Non-invasive sudden death risk stratification

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Most sudden cardiac deaths are caused by fatal ventricular arrhythmias (ventricular tachycardia [VT] and fibrillation) in patients with and without known structural heart diseases. Given the large number of patients potentially at risk for developing ventricular arrhythmias, any strategy for treating them prophylactically requires efficient and effective risk stratification. Both non-invasive and invasive testing may be used for prognostic evaluation of patients with heart diseases.

The optimal way to use them in the risk stratification for sudden cardiac death will depend in part on the goals of screening. At present risk markers perform better at identifying low-risk patients who may not need an implantable cardioverter-defibrillator (ICD), because all tests have a high negative predictive accuracy. In our opinion an electrophysiological test should not be performed and an ICD should not be implanted in post-myocardial infarction patients with moderate left ventricular dysfunction (left ventricular ejection fraction 30-40%) with a preserved autonomic balance and without non-sustained VT. In MADIT II-like patients electrophysiological testing does not seem necessary and an ICD could not be implanted only in patients with a negative T-wave alternans test.

Most of the data available refer to patients with ischemic cardiomyopathy but the preliminary data on T-wave alternans suggest its usefulness in patients with non-ischemic cardiomyopathy too, although a large definitive study has not yet been completed in this important population.

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Introduction

Sudden cardiac death accounts for approximately 400 000 deaths each year in the United States and remains a health problem of epidemic proportions. Most sudden cardiac deaths are caused by fatal ventricular arrhythmias (ventricular tachycardia [VT] and fibrillation) in patients with and without known structural heart diseases[1,2]. Identifying patients at risk for these arrhythmias remains a major challenge because < 2% of patients who have sudden cardiac arrest are resuscitated and survive hospital discharge. Given the large number of patients potentially at risk for developing ventricular arrhythmias, any strategy for treating them prophylactically requires efficient and effective risk stratification. A number of recently completed randomized clinical trials showed that implantable cardioverter-defibrillators (ICDs) can prevent sudden cardiac death in selected high-risk patients. These trials have used different methods for identifying patients at risk for sudden cardiac death. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT) identified patients with left ventricular dysfunction and non-sustained VT who had VT induced by programmed ventricular stimulation[3,4]. These two studies demonstrated that implantation of an ICD can reduce the risk of death in these high-risk patients. In contrast, in the Coronary Artery Bypass Graft (CABG) Patch Trial, which identified a group of high-risk patients with left ventricular dysfunction and an abnormal signal-averaged ECG who were undergoing elective bypass surgery, implantation of an ICD did not reduce all-cause mortality[5]. When viewed together, the CABG Patch Trial, MADIT and MUSTT raise an important issue about our understanding of high-risk patients: not all high-risk patients benefit from ICD therapy. Based on these trials, the only patients in whom the prophylactic implantation of an ICD has proven beneficial are those identified by documented spontaneous non-sustained or inducible sustained ventricular arrhythmias.

The publication of MADIT II radically changed our knowledge in identifying which patients may derive benefit from the implantation of a prophylactic ICD[6]. MADIT II aimed to evaluate the effects of an ICD on survival in patients with prior myocardial infarction (MI) (≥ 1 month

before enrollment) and severe impairment of left ventricular ejection fraction (LVEF) (< 30%). The study population included 1232 patients from 76 centers mainly in the United States. Patients were randomized with a 3:2 ratio to ICD (742 patients) or conventional medical therapy (490 patients), endpoint of the study was all-cause mortality. The main clinical and demographic characteristics as well as medical therapy resulted not significantly different in the two groups of patients. At a mean follow-up of 20 months, mortality was 19.8% in the medically treated group and 14.2% in the ICD group. Hazard ratio for the risk of death from all-causes was 0.69 (95% confidence interval [CI] 0.51-0.93, p = 0.016) with a risk reduction of 31% in patients implanted with an ICD compared with those treated with medical therapy. Kaplan-Meier survival curves diverged at 9 months from the enrollment showing a mortality reduction of 12 and 28% at 1 and 2 years, respectively. Based on these results, the prophylactic implant of an ICD improved survival in patients with prior MI and severely impaired left ventricular function.

