

# Risk stratification in nonischemic dilated cardiomyopathy: Current perspectives

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## Abstract

*The clinical goals of risk stratification of sudden death are to identify subjects who are at high risk of, and eventually to reduce the incidence of, sudden death. Numerous studies have described risk stratification techniques for serious cardiac events in patients following myocardial infarction. However, relatively little information is available regarding nonischemic dilated cardiomyopathy. A number of diagnostic methods have been used for risk stratification of patients with nonischemic dilated cardiomyopathy, including presence of syncope, ambulatory electrocardiographic monitoring, programmed ventricular stimulation, QRS duration, QT interval dispersion, QT interval dynamicity, signal-averaged ECG, heart rate variability, heart rate turbulence, baroreflex sensitivity, heart rate recovery, exercise recovery ventricular ectopy, fragmented QRS and cardiac magnetic resonance imaging. In this review, existing data regarding risk stratification of sudden cardiac death in nonischemic dilated cardiomyopathy will be summarized and its implications in clinical practice will be reviewed. (Cardiol J 2010; 17, 3: 219–229)*

**Key words:** risk stratification, sudden cardiac death, nonischemic cardiomyopathy

## Introduction

Nonischemic dilated cardiomyopathy (NIDCM) is a primary disease of the myocardium, characterized by left or biventricular dilatation and systolic contractile dysfunction. The incidence of NIDCM is five to eight cases per 100,000 population per year [1, 2]. Approximately half of patients with recently diagnosed NIDCM die within the first year [3]. Affected patients have impaired systolic function and may develop heart failure (HF). The presenting manifestations may include lethal arrhythmias and sudden cardiac death (SCD) which could occur at any stage of the disease. The majority of SCDs occur in patients who are defined as low risk, including patients with New York Heart Association (NYHA) functional class I or II. The incidence of SCD in NYHA class IV HF is also high, but the risk

of HF makes SCD the second cause of death in this category of patients [4, 5].

With the advent of implantable cardioverter defibrillators (ICDs), it is now possible to prevent SCD. However, the critical issue is to identify the patients who benefit the most. In order to balance the potential risks of device implantation with the associated cost, many investigators have tried to establish risk stratifications. Risk stratification should particularly involve a process of distinguishing subjects at relatively high risk of future major events.

A number of diagnostic methods have been used for risk stratification of patients with NIDCM, including presence of syncope, ambulatory electrocardiographic monitoring, programmed ventricular stimulation, QRS duration, QT interval dispersion, QT interval dynamicity, signal-averaged ECG,

heart rate variability, heart rate turbulence, baroreflex sensitivity, heart rate recovery, recovery ventricular ectopy, fragmented QRS and cardiac magnetic resonance imaging [4]. However, effective and clinically useful risk stratification in NIDCM patients remains a challenge. Low ejection fraction and advanced NYHA functional class are proven important risk factors. However, the high sensitivity of these parameters means less specificity. Moreover, preserved left ventricular function is increasingly seen in HF patients, and there is very limited data regarding risk stratification in that population [6]. The purpose of this review is to summarize the risk stratification methods of SCD in NIDCM and to look at the implications of these methods in clinical practice.

### Syncope

In several clinical studies, patients with NIDCM who experienced syncope have been shown to be at high risk of sudden death [7]. In comparison to patients without documented ventricular tachycardia (VT)/ventricular fibrillation (VF) but with a history of unexplained syncope, patients who have survived documented cardiac arrest reveal similar mortality [8]. In one particular study, Middlekauff et al. [9] reported a one-year actuarial SCD risk of 45% in patients with advanced HF (51% due to NIDCM) and syncope, versus 12% in patients with advanced HF who had not experienced syncope. Brembilla-Perrot et al. [10] described a high prevalence (70%) of previous syncopal events in NIDCM patients with SCD over a mean follow-up duration of two years. Most of the mortality associated with NIDCM and syncope can be attributed to sudden cardiac death. In another study, Fruhwald et al. [11] found a large proportion (83%) of deaths in patients with NIDCM and syncope were characterized as SCD.

