain ME, El Sherif N, et al. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. J Am Coll Cardiol. 1991; 17: 999-1006.
38. Gatzoulis KA, Carlson MD, Biblo LA, et al. Time domain analysis of the signal averaged electrocardiogram in patients with a conduction defect or a bundle branch block. Eur Heart J. 1995; 16: 1912-1919.
39. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. Circulation. 1986; 74: 1280-1289.
40. Gomes JAC, Barreca P, Horowitz S et al. Signal averaging of the QRS complex in myocardial infarction: relationship between ejection fraction and wall motion abnormalities (abstr). Circulation. 1985; 72 (suppl III): III-212.
41. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. J Am Coll Cardiol. 1987; 10: 349-357.
42. el-Sherif N, Ursell SN, Bekheit S, et al. Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. Am Heart J. 1989; 118: 256-264.
43. Gomes JA, Cain ME, Buxton AE, Josephson ME, Lee KL, Hafley GE. Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. Circulation. 2001; 104: 436-441.
44. Ikeda T, Sakata T, Takami M, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. J Am Coll Cardiol. 2000; 35: 722-730.
45. Steinberg JS, Hochman JS, Morgan CD, et al. Effects of thrombolytic therapy administered 6 to 24 hours after myocardial infarction on the signal-averaged ECG. Results of a multicenter randomized trial. LATE Ancillary Study Investigators. Late Assessment of Thrombolytic Efficacy. Circulation. 1994; 90: 746-752.
46. Denes P, el-Sherif N, Katz R, et al. Prognostic significance of signal-averaged electrocardiogram after thrombolytic therapy and/or angioplasty during acute myocardial infarction (CAST substudy). Cardiac Arrhythmia Suppression Trial (CAST) SAECG Substudy Investigators. Am J Cardiol. 1994; 74: 216-220.
47. Bauer A, Guzik P, Barthel P et al. Reduced prognostic power of ventricular late potentials in post infarction patients of the reperfusion era. Eur Heart J. 2005; 26: 755-761.
48. Lee KL, Lau CP. The use of signal-averaged electrocardiogram in risk stratification after acute myocardial infarction in the modern era. Eur Heart J. 2005; 26: 747-748.
49. Zipes DP, Camm AJ, Borggrefe et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. J Am Coll Cardiol. 2006; 48: e247-346
50. Sheldon SH, Gard JJ, Asirvatham SJ. Premature ventricular contractions and non-sustained ventricular tachycardia: association with sudden cardiac death, risk stratification, and management strategies. Indian Pacing Electrophysiol J. 2010; 10: 357-371.
51. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. Am J Cardiol. 1984; 54: 31-36.
52. Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. J Am Coll Cardiol. 1987; 10: 231-242.
53. Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. Circulation. 1993; 87: 312-322.
54. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol. 1999; 34: 912-948.
55. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of

effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet. 1997; 349: 667-674.
56. Mäkikallio TH, Barthel P, Schneider R, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. Eur Heart J. 2005; 26: 762-769.
57. Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. J Clin Invest. 2005; 115: 2025-2032.
58. Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. Circ Res. 2003; 93: 638-645.
59. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation. 1952; 6: 378-388.
60. Rudehill A, Sundqvist K, Sylvén C. QT and QT-peak interval measurements. A methodological study in patients with subarachnoid haemorrhage compared to a reference group. Clin Physiol. 1986; 6: 23-37.
61. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation. 1978; 57: 1074-1077.
62. Arsenos P, Gatzoulis KA, Dilaveris P, et al. The rate-corrected QT interval calculated from 24-hour Holter recordings may serve as a significant arrhythmia risk stratifier in heart failure patients. Int J Cardiol. 2011; 147: 321-323.
63. Tsagalou EP, Anastasiou-Nana MI, Karagounis LA et al. Dispersion of QT and QRS in patients with severe congestive heart failure: relation to cardiac and sudden death mortality. Hellenic J Cardiol. 2002; 43: 209-215.
64. Chevalier P, Burri H, Adeleine P, et al. QT dynamicity and sudden death after myocardial infarction: results of a long-term follow-up study. J Cardiovasc Electrophysiol, 2003; 14: 227-233.
65. Couderc JP, Zareba W, McNitt S, et al. Repolarization variability in the risk stratification of MADIT II patients. Europace 2007; 9: 717-723.
66. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation. 1997; 96: 1557-1565.
67. Dilaveris P, Gialafos E, Pantazis A, et al. Spatial aspects of ventricular repolarization in postinfarction patients. Pacing Clin Electrophysiol. 2001; 24: 157-165.
68. Giannopoulos G, Dilaveris P, Batchvarov V, et al. Prognostic significance of inverse spatial QRS-T angle circadian pattern in myocardial infarction survivors. J Electrocardiol. 2009; 42: 79-84.
69. Verrier RL, Kumar K, Nearing BD. Basis for sudden cardiac death prediction by T-wave alternans from an integrative physiology perspective. Heart Rhythm. 2009; 6: 416-422.
70. Verrier RL, Klingenheben T, Malik M, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol. 2011; 58: 1309-1324.
71. Verrier RL, Nearing BD, La Rovere MT et al. Ambulatory electrocardiogram-based tracking of T wave alternans in postmyocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. J Cardiovasc Electrophysiol. 2003; 14: 705-711.
72. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med. 1994; 330: 235-241.
73. Gold MR, Bloomfield DM, Anderson KP, et al. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol. 2000; 36: 2247-2253.
74. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol. 2006; 47: 456-463.
75. Costantini O, Hohnloser SH, Kirk MM, et al. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. J Am Coll Cardiol. 2009; 53: 471-479.
76. Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive risk assessment early after a myocardial infarction the REFINE study. J Am Coll Cardiol. 2007; 50: 2275-2284.
77. Ikeda T, Yoshino H, Sugi K et al. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction. J Am Coll Cardiol. 2006; 48: 2268-2274.
78. Stein PK, Sanghavi D, Domitrovich PP, Mackey RA, Deedwania P. Ambulatory ECG-based T-wave alternans predicts sudden cardiac death in high-risk post-MI patients with left ventricular dysfunction in the EPHESUS study. J Cardiovasc Electrophysiol 2008; 10: 1037-1042.
79. Chow T, Kereiakes DJ, Onufer J, et al. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. J Am Coll Cardiol. 2008; 52: 1607-1615.
80. Gold MR, Ip JH, Costantini O, et al. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. Circulation. 2008; 118: 2022-2028.
81. Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J. 2009; 30: 689-698.
82. Ikeda T, Yusu S, Nakamura K, Yoshino H. Risk stratification for sudden cardiac death. Circ J. 2007; 71 Suppl A: A106-A114.
83. Robertson D, Johnson GA, Robertson RM, Nies AS, Shand DG, Oates JA. Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. Circulation. 1979; 59: 637-643.
84. Schwartz PJ. The autonomic nervous system and sudden cardiac death. Eur Heart J. 1998; 19 (Suppl F): F72-F80.
85. Rosenblueth A, Simeone F. The interrelations of vagal and accelerator effects on the cardiac rate. Am J Physiol. 1934; 110: 42-55.
86. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996; 17: 354-381.
87. Bauer A, Malik M, Schmidt G, et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninva-

sive Electrophysiology Consensus. J Am Coll Cardiol. 2008; 52: 1353-1365.
88. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet. 1998; 351: 478-484.
89. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet. 2006; 367: 1674-1681.
90. Kannel WB, Gagnon DR, Cupples LA. Epidemiology of sudden coronary death: population at risk. Can J Cardiol. 1990; 6: 439-444.
91. Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate: a risk factor for cardiovascular death in elderly men. Arch Intern Med. 1999; 159: 585-592.
92. Shaper AG, Wannamethee G, Macfarlane PW, Walker M. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. Br Heart J. 1993; 70: 49-55.
93. Zuanetti G, Mantini L, Hernandez-Bernal F, et al. Relevance of heart rate as a prognostic factor in patients with acute myocardial infarction: insights from the GISSI-2 results. Eur Heart J. 1998; 19 Suppl F: F19-26.
94. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005; 352: 1951-1958.
95. Arsenos P, Gatzoulis K, Gialernios T, et al. Mean heart rate from 24-hour Holter recordings predicts total mortality in heart failure patients. Europace. 2011; 13 (Suppl 1): i18-i19.
96. Schwartz PJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial ischemia in conscious dogs with anterior myocardial infarction. Circulation. 1980; 62: 1256-1265.