More recently three studies further supported the clinical relevance of ICD in different groups of patients, in all cases selected by clinical data and LVEF, without additional non-invasive/invasive risk markers.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial included 458 patients with non-ischemic dilated cardiomyopathy, LVEF < 36%, and premature ventricular complexes or non-sustained VT[7]; mean LVEF was 21%. A total of 229 patients were randomly assigned to receive standard medical therapy and 229 standard medical therapy plus ICD. At a mean follow-up of 29 months, there were 68 deaths: 28 in the ICD group, as compared with 40 in the standard therapy group (hazard ratio 0.65, 95% CI 0.40-1.06, p = 0.08). The mortality rate at 2 years was 14.1% in the standard therapy group and 7.9% in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard therapy group (hazard ratio 0.20, 95% CI 0.06-0.71, p = 0.006). The authors concluded that in patients with severe, non-ischemic dilated cardiomyopathy the implantation of an ICD significantly reduced the risk of sudden death from arrhythmia and was associated with a non-significant reduction in the risk of death from any cause.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial tested the hypothesis that prophylactic cardiac resynchronization therapy (CRT) with or without a defibrillator-backup would reduce the risk of death and hospitalization among patients with advanced congestive heart failure (CHF) and intraventricular conduction delay[8]. A total of 1520 patients with advanced CHF (NYHA class III or IV) of both ischemic and non-ischemic etiology, QRS interval ≥ 120 ms, PR interval > 150 ms and left ventricular end-diastolic diameter > 60 mm were randomly assigned in a 1:2:2 ratio to receive optimal pharmacological therapy alone or CRT or CRT plus ICD therapy. The primary endpoint was the time to death from or hospitalization for any cause. As compared with optimal pharmacological therapy alone, both CRT and CRT plus ICD significantly reduced the primary endpoint (hazard ratio 0.81 and 0.80; p = 0.014 and p = 0.01 respectively). CRT reduced the risk of the secondary endpoint of death from any cause by 24% (p = 0.059), CRT plus defibrillator-backup reduced the risk by 36% (p = 0.003). In conclusion, in patients with advanced CHF and prolonged QRS interval, combined electrical therapy (CRT + ICD) significantly reduced all-cause mortality.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) compared the impact on all-cause mortality of three different treatments in patients affected by mild to moderate CHF (NYHA class II-III) of both ischemic and non-ischemic etiology with LVEF ≤ 35%: placebo, amiodarone (200-400 mg/day), ICD[9]. The primary endpoint of the study was all-cause mortality. At 45 months of follow-up, any significant difference was observed between amiodarone and placebo groups; conversely, a clear reduction in all-cause mortality was observed in patients treated with an ICD in comparison with placebo group patients (hazard ratio 0.77, p = 0.007). These data strongly support the use of ICD in such a setting of CHF patients; moreover, further evidence about the inefficacy of amiodarone in reducing deaths from any cause is showed, as well as previously found in clinical trials after MI like the European Myocardial Infarct Amiodarone Trial (EMIAT)[10] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT)[11].

Get with the guidelines and recommendations

On the basis of the recent recommendations of the Task Force of the European Society of Cardiology about sudden cardiac death, an ICD has to be implanted (class I) in "MADIT-MUSTT-like" patients; an ICD may also be recommended in "MADIT II-like" patients (class IIA); in non-ischemic dilated cardiomyopathy the use of ICDs for primary prevention of sudden cardiac death is still debated and ICD implantation is considered a class IIB indication[12,13]. More recently in the United States a critical reappraisal of the ICD indications for primary prophylaxis of sudden cardiac death was performed: the use of an ICD has been recommended in non-ischemic and ischemic heart diseases with LVEF < 30%.

Focus on risk stratification

Prior to the above-mentioned studies, the aim of non-invasive risk stratification was at identifying pa-

tients at high enough risk to warrant treatment as aggressive as an ICD (sensitivity was sacrificed in order to maximize positive predictive accuracy). This approach was based on the assumption that ICDs are expensive, associated with some risks, and thus should be reserved for patients who are extremely likely to need them. Non-invasive risk stratifying tests were judged based on their positive predictive accuracy. The results of the above studies are now associated with a transition to a completely different type of thinking: specificity has been sacrificed in an attempt to maximize sensitivity. This new approach is based on the assumption that ICDs can be implanted more easily, less expensively and with smaller risk and should not be reserved only for the highest-risk patients. The focus of non-invasive risk stratifying testing will be on maximizing negative predictive accuracy.

This article reviews: 1) the role of heart rate variability (HRV) and baroreflex sensitivity (BRS) testing which have been suggested by the Task Force of the European Society of Cardiology as class I tools in the risk stratification of post-MI patients with and without CHF, 2) the role of T-wave alternans (TWA) analysis, a more recent and promising non-invasive risk marker, and 3) the role of electrophysiological (EP) study, which is included in the risk stratification algorithm of MADIT and MUSTT trials.

Heart rate variability

The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death, encouraging the development of quantitative markers of autonomic activity. HRV represents one of the most promising such markers: the phenomenon is the oscillation in the interval between consecutive heart beats as well as the oscillations between consecutive instantaneous heart rates. As many commercial devices now provide automated measurement of HRV, the cardiologist has been provided with a simple tool for both research and clinical studies.

Measurement of HRV may be evaluated by a number of methods: perhaps the simplest to perform are the time-domain measures[14]. In a continuous ECG record, each QRS complex is detected and the so-called normal-to-normal (NN) intervals are determined. From this series of intervals statistical time-domain measures can be calculated and the most common of these is standard deviation of all NN interval (SDNN)[14]. The series of NN intervals can also be converted into a geometric pattern such as the HRV triangular index measurement which is the integral of the density distribution divided by the maximum of the density distribution of all NN intervals[14].

Frequency-domain analysis of HRV provides the power spectral density which is the information of how power (i.e. variance) distributes as a function of frequency[14]. Methods for the calculation of power spectral density may be generally classified as non-parametric and parametric, which provide comparable results[14]. Three main spectral components are distinguished in a spectrum calculated from short-term recordings of 2 to 5 min: very low-frequency (VLF), low-frequency (LF), and high-frequency (HF) components[14]. The representation of LF and HF emphasizes the controlled and the balanced behavior of the two branches of the autonomic nervous system, with LF representing mainly sympathetic and HF parasympathetic activity respectively, while VLF assessed from short-term recording has a still unclear meaning[14]. Spectral analysis may also be used to analyze the sequence of NN intervals in the entire 24-hour period. The results include an ultra-LF component in addition to the above-mentioned ones[14].