The diagnostic value of electrophysiological testing is limited in predicting SCD in patients with NIDCM and syncope. Data on ICD implantation in the population of patients with NIDCM and syncope is limited to smaller, uncontrolled observational clinical studies. Knight et al. [8] published a prospective analysis of 14 patients with NIDCM and unexplained syncope who underwent ICD implantation versus a comparator group of 19 survivors of SCD with NIDCM. They reported a high incidence (50%) of appropriate defibrillator shocks in the NIDCM patients with syncope. This was comparable to the rate of corresponding events (42%) in those who had survived cardiac arrest. Furthermore, there was no significant difference in mor-

tality (28% in those with syncope and 32% in SCD survivors) between the two groups.

In one recent study, Phang et al. [12] compared 108 consecutive patients with NIDCM presenting with syncope to 71 patients with NIDCM who presented with sustained ventricular arrhythmias, with regard to freedom from any ventricular arrhythmias or life-threatening arrhythmias and all-cause mortality. In this large group of patients with NIDCM presenting with syncope, they found that such patients were at high risk of ventricular arrhythmias and mortality, as high as patients with NIDCM presenting with sustained ventricular arrhythmias.

Based on the available scientific evidence in patients with NIDCM, American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities [13] recommends ICD implantation as reasonable for patients with unexplained syncope, significant left ventricular (LV) dysfunction, and NIDCM.

### Ambulatory electrocardiographic monitoring

The value of detection of asymptomatic ventricular arrhythmias in patients with systolic ventricular dysfunction is controversial. Many HF specialists specifically do not recommend performing ambulatory electrocardiography (AECG) monitoring in patients without symptoms of palpitations or syncope. This advice is derived from the numerous antiarrhythmic trials that showed increased mortality using class IA, class IC, and class III antiarrhythmic agents [14, 15].

The incidence of non-sustained ventricular tachycardia (NSVT) in patients with NIDCM varies from 33–79% [16, 17]. The prognostic significance of NSVT in AECG monitoring in patients with NIDCM has been previously explored in relatively small observational studies. Meinertz et al. [18] (in 74 patients with NIDCM) and Unverferth et al. [19] (in 69 patients with NIDCM) found a significant association between the presence of ventricular arrhythmias detected on AECG and the risk of mortality in patients with NIDCM. In contrast, von Olshausen et al. [20] (in 73 patients with NIDCM) and Costanzo-Nordin et al. [21] reported that the presence of NSVT on AECG did not predict poor clinical outcome in patients with NIDCM. Iacoviello et al. [22] recently reported that detection of NSVT on AECG significantly improved risk stratification in 179 consecutive NIDCM patients.

Baker et al. [23] recently assessed a cohort of 144 patients with NIDCM. Non-sustained ventri-

cular tachycardia was found in 31% of patients during AECG monitoring. Age, low ejection fraction, higher mean heart rate, lower heart rate range, and presence of NSVT were found as predictors of mortality. In another study, Grimm et al. [24] assessed a cohort of 343 patients with NIDCM using multiple diagnostic tests to assess risk for SCD. The presence of NSVT on AECG was associated with a trend towards an increased risk of major arrhythmic events without statistical significance. Grimm et al. [25] examined the prognostic significance of the rate and length of NSVT on AECG recorded in same cohort of 343 patients with NIDCM. NSVT was defined as  $\geq$  three consecutive ventricular premature beats at  $> 120$  bpm. Patients with 3–4 beat runs of NSVT had arrhythmia-free survival comparable to patients without NSVT on AECG. The incidence of major arrhythmic events during follow-up was 2% in patients without NSVT, 5% in patients with 5–9 beat runs of NSVT and 10% in patients with  $\geq$  ten beat runs of NSVT. Unlike the length, the rate of NSVT was similar in patients with versus without subsequent major arrhythmic events ( $163 \pm 23$  vs  $160 \pm 24$  bpm). Therefore, the length, but not the rate, of NSVT on AECG was found as a predictor of major arrhythmic events in patients with NIDCM.