97. Schwartz PJ, Billmann GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. Circulation. 1984; 69: 790-800.
98. Kolman BS, Verrier RL, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions. Circulation. 1975; 52: 578-585.
99. Kleiger R, Miller J, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol. 1987; 59: 256-262.
100. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation. 1992; 85: 164-171.
101. Pincus SM, Viscarello RR. Approximate entropy: a regularity measure for fetal heart rate analysis. Obstet Gynecol. 1992; 79: 249-255.
102. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos. 1995; 5: 82-87.
103. Arsenos P, Gatzoulis K, Manis G, et al. a1 exponent from detrended fluctuation analysis (DFA) of heartbeat time series predicts total mortality in heart failure patients. Europace. 2011; 13 (suppl 3): NP. doi: 10.1093/europace/eur229.
104. Kyrlagitsis SK, Papaioannou TG, Gatzoulis KA, et al. Chaos theory and heart rate variability: basic principles and clinical applications. Hellenic J Cardiol. 2011; 52: 329-343. [Greek]
105. Papaioannou VE. Heart rate variability, baroreceptor function and heart rate turbulence: possible origin and implications. Hellenic J Cardiol. 2007; 48: 278-289.
106. Thurner S, Feurstein MC, Teich MC. Multiresolution wavelet analysis of heart beat intervals discriminates healthy patients from those with cardiac pathology. Physical Review Letters. 1998; 80: 1544-1547.
107. Arsenos P, Gatzoulis K, Manis G, et al. Decreased scale-specific heart rate variability after multiresolution wavelet analysis predicts sudden cardiac death in heart failure patients. Int J Cardiol. 2012; 154: 358-360.
108. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol. 2005; 10: 88-101.
109. Hedman A, Hartikainen J, Hakumäki M. Physiological background underlying short-term heart rate variability. Ann Noninvasive Electrocardiol. 1998; 3: 267-280.
110. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981; 213: 220-222.
111. Reed MJ, Robertson CE, Addison PS. Heart rate variability measurements and the prediction of ventricular arrhythmias. QJM. 2005; 98: 87-95.
112. Pomeranz B, Macaulay RJ, Caudill MA, et al. Am J Physiol. 1985; 248 (1 Pt 2): H151-H153.
113. Pagani M, Lombardi F, Guzzetti S et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Resc 1986; 59: 178-193
114. Montano N, Lombardi F, Gnecchi Ruscone T, et al. Spectral analysis of sympathetic discharge, R-R interval and systolic arterial pressure in decerebrate cats. J Auton Nerv Syst. 1992; 40: 21-31.
115. Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation. 1997; 95: 1441-1448.
116. Rimoldi O, Pierini S, Ferrari A, Cerutti S, Pagani M, Malliani A. Analysis of short-term oscillations of R-R and arterial pressure in conscious dogs. Am J Physiol. 1990; 258: H967-976.
117. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation. 1991; 84: 482-492.
118. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation. 1997; 96: 3224-3232.
119. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very low frequency RR interval oscillations in humans. Circulation 1998; 98: 547-555.
120. Campbell BC, Sturani A, Reid JL. Evidence of parasympathetic activity of the angiotensin converting enzyme inhibitor, captopril, in normotensive man. Clin Sci (Lond). 1985; 68: 49-56.
121. Bonaduce D, Marciano F, Petretta M, et al. Effects of converting enzyme inhibition on heart period variability in patients with acute myocardial infarction. Circulation. 1994; 90: 108-113.
122. Kitney RI. An analysis of the thermoregulatory influences on heart-rate variability. In: Kitney RI, Rompelman O (Editors): The study of heart rate variability. Oxford: Clarendon Press; 1980. pp 81-106.

123. Bernardi L, Valle F, Coco M, Calciati A, Sleight P. Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. Cardiovasc Res. 1996; 32: 234-237.
124. Shiomi T, Guilleminault C, Sasanabe R, Hirota I, Maekawa M, Kobayashi T. Augmented very low frequency component of heart rate variability during obstructive sleep apnea. Sleep. 1996; 19: 370-377.
125. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. Am J Cardiol. 1992; 69: 891-898.
126. Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation. 1996; 94: 432-436.
127. 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.
128. Toledo E, Gurevitz O, Hod H, Eldar M, Akselrod S. Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. Am J Physiol Regul Integr Comp Physiol. 2003; 284: R1079-1091.