Also non-linear methods are available for HRV analysis because non-linear phenomena are involved in the genesis of HRV. At present, the non-linear methods represent promising tools for HRV assessment but standards are lacking and the full scope of this method cannot be assessed[14].

Clinical studies. Most of clinical studies about HRV evaluated its prognostic role after MI in 24-hour Holter recordings before hospital discharge. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, performed in the thrombolytic era, showed that SDNN < 70 ms was associated with a significantly higher risk of cardiac death and non-fatal cardiac arrest at a follow-up of 2 years in a large population of 1284 patients with a recent MI; the relative risk of SDNN < 70 ms was 3.2[15].

Other studies showed the prognostic impact of the geometrical methods (i.e. triangular index) in the risk stratification of post-MI patients[16,17]. In these studies a depressed HRV triangular index was a predictor of arrhythmic events independent of LVEF, ventricular late potentials and frequent or repetitive ventricular premature beats at Holter monitoring.

An analysis performed using the Holter recordings from the Multicenter Post-Infarction Project (MPIP) showed that also frequency-domain analysis of HRV significantly correlated with the occurrence of fatal arrhythmic events after MI[18]. Moreover, VLF spectral component showed the highest correlation with arrhythmic death at multivariate analysis (relative risk 2.5). On the contrary spectral component at LF or HF had weak and not significant association with mortality.

A recent study focused on a novel frequency domain index for post-infarction risk stratification[19]. Prevalent LF oscillation index (averages of LF peaks detected in 5-min sequences from 24-hour Holter recordings) was determined in the placebo population

of the EMIAT trial. In a multivariate Cox regression model including clinical risk factors, mean RR interval, HRV index, LF and HF HRV spectral power, and heart rate turbulence, this index was the most powerful mortality predictor, with a relative risk of 4.6 (95% CI 2.2-9.3, p = 0.00003). Its predictive power was also blindly validated in the population of the ATRAMI trial: at multivariate analysis including age, LVEF, BRS, mean RR interval, SDNN, LF and HF HRV spectral power, and heart rate turbulence, only LVEF and prevalent LF oscillation index were significant predictors, with relative risks of 4.2 (95% CI 1.5-11.7, p = 0.007) and 3.6 (95% CI 1.3-10.5, p = 0.02), respectively. Thus this innovative analysis of frequency-domain HRV provides a new potent and independent risk marker in post-MI patients.

Few data are available about the prognostic significance of HRV in patients affected by CHF. In the UK-heart study, the prognostic value of HRV was examined in 433 outpatients with CHF, NYHA class I to III, mean LVEF 41%[20]. Time-domain HRV indices and conventional prognostic indicators were related to death by multivariate analysis. The annual mortality rate for the study population in SDNN subgroups was 5.5% for > 100 ms, 12.7% for 50 to 100 ms, and 51.4% for < 50 ms. Concerning frequency-domain measures of HRV, a recent study demonstrated in a cohort of patients with moderate CHF that sudden death was independently predicted by a model including LF power during controlled breathing ≤ 13 ms^2 and left ventricular end-diastolic diameter ≥ 77 mm (relative risk 3.7 and 2.6 respectively)[21].

On the basis of the available data we think that some measures of HRV are effective, simple and low-cost tools which are available for clinicians for the risk stratification of post-MI patients. Thus a larger and systematic use of them should be encouraged as suggested by the Task Force of the European Society of Cardiology. Further studies are needed to support a systematic use of HRV as a risk marker in CHF.

Baroreflex sensitivity

Arterial baroreceptors play an important role in the physiological mechanisms governing the adjustment of cardiovascular system to several conditions. Their stimulation induces arterial pressure changes with modulation of sympatho-vagal activity. Many observations showed that ischemic heart disease and CHF can modify BRS causing inappropriate activity of the sympathetic system. Although several methods have been proposed to measure BRS, the methodology most extensively used in the clinical setting relies on intravenous administration of phenylephrine, a pure alpha-agonist drug that activates arterial baroreceptors and leads to a reflex bradycardia, which can be measured as RR interval prolongation. BRS is quantified in ms of RR interval prolongation for each mmHg of arterial pressure increase.

Clinical studies. Several studies have demonstrated that in comparison with normal subjects, BRS is significantly depressed in post-infarction patients and in patients with heart failure (Fig. 1).

In the ATRAMI study BRS was found to be a significant predictor of cardiac mortality[15]; during 21 months of follow-up, BRS < 3 ms/mmHg carried a significant multivariate risk (2.8) of cardiac mortality. Over age 65, the predictive power of BRS declined much more markedly than HRV; for this reason the specific prognostic value was higher below age 65 for BRS and above age 65 for HRV.