Despite the fact that we have evidence from several studies, the prognostic importance of NSVT or frequent ventricular arrhythmias has not fully been understood. Clinical studies have shown that NSVT is predominantly a marker of risk for cardiac mortality but is not very efficient in selecting a high risk group for SCD.

### Programmed ventricular stimulation

Programmed ventricular stimulation (PVS) has been useful for risk stratification in patients with coronary artery disease (CAD), but its utility in patients with NIDCM has been controversial. Utilization of PVS in NIDCM has been studied in rather small and inhomogeneous groups [26]. The commonest finding of PVS in patients with NIDCM is polymorphic VT or VF which is a non-specific arrhythmia [27]. In addition, the variability of stimulation protocols makes assessment of predictive values difficult. For instance, in the studies of Stamato et al. [28] and Hammill et al. [29], there was no inducible sustained polymorphic VT or VF. In contrast, Grimm et al. [30] reported the incidence of inducible sustained polymorphic VT or VF as 29%. This discrepancy might reflect differences in patient selection and stimulation protocol.

Grimm et al. [30] assessed the role of PVS for arrhythmia risk prediction in 34 patients with NIDCM and spontaneous NSVT. Arrhythmic events occurred in 31% of patients with inducible sustained ventricular arrhythmias, compared to 24% of patients without inducible sustained ventricular arrhythmias at PVS, but there was no statistically significant difference. Inducibility of sustained monomorphic VT as well as inducibility of polymorphic VT or VF at PVS failed to predict subsequent arrhythmic events. Becker et al. [26] investigated the prognostic role of asymptomatic NSVT and PVS in 99 patients with NIDCM. They suggested that PVS was inappropriate to specifically identify patients at high risk of SCD because of a low inducibility rate (7%) and a relatively poor positive predictive value for subsequent arrhythmic events (29%).

### QRS duration

QRS duration is a simple measure of the duration of ventricular activation measured on the 12-lead ECG and is a manifestation of intraventricular or interventricular conduction delay. Prolongation of QRS (120 ms) on 12-lead electrocardiogram occurs in 14–47% of patients with HF [31]. Left bundle branch block (BBB) is far more common than right BBB. Left-sided intraventricular conduction delay is associated with more advanced myocardial disease, worse left ventricular (LV) function, poorer prognosis, and a higher all-cause mortality rate compared to narrow QRS complex. Baldasseroni et al. [32] demonstrated that NYHA class III–IV HF patients with QRS prolongation (left BBB) have an increased mortality at one year. Silverman et al. [33] investigated the impact of the etiology of HF on the prognostic importance of a prolonged QRS and an abnormal SAECG in 200 patients with HF. Patients were categorized according to etiology of HF and electrocardiographic parameters. The mortality of patients with a prolonged QRS was compared to the mortality in those with both abnormal and normal SAECGs. NIDCM patients with a prolonged QRS had significantly worse survival than other patients. However, nonischemic patients with an abnormal SAECG did not have a worse prognosis than patients with a normal SAECG. In contrast, a prolonged QRS was not a predictor of poor prognosis in patients with ischemic cardiomyopathy [33].

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was a randomized, placebo-controlled study designed to determine whether amiodarone or a single-chamber ICD programmed to shock only would reduce all-cause mortality when

compared to a placebo in patients with dilated cardiomyopathy (ischemic or nonischemic), NYHA functional class II and III HF, and LV dysfunction (LVEF 35%) [34]. A total of 2,521 patients were enrolled with randomization to ICD (n = 829), amiodarone therapy (n = 845), or placebo (n = 847). The median age of patients was 60 years (range 19–90). Both ischemic and nonischemic patient groups were found to benefit from ICD therapy. When stratifying the ECG data in the ICD versus placebo groups, ICD therapy was associated with a significant reduction in the risk of mortality compared to placebo, regardless of the ECG measure, including QRS duration < 120 ms or 120 ms. Another analysis found that although ICD shock rates were highest in patients with a longer QRS duration, patients with a narrow QRS also experienced a significant number of shocks, suggesting that treatment is warranted for this group [34]. Dhar et al. [35] evaluated the prognostic significance of QRS duration for arrhythmic outcomes in 1,232 patients who were enrolled in the Multi-center Automatic Defibrillator Implantation Trial (MADIT) II. Patients were randomized to ICD implant plus conventional medical therapy versus conventional medical therapy alone, in a 3:2 ratio. In the medically-treated arm, the 138 patients (29%) with QRS duration  $\geq$  140 ms exhibited more than a doubled risk of SCD. However, in the ICD-treated arm, the 255 patients (35%) with QRS duration  $\geq$  140 ms showed no difference in time to SCD or first appropriate ICD therapy for rapid VT/VF compared to those with QRS duration < 140 ms.