129. Bauer A, Schmidt G. Heart rate turbulence. J Electrocardiol. 2003; 36 Suppl: 89-93.
130. Ghuran AR, Reid F, La Rovere MT, et al; ATRAMI Investigators. Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (The Autonomic Tone and Reflexes After Myocardial Infarction substudy). Am J Cardiol. 2002; 89: 184-190.
131. Hohnloser SH, Klingenheben T, van de Loo A, Hablawetz E, Just H, Schwartz PJ. Reflex versus tonic vagal activity as a prognostic parameter in patients with sustained ventricular tachycardia or ventricular fibrillation. Circulation. 1994; 89: 1068-1073.
132. 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.
133. Bauer A, Malik M, Schmidt G, et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. J Am Coll Cardiol. 2008; 52: 1353-1365.
134. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation. 2003; 108: 1221-1226.
135. Arsenos P, Gatzoulis K, Gialernios T, et al. Turbulence onset of heart rate predicts total mortality in heart failure patients (APRET). Europace. 2011; 13 (suppl 1): i47-i82. doi: 10.1093/europace/euq492
136. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res. 1991; 68: 1471-1481.
137. Arsenos P, Gatzoulis K, Manis G et al. Reduced deceleration capacity of heart rate risk stratifies patients presenting with preserved left ventricular ejection fraction (LVEF>35%) for sudden cardiac death. Europace (2011) 13 (suppl 3): NP. doi: 10.1093/europace/eur229
138. Bauer A, Bathel P, Müller A, et al. Risk prediction by heart rate turbulence and deceleration capacity in postinfarction patients with preserved left ventricular function retrospective analysis of 4 independent trials. J Electrocardiol. 2009; 42: 597-601.
139. Bauer A, Barthel P, Schneider R, et al. Improved Stratification of Autonomic Regulation for risk prediction in postinfarction patients with preserved left ventricular function (ISAR-Risk). Eur Heart J. 2009; 30: 576-583.
140. Fogoros RN. Electrophysiologic Testing. 3rd Edition. Massachusetts, USA: Blackwell Science; 1999. p 174.
141. Spielman SR, Greenspan AM, Kay HR, et al. Electrophysiologic testing in patients at high risk for sudden cardiac death. I. Nonsustained ventricular tachycardia and abnormal ventricular function. J Am Coll Cardiol. 1985; 6: 31-40.
142. Buxton AE, Marchlinski FE, Flores BT, Miller JM, Doherty JU, Josephson ME. Nonsustained ventricular tachycardia in patients with coronary artery disease: role of electrophysiologic study. Circulation. 1987; 75: 1178-1185.
143. Bourke JP, Richards DA, Ross DL, Wallace EM, McGuire MA, Uther JB. Routine programmed electrical stimulation in survivors of acute myocardial infarction for prediction of spontaneous ventricular tachyarrhythmias during follow-up: results, optimal stimulation protocol and cost-effective screening. J Am Coll Cardiol. 1991; 18: 780-788.
144. Daubert JP, Zareba W, Hall WJ, et al. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol. 2006; 47: 98-107.
145. De Ferrari GM, Rordorf R, Frattini F, Petracci B, De Filippo P, Landolina M. Predictive value of programmed ventricular stimulation in patients with ischaemic cardiomyopathy: implications for the selection of candidates for an implantable defibrillator. Europace. 2007; 9: 1151-1157.
146. Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J. 2009; 30: 689-698.
147. Gatzoulis K, Arsenos P, Dilaveris P et al. Programmed ventricular stimulation when compared with the non-invasive risk stratifiers for sudden cardiac death prediction among severe heart failure patients. Europace 2011; 13 (Suppl 1): i22-i23 doi: 10.1093/europace/euq479
148. Exner D. Noninvasive risk stratification after myocardial infarction: rationale, current evidence and the need for definitive trials. Can J Cardiol. 2009; 25 Suppl A: 21A-27A.
149. Goldberger JJ, Buxton AE, Cain M, et al. Risk stratification for arrhythmic sudden cardiac death: identifying the roadblocks. Circulation. 2011; 123: 2423-2430.
150. Locati ET. Can non-invasive parameters of sympatho-vagal modulation derived from Holter monitoring contribute to risk stratification for primary implantable cardiac-defibrillator implantation? Europace. 2011; 13: 776-779.