A subanalysis performed in the ATRAMI patients with LVEF < 35% has a particular clinical relevance[22]. This analysis showed the predictive accuracy of a com-

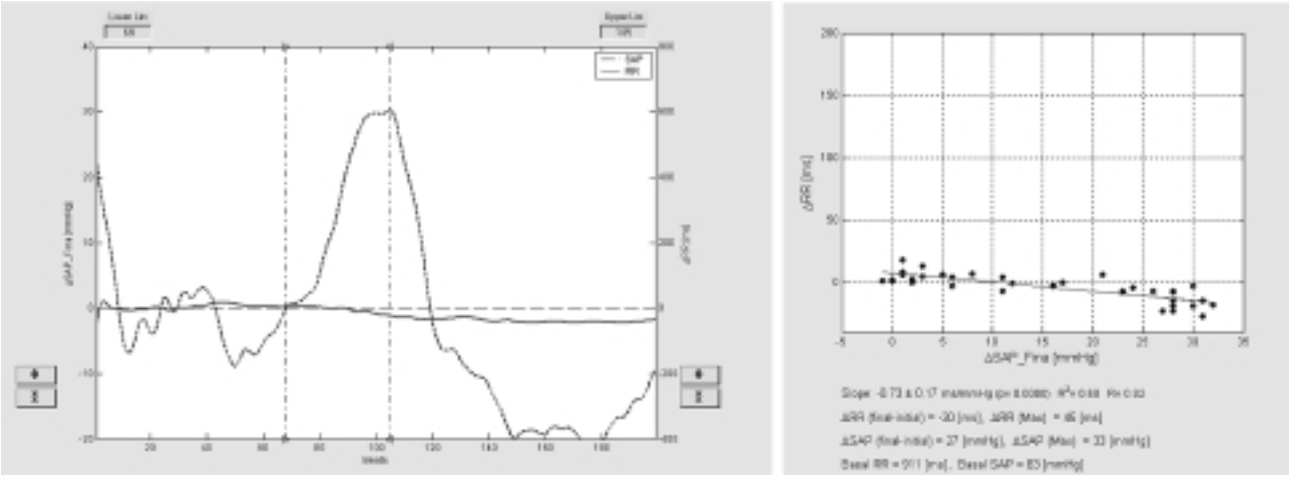

Figure 1. *Results of a phenylephrine test in a patient with post-infarction left ventricular dysfunction, implanted with a cardioverter-defibrillator and a biventricular pacemaker. Beat-to-beat changes in systolic arterial pressure (SAP) and in RR intervals are compared with baseline values* (left panel). *In this patient, heart arte did not change despite a clear-cut increase in SAP. Accordingly, the slope of the regression line expressing baroreflex sensitivity is extremely depressed (0.73 ms/mmHg)* (right panel).

bined use of non-sustained VT and autonomic markers. The absence of non-sustained VT and the presence of a BRS ≥ 3 ms/mmHg identified a subgroup of patients (55% of the studied population) who had a cardiac mortality < 5% at 2 years; on the contrary the remaining 45% of subjects who had one or both abnormal indexes had a cardiac mortality at 2 years of 15-30%. These data are particularly interesting if we focus on the identification of low-risk patients, which is the new target of risk stratification in patients with left ventricular dysfunction. From this study we can also argue that a subgroup of approximately 25% of post-MI patients with LVEF < 35%, who have a depressed BRS < 3 ms/mmHg but no episodes of non-sustained VT, may have a poor prognosis with a cardiac mortality at 2 years of approximately 20% despite the absence of spontaneous non-sustained arrhythmias. This finding suggests that in post-MI patients with > 30% LVEF ≤ 40% not only the presence of non-sustained VT (MADIT-MUSTT screening algorithm), but also autonomic indexes should be investigated, for a more complete evaluation of both arrhythmic risk and indication to EP study.

As for HRV, limited data are available about the prognostic role of BRS in CHF patients. BRS was assessed in 282 CHF patients in sinus rhythm receiving stable medical therapy with moderate to severe CHF and severely depressed LVEF[23]. The BRS of the entire population averaged 3.9 ± 4.0 ms/mmHg and was significantly related to LVEF and hemodynamic parameters. At multivariate analysis, BRS was an independent predictor of death after adjustment for non-invasive known risk factors but not when hemodynamic indexes were also considered, except for patients with severe mitral regurgitation in whom BRS provided information of incremental prognostic value.

In conclusion the analysis of BRS has a significant prognostic value in patients after MI. In such patients the assessment of BRS is highly recommended in addition to non-sustained VT in order to identify true low-risk population about those included in ICD studies. In CHF setting no enough data to prognosticate by means of BRS are available and further studies are needed to better understand its prognostic role.

T-wave alternans

TWA is a beat-to-beat fluctuation in the amplitude or morphology of the T wave that alternates every other beat and has been closely associated with ventricular arrhythmias and sudden cardiac death. More recently, using sensitive signal processing techniques, the detection of microvolt level, virtually unapparent TWA was found to be a potent predictor of life-threatening ventricular arrhythmias in several subgroups of patients (Fig. 2).

Several studies demonstrated macroscopic TWA in different clinical conditions that are associated with