In contrast to the studies presented above, in the Marburg Cardiomyopathy Study, Grimm et al. [24] reported no significant correlation between intraventricular conduction delay and SCD during the follow-up. In the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study, 458 NIDCM patients with a left ventricular ejection fraction (LVEF) of  $\leq$  35%, and premature ventricular complexes or NSVT were enrolled. There was no significant association between QRS duration and all-cause mortality [36].

Although the data is not uniform, a moderate amount of data showed that increased QRS duration identifies patients at higher risk of SCD. Prospective trials specifically designed to address this issue are needed for the use of QRS duration to further stratify risk for SCD in patients with NIDCM.

### QT dispersion and QT interval dynamicity

Ventricular repolarization is a critical time in the cardiac cycle, playing a considerable role in the

pathophysiology of malignant arrhythmias. Twelve-lead ECG measurements of the QT interval (i.e. QT interval and QTd) are considered a global index of the duration. Dispersion of repolarization in the ventricular myocardium has largely been investigated in order to better identify patients with various clinical conditions prone to experience major arrhythmic events [22, 37]. It has been reported that an increased QT dispersion is associated with arrhythmic events in various clinical settings, such as long QT syndrome, HF, coronary artery disease, post-myocardial infarction or hypertrophic cardiomyopathy [37]. However, the ability of QT dispersion (QTd) to identify cardiac patients at high risk of sudden death remains uncertain due to conflicting findings. This could be due to the fact that ECG parameters poorly reflect the complexity of the ventricular repolarization process depending on different dynamic components as transmembrane ion currents, heart rate, and autonomic nervous system activity [22].

Galinier et al. [38] reported that QTd was significantly higher in NIDCM patients with SCD. In multivariate analysis, only a QTd > 80 ms was an independent predictor of sudden death and arrhythmic events in NIDCM, but not in ischemic heart disease. Fei et al. [39] found, in 60 patients with NIDCM, that there was no significant difference in QTd between survivors and those who died or were transplanted during follow-up. Furthermore, no significant difference in QTd was observed between patients with and without VT detected on AECG. Grimm et al. [40] investigated QTd in 107 patients with NIDCM compared to 100 healthy matched controls. The usefulness of QTd for risk stratification was limited due to the large overlap of QTd among patients with and without arrhythmic events during a follow-up of  $13 \pm 7$  months. Grimm et al. [24] also found negative results with QTc dispersion with a longer follow-up in 343 patients with NIDCM in the Marburg Cardiomyopathy Study. Fauchier et al. [41] recently assessed the role of QTd for the long-term risk of cardiac death and of major arrhythmic events in 162 NIDCM patients. They reported that QT dispersion was not a predictor of cardiac death in univariate or in multivariate analysis, and was of similar value for patients with or without bundle branch block.

QT dynamicity is the one of the novel methods that could be used in risk stratification of SCD. The QT dynamicity indices considered in the studies were: the QT-slope (the slope of the regression line between QT and RR during the 24-hour period) and the mean QT corrected for heart rate (Bazett's

formula). Iacoviello et al. [22] assessed the QT interval dynamicity in 179 consecutive NIDCM patients without a history of sustained VT and/or VF at enrollment. During a mean follow-up of 39 months, nine patients died suddenly and 15 experienced VT and/or VF. At multivariate analysis, LVEF, NSVT and QTc-slope were significantly associated with arrhythmic events. Increased QTc-slope in patients with NIDCM was associated with the occurrence of major arrhythmic events regardless of other clinical variables, suggesting its clinical usefulness in stratifying arrhythmic risk. The limitations of QT/RR slope analysis are strictly related to the feasibility of measuring. Patients with atrial fibrillation or paced rhythm, as well as those with abnormal ventricular repolarization, could not be optimally evaluated [22].