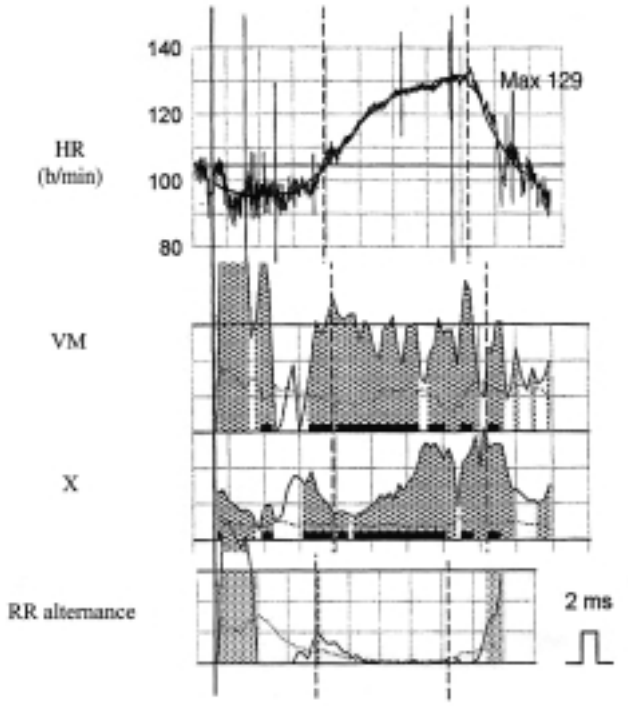

Figure 2. *An example of a positive T-wave alternans tracing from a patient with congestive heart failure* (upper panel). *The* lower panel *shows a portion of T-wave alternans report from the CH2000 system (Cambridge Heart, Inc., Bedford, MA, USA) and includes a plot of heart rate (HR)* (top), *a plot of the magnitude of T-wave alternans over time in vector leads (VM and X)* (middle) *and a plot of RR alternance* (bottom). *The magnitude of T-wave alternans increases as HR increases and reaches the threshold value of 1.9 μV and is shaped in grey. The altenans ratio (K score) is ≥ 3.*

malignant ventricular arrhythmias including long QT syndrome, acute myocardial ischemia and infarction, Prinzmetal's angina and electrolyte derangements[24-30]. TWA is caused by primary alternations in the repolarization phase of the action potential[31,32]. Moreover, above a critical heart rate threshold, repolarization potentials from adjacent regions of the ventricle alternated with opposite phase, that is discordant alternans, causing spatial gradients of repolarization and determining an EP substrate for functional block, reentry and ventricular fibrillation. When electrotonic uncoupling by a structural barrier is present, there is a higher probability of discordant alternans at lower critical heart rate threshold which, inducing a maximum spatial gradient of repolarization, may cause a unidirectional block, reentry, and sustained monomorphic VT. In either case, TWA suggests the presence of EP properties of the myocardium that are associated with the genesis of ventricular arrhythmias.

Clinical studies. The original studies of TWA included different subgroups of very high-risk patients. The first of them was published in 1994 by Rosenbaum et al.[33] and was performed in a group of patients who underwent EP study because of non-fatal sustained ventricular tachyarrhythmias, syncope or, in a minority of cas-

es, supraventricular arrhythmias. Results showed a strong relationship between the presence of TWA evaluated during atrial pacing and the inducibility of ventricular tachyarrhythmias during EP testing as well as 20-month arrhythmia-free survival. Subsequent similar studies confirmed the association between TWA measured during bicycle exercise and both inducible and spontaneous ventricular arrhythmias in patients who underwent EP study and also in ICD recipients[34-36]. It is also important to note that a good reproducibility of both TWA testing results and TWA heart rate threshold was demonstrated during both atrial pacing and exercise-induced sinus tachycardia[37].

A number of small studies in patients with CHF suggest that TWA is associated with an increased risk of ventricular arrhythmias and sudden death. Klingenheben et al.[38] evaluated 107 CHF patients without history of sustained ventricular arrhythmias over a mean follow-up period of 15 months. Patients had a mean LVEF of 28%, coronary artery disease in 67% of cases, received angiotensin-converting enzyme inhibitors and beta-blockers in 93 and 42% of cases, respectively. In this study TWA was a strong and significant predictor of arrhythmic events. Remarkably, none of the patients with a negative TWA test had an arrhythmic event showing a very high negative predictive value. Similar results were found in a study of our group which included 46 patients with CHF, NYHA class III in 35%, mean LVEF 29%, ischemic etiology in 61%[39]; at a mean follow-up of 1.6 years a significant relationship with cardiac death was found: 7 of 23 (30%) patients with positive TWA died during follow-up. Interestingly, also in our study none of 13 patients who had negative TWA died or had malignant ventricular arrhythmias.

The prognostic value of TWA was also confirmed in patients with dilated non-ischemic cardiomyopathy. Hohnloser et al.[40] studied 137 patients with dilated cardiomyopathy, mean age 55 years and LVEF 29%, demonstrating results similar to those found in CHF patients of both etiologies. More recently, at the last Scientific Sessions of the American Heart Association, Costantini et al.[41] showed preliminary results of a study that included 282 patients with a LVEF ≤ 40% and dilated non-ischemic cardiomyopathy. The study tested the hypothesis that a negative TWA would identify patients at low risk of death. The primary endpoint of the study was actuarial all-cause mortality at 2 years. TWA testing was normal (negative) in 95 patients (34%), and abnormal (positive or indeterminate) in 187 patients (66%). None of the patients with a normal TWA test and 12 patients with an abnormal TWA test (8.6%) died ($p \leq 0.02$), further supporting the very high negative predictive value of a negative TWA.

Results of the Marburg Cardiomyopathy Study contradicted the above-mentioned promising results[42]. In this study arrhythmia risk stratification was performed prospectively in 343 patients with idiopathic dilated cardiomyopathy, including analysis of LVEF, signal-averaged ECG, arrhythmias on Holter ECG, QTc dispersion, HRV, BRS, and TWA. During a mean follow-up of 52 months, major arrhythmic events occurred in 46 patients (13%). On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of ejection fraction (95% CI 1.5-3.3, $p = 0.0001$), whereas beta-blocker therapy was associated with a trend toward lower arrhythmia risk (relative risk 0.6, 95% CI 0.3-1.2, $p = 0.13$). Thus in this study TWA as well as other non-invasive risk markers did not seem to be helpful for arrhythmia risk stratification. However some criticisms should be underlined: 1) interpretation of TWA results was not based on a "negative and non-negative" classification, in fact of 38 arrhythmic events, 31 (81%) occurred in the 191 (16%) patients with a non-negative result in comparison to 7 of 72 (10%) patients with a negative TWA ($p = 0.06$); 2) more importantly, as reported by the same authors, the use of beta-blockers in this study was not uniform and many patients did not have beta-blocker therapy at study entry, when risk stratification was performed, and received it during follow-up (52 vs 73%); 3) beta-blockers were withheld for 24 hours before TWA testing whenever possible because the development of TWA is critically dependent on heart rate. This may have increased the proportion of false positive results, with a possible unapparent change of TWA from positive to negative during the follow-up period; 4) the rate of events was very low in the proportion of 3% per year making the follow-up significantly longer (4.3 years) than the follow-up available in the other TWA studies (in general 2 years).

On the basis of these conflicting results further studies are needed in order to define the prognostic value of this promising marker in patients with non-ischemic cardiomyopathy. A large multicenter prospective study is currently ongoing in Italy, the ALPHA Study (T-wave alternans in patients with heart failure). Its aim is to assess the prognostic power of TWA in a large cohort of patients with non-ischemic dilated cardiomyopathy in NYHA class II-III and a LVEF ≤ 40%[43].

TWA has also been demonstrated to be an effective tool for identifying high-risk patients after MI. Ikeda et al.[44] evaluated the prognostic significance of TWA between 2 and 10 weeks after an acute MI in a large cohort of 850 consecutive unselected patients. During a mean follow-up of 25 months, only TWA and LVEF ≤ 40% were significant multivariate predictors for primary events, defined as sudden cardiac death or resuscitated ventricular fibrillation (relative hazard 5.9 [$p = 0.007$] and 4.4 [$p = 0.005$], respectively). In contrast, Tapanainen et al.[45] reported that TWA was not associated with increased mortality in a study of 379 patients after MI. This study was flawed, however, because the TWA study was performed too early after MI (8.1 ± 2.4 days) when TWA is believed to be unstable and unreliable.

Interestingly, two recent studies strongly support the potential role of TWA in the risk stratification of "MADIT II-like" patients. In 129 post-MI patients all with a LVEF < 30%, TWA testing was prospectively assessed[46]. At 24 months of follow-up, no sudden cardiac death or cardiac arrest was seen among patients who tested TWA negative, compared with an event rate of 15.6% among the remaining patients. More recently, a study evaluated the ability of microvolt TWA to identify groups at high and low risk of dying among heart failure patients who met MADIT II criteria for ICD prophylaxis[47]. The primary endpoint was 2-year all-cause mortality. Of 177 MADIT II like patients included in the study, 32% had a QRS duration > 120 ms, and 68% had an abnormal (positive or indeterminate) microvolt TWA test. During an average follow-up of 20 months, 20 patients died and patients with an abnormal TWA test were compared to those with a normal (negative) test. The hazard ratios for 2-year mortality was 4.8 (p = 0.020) and the actuarial mortality rate was substantially lower among patients with a normal TWA test (3.8%) with a corresponding false-negative rate of 3.5%. Interestingly, in this study TWA test resulted a better predictor than QRS complex duration, an index recommended in the United States for selection of MADIT II patients suitable for ICD therapy, in identifying both high-risk and low-risk groups.

TWA is strongly associated with an increased risk of developing ventricular arrhythmias. It is important to note, however, that many of the completed studies are numerically small, and some included extremely high-risk patients (those who had already sustained ventricular arrhythmias), factors that would tend to overestimate the magnitude of risk associated with the presence of TWA.

The clinical application of TWA remains to be defined in larger clinical studies because, to date, no randomized treatment trials are available. Larger prospective epidemiological studies and treatment trials, like the ALPHA study and two other ongoing (ABCD and MASTER) trials, will be necessary to achieve a better estimate of the magnitude of the risk associated with TWA and a better definition of its clinical utility in identifying patients at increased risk of ventricular arrhythmias.

Electrophysiological testing

EP testing is an invasive tool potentially useful for post-MI risk stratification, while it is well known that this procedure is not useful for risk stratification in non-ischemic cardiomyopathy. The endpoint of EP study is the induction of sustained monomorphic VT with a heart rate < 260-270 b/min, which represents an independent predictor of arrhythmic events during the follow-up period. However, programmed ventricular stimulation alone as a predictor of sudden cardiac death in the general MI population without spontaneous arrhythmias cannot be recommended[12,13] and EP study may be used for prognostic evaluation only in patients preselected by non-invasive techniques. A two-step strategy based on the combined use of non-invasive tests and EP study was for the first time prospectively evaluated in a study from our group[17]; 303 surviving patients of acute MI underwent non-invasive evaluation, those who had ≥ 2 variables among LVEF < 40%, ventricular late potentials and repetitive ventricular premature complexes at Holter ECG were considered eligible for EP study. Of 67 eligible patients, 47 (70%) consented to undergo programmed stimulation. A positive test was found to be the strongest independent predictor of events. With a good sensitivity (81%), a two-step strategy selected a group of post-MI patients at sufficiently high risk (event rate 65%) to be considered candidates for interventional therapy. Similar results were shown later by two further studies[48,49]. Moreover, it is also important to note that a two-level strategy was evaluated by Wilber et al.[50] in patients with ischemic cardiomyopathy with LVEF < 40% and non-sustained VT. Results of this study, which showed a rate of sudden death-cardiac arrest at 2 years of 50% in inducible-not suppressed patients, were at the basis of the risk stratification algorithm of MADIT and MUSTT trials.