### Signal averaged ECG

Signal-averaged ECG is used to detect the occurrence of late activation within the myocardium (late potentials) noninvasively by means of surface ECG electrodes. As the late potentials are small in amplitude (in the microvolt range), the only way to obtain an acceptable signal-to-noise ratio from the body surface is to average together hundreds of QRS complexes to determine a mean QRS morphology [42].

Typically, three parameters are assessed in SAECG: the duration of the filtered QRS (fQRS) complex, the duration of any low-amplitude signal (LAS; signal,  $< 40 \mu\text{V}$ ), and the root-mean-square (RMS) voltage in the last 40 ms of the QRS. Many investigators consider the SAECG to be 'abnormal' if any two of these three parameters are abnormal. The normal values for SAECG are instrument-specific and dependent on gender [43]. SAECG appears to be useful in arrhythmia risk stratification of patients with ischemic heart disease. Most of the studies concerning the prognostic value of SAECG in homogenous populations with NIDCM gave conflicting results [44].

Mancini et al. [45] found abnormal SAECG as a predictor of death and/or VT in 114 patients with NIDCM who referred for heart transplantation. Although the results of this study in high-risk patients were promising, the prognostic value of SAECG remained unknown because there have been no large studies in mildly symptomatic patients with NIDCM. Another important point in this study was the inclusion of individuals with BBB, which compromises the utility of the SAECG as an adequate method for risk stratification in this population. In the first year of follow-up, survival was 95% in pa-

tients with a normal SAECG, 88% in patients with a BBB, and only 39% in patients with an abnormal SAECG [45]. Fauchier et al. [44] evaluated the long-term prognostic value of SAECG in 131 patients with NIDCM. Late potentials on SAECG were present in 27% of the patients. Patients with late potentials had an increased risk of all-cause cardiac death and of arrhythmic events.

In contrast, Silverman et al. [33] found that an abnormal SAECG was an independent predictor of all-cause death in patients with HF due to ischemia, whereas this was not the case in patients classified as having NIDCM. On the other hand, Turitto et al. [46] found that the two-year actuarial survival free of arrhythmic events was similar in patients with or without abnormal findings on SAECG. Galinier et al. [47] prospectively followed 151 patients with HF, 48% of whom were diagnosed with NIDCM. At baseline, late potentials were detected in 34% of the NIDCM patients, which was similar to the incidence of late potentials in patients with HF due to CAD. Late potentials were not found to be predictive of total mortality or sudden cardiac death. In the Marburg Cardiomyopathy Study, Grimm et al. [24] performed arrhythmia risk stratification in 343 patients with NIDCM, including analysis of LVEF and size by echocardiography, SAECG, AECG, QTc dispersion, heart rate variability, baroreflex sensitivity, and microvolt T-wave alternans (TWA). SAECG, baroreflex sensitivity, heart rate variability, and TWA were not found to be useful for arrhythmia risk stratification.

Based on the data presented above, an abnormal result on SAECG might be a marker of increased risk of sustained ventricular tachycardia or death. SAECG appears to have a superior negative predictive value, with the caution that the presence of bundle branch block may significantly lower the specificity of SAECG. However, the poor positive predictive value for arrhythmic events and decreased specificity in the significant number of patients with bundle branch block reduces the value of this test.

### T wave alternans

TWA is an ECG phenomenon defined as beat-to-beat alternation of the morphology, amplitude, and/or polarity of the T-wave. It refers to alternation of the electrocardiographic ST-segment, T- and U-wave. The use of TWA relies upon microvolt level fluctuations that are invisible to the naked eye but require computerized signal processing methods to be demonstrated.

Adachi et al. [48] evaluated TWA as a predictor of arrhythmic events and sudden cardiac death in 82 patients with NIDCM. During an average follow-up duration of 24 months, ten patients experienced arrhythmic events. Nine of them had a positive TWA; the negative and positive predictive values of TWA were found to be, respectively, 97% and 30%, whereas the relative risk was 10.2.

Kitamura et al. [3] studied 104 patients with NIDCM with the goal of assessing whether the heart rate threshold at which TWA appears (onset heart rate) would be of prognostic value. Onset of TWA with heart rates below 100/minute conferred increased risk of SCD or sustained VT/VF, with a predictive accuracy of 78%. Hohnloser et al. [49] assessed the predictive value of TWA and of conventional risk stratifiers in 137 patients with NIDCM. Arrhythmic events occurred in 13 patients who were positive, two who were negative, and three who were indeterminate for TWA. At multivariate analysis, TWA was the only independent predictor of an arrhythmic event, whereas LVEF, heart rate variability (HRV), and the presence of NSVT did not show a significant predictive value. In the multicenter study by Bloomfield et al. [50] NIDCM was present in 282 patients (51%). The two-year event rates for the primary end point (all-cause mortality or non-fatal VT) were 13.3% and 0% respectively among patients with abnormal and normal TWA tests.

In contrast to these positive findings, Grimm et al. [24] did not find TWA to predict the risk of arrhythmias in a population of 343 patients with NIDCM, of whom 263 were in sinus rhythm and underwent the analysis. On multivariate analysis, only reduced LVEF proved to be a significant predictor of arrhythmic events, whereas TWA, HRV, baroreceptor sensitivity (BRS), and the presence of late potentials had no additional value.

The T-wave Alternans in Patients with Heart failure (ALPHA) study evaluated the independent predictive value of TWA in 446 patients with NIDCM [51]. Patients with a history of cardiac arrest or sustained VT were excluded. The primary end point of the study was the combination of cardiac death and life-threatening arrhythmias; the secondary end points were total mortality and the combination of arrhythmic death and life-threatening arrhythmias. Enrolled patients were followed up for 18 to 24 months (median time 19 months); during this follow-up, 28 patients died (18 of cardiac causes and seven of sudden death) and 11 patients had symptomatic sustained VT or VF. The TWA test was negative in 34.6% of the patients, positive in 44.8%, and indeterminate in 20.6%. Primary end point rates

in patients with abnormal and normal TWA tests were 6.5% (95% confidence interval [CI]: 4.5–9.4%) and 1.6% (95% CI: 0.6–4.4%), respectively. The study concluded that patients with a normal TWA test have a very good prognosis and are likely to benefit little from ICD therapy [51]. Also in a recent meta-analysis, De Ferrari et al. [52] evaluated 1,456 NIDCM patients and reported that abnormal (both positive and indeterminate) TWA patients have a three times greater risk compared to normal TWA patients. Despite these significant results, which points to TWA as the most effective risk stratifier in this population of patients, the positive predictive value of the test remains relatively low.

The ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death recommends the use of TWA as reasonable to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias (Class II, Level of Evidence: A) [5].

### Heart rate variability

Measures of autonomic function have been evaluated to estimate risk for SCD. Heart rate variability is an indirect measure of cardiac autonomic activity, which is the evaluation of beat to beat variability of the R-R interval. Required data is obtained from digitized AECG tracings. HRV can be analyzed in the time domain or in the frequency domain [42]. Common time-domain measures of HRV include the following: SDNN, the standard deviation (SD) of the R-R interval; SDANN, the SD of the five-minute mean R-R intervals tabulated over an entire day and the SD index; and the mean of the five-minute SDs of the R-R interval tabulated over the entire day. Frequency domain measures of HRV are usually classified according to the following range of frequencies analyzed: ultra-low frequency (ULF; < 0.0033 Hz); very low frequency (VLF; 0.0033–0.04 Hz); low frequency (LF; 0.04–0.15 Hz); high frequency (HF; 0.15–0.40 Hz) or total power [42].

Previous studies have proven that HRV is predictive of arrhythmic occurrences following myocardial infarction [5]. Observational studies also suggest that it may be useful in the presence of NIDCM [5]. Fauchier et al. [53] found a weak to moderate correlation between SDNN and left ventricular function in 93 patients with