However, doubts now exist about the real utility of this EP test in the risk stratification cascade. Since the target of risk stratification is now the identification of low-risk patients, the negative predictive value of EP testing is not different from that of non-invasive tests, as shown by a meta-analysis of Bailey et al.[51] (96 vs 94-96%) which analyzed data from 44 reports about arrhythmic risk stratification after MI. Moreover, according to data from the MUSTT trial registry, with regard to the endpoint "arrhythmic death or cardiac arrest", patients who had a negative EP testing showed a high risk of events (12 and 24% at 2 and 5 years), despite a significant statistical difference in comparison to patients with inducible sustained VT[52]. Finally in the MADIT II trial EP testing was performed in the ICD arm. According to results presented in international meetings, the MADIT II investigators reported that positive EP testing was predictive of subsequent sustained VT but not of ventricular fibrillation, as recorded by the ICD during the follow-up period, suggesting that EP testing may not be useful in the prediction of sudden cardiac death.

Temporal aspects of improved survival with the implanted defibrillator

Concerning the survival benefit induced by the ICD therapy in post-MI patients, it is important to underline the relationship between the time from the index MI and the beginning of the therapeutic intervention.

Wilber et al.[53] analyzed whether mortality risk and survival benefit depend on the elapsed time from MI in the MADIT II population. The two treatment groups (ICD vs conventional therapy) were analyzed by time from MI divided into quartiles (< 18, 18 to 59, 60 to 119, and ≥ 120 months). For ICD, covariate-adjusted hazard ratios for the risk of death were 0.97 (95% CI 0.51-1.81, p = 0.92) for recent MI (< 18 months) and 0.55 (95% CI 0.39-0.78, p = 0.001) for remote MI (≥ 18 months). The authors concluded that the survival benefit associated with ICDs seems to be not significant in patients with recent MI.

Results of DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) are in agreement with this finding[54]. This study included patients with recent MI (6-40 days), LVEF ≤ 35% and depressed HRV who were randomized to receive ICD or conventional medical therapy. Kaplan-Meier curves showed a non-significant difference in the risk of death from any cause between the two groups of patients. This is due to a significant reduction of arrhythmic death in the ICD group which is counterbalanced by an equal increase in the risk of non-arrhythmic death.

In a recent further analysis from MADIT II the rate of non-sudden cardiac death was significantly higher in the ICD than in the conventional therapy group (p = 0.003) in the early post-MI period, while the rate of late non-sudden cardiac death was similar in the two treatment arms (p = 0.11)[55]. These data suggest a relevant question about the optimal timing for both risk stratification and ICD implantation after MI. Probably the first months after the ischemic event are characterized by dynamic changes in both left ventricular function and EP properties of the myocardium due to both remodeling process, residual ischemic burden, and late therapy effects and do not represent the best time for prognostic evaluation, which should be postponed later, when more stable functional and clinical conditions are present.

Conclusion

Both non-invasive and invasive testing may be used for prognostic evaluation of patients with heart diseases.

The optimal way to use them in the risk stratification for sudden cardiac death will depend in part on the goals of screening. At present risk markers perform better at identifying low-risk patients who may not need an ICD, because all tests have a high negative predictive accuracy. In our opinion an EP test should not be performed and an ICD should not be implanted in post-MI patients with moderate left ventricular dysfunction (LVEF 30-40%) with a preserved autonomic balance and without non-sustained VT. In MADIT II-like patients EP testing does not seem necessary and an ICD could not be implanted only in patients with a negative TWA test.

Most of the available data refer to patients with ischemic cardiomyopathy but preliminary data on TWA suggest its usefulness in patients with non-ischemic cardiomyopathy too, although a large definitive study has not yet been completed in this important population.

References

1. Myerburg RJ, Interian AJ, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997; 80: 10F-19F.
2. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998; 98: 2334-51.
3. Moss AK, 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: 1993-40.
4. Buxton AE, 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: 1882-90.
5. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 1997; 337: 1569-75.
6. Moss AJ, Zareba W, Hall WJ, et al, for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-83.
7. Kadish A, Dyer A, Daubert JP, et al, for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004; 350: 2151-8
8. Bristow MR, Saxon LA, Boehmer J, et al, for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140-50.
9. Bardy GH, Lee KL, Mark DB, et al, for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225-37.
10. 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: 667-74.
11. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet 1997; 349: 675-82.
12. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2001; 22: 1374-450.
13. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2003; 24: 13-5.

14. Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurements, physiological interpretation and clinical use. Eur Heart J 1996; 17: 354-81.
15. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart rate variability in prediction of total mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998; 351: 478-84.
16. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol 1991; 18: 687-97.
17. Pedretti R, Etro MD, Laporta A, Sarzi Braga S, Carù B. Prediction of late arrhythmic events after acute myocardial infarction from combined use of noninvasive prognostic variables and inducibility of sustained monomorphic ventricular tachycardia. Am J Cardiol 1993; 71: 1131-41.
18. 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: 167-71.
19. Wichterle D, Simek J, La Rovere MT, Schwartz PJ, Camm AJ, Malik M. Prevalent low-frequency oscillation of heart rate: novel predictor of mortality after myocardial infarction. Circulation 2004; 110: 1183-90.
20. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 1998; 98: 1510-6.
21. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003; 107: 565-70.
22. La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias. Implications for clinical trials. Circulation 2001; 103: 2072-7.
23. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. Circulation 1997; 96: 3450-8.
24. Schwartz PJ, Malliani A. Electrical alternans of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. Am Heart J 1975; 89: 45-50.
25. Puletti M, Curione M, Righetti G, Jacobellis G. Alternans of the ST segment and T wave in acute myocardial infarction. J Electrocardiol 1980; 13: 297-300.
26. Hohnloser SH, Huikuri HV, Schwartz PJ, et al. T wave alternans in post myocardial infarction patients (ACES Pilot Study). (abstr) J Am Coll Cardiol 1999; 33: 144A.
27. Kleinfeld MJ, Rozanski JJ. Alternans of the ST segment in Prinzmetal's angina. Circulation 1977; 55: 574-7.
28. Cheng TC. Electrical alternans. An association with coronary artery spasm. Arch Intern Med 1983; 143: 1052-3.
29. Reddy CV, Kiok JP, Khan RG, El-Sherif N. Repolarization alternans associated with alcoholism and hypomagnesemia. Am J Cardiol 1984; 53: 390-1.
30. Shimoni Z, Flatau E, Shiller D, Barzilay E, Kohn D. Electrical alternans of giant U waves with multiple electrolyte deficits. Am J Cardiol 1984; 54: 920-1.
31. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanisms linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999; 99: 1385-94.
32. Watanabe MA, Fenton FH, Evans SJ, Hastings HM, Karma A. Mechanisms for discordant alternans. J Cardiovasc Electrophysiol 2001; 12: 196-206.
33. 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: 235-41.
34. Estes NAM III, Michaud G, Zipes DP, et al. Electrical alternans during rest and exercise as predictors of vulnerability to ventricular arrhythmias. Am J Cardiol 1997; 80: 1314-8.
35. 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: 2247-53.
36. Hohnloser SH, Klingenheben T, Li YG, Zabel M, Peetermans J, Cohen RJ. T-wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. J Cardiovasc Electrophysiol 1998; 9: 1258-68.
37. Hohnloser SH, Klingenheben T, Zabel M, et al. T wave alternans during exercise and atrial pacing in humans. J Cardiovasc Electrophysiol 1997; 8: 987-93.
38. Klingenheben T, Hohnloser SH, Cohen RJ, et al. Predictive value of T-wave alternans in patients with congestive heart failure. Lancet 2000; 356: 651-2.
39. Sarzi Braga S, Vaninetti R, Laporta A, Picozzi A, Pedretti RFE. T-wave alternans is a predictor of death in patients with congestive heart failure. Int J Cardiol 2004; 93: 31-8.
40. Hohnloser SH, Klingenheben T, Bloomfield D, Dabbous O, Cohen RJ. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. J Am Coll Cardiol 2003; 41: 2220-4.
41. Costantini O, Kaufman ES, Bloomfield DM, et al. Patients with a nonischemic cardiomyopathy and a negative T-wave alternans stress test are at a low risk of death. (abstr) Circulation 2004; 110 (Suppl): III-667.
42. Grimm W, Christ M, Bach J, Muller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. Circulation 2003; 108: 2883-91.
43. Salerno-Uriarte JA, Pedretti RF, Tritto M, De Ferrari GM, Klersy C, Sallusti L. The ALPHA study (T-wave alternans in patients with heart failure): rationale, design and endpoints. Ital Heart J 2004; 5: 587-92.
44. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. Am J Cardiol 2002; 89: 79-82.
45. Tapanainen JM, Still AM, Airaksinen KE, Huikuri HV. Prognostic significance of risk stratifiers of mortality, including T-wave alternans, after acute myocardial infarction. Results of a prospective follow-up study. J Cardiovasc Electrophysiol 2001; 12: 645-52.
46. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. Lancet 2003; 362: 125-6.
47. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 2004; 110: 1885-9.
48. Zoni Berisso M, Molini D, Mela GS, et al. Value of programmed ventricular stimulation in predicting sudden death and sustained ventricular tachycardia in survivors of acute myocardial infarction. Am J Cardiol 1996; 77: 673-80.
49. Andresen D, Steinbeck G, Brüggeman T, el al. Risk stratification following myocardial infarction in the thrombolytic

era: a two-step strategy using noninvasive and invasive methods. J Am Coll Cardiol 1999; 33: 131-8.
50. Wilber DJ, Olshansky B, Moran JF, Scanlon PJ. Electrophysiological testing and nonsustained ventricular tachycardia. Use and limitations in patients with coronary artery disease and impaired ventricular function. Circulation 1990; 82: 350-8.
51. 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: 1902-11.
52. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 2000; 342: 1937-45.
53. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. Circulation 2004; 109: 1082-4.
54. Hohnloser SH, Kuck KH, Dorian P, et al, for the DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004; 351: 2481-8.
55. Moss AJ, Vyas A, Greenberg H, et al. Temporal aspects of improved survival with the implanted defibrillator (MADIT-II). Am J Cardiol 2004; 94: 312-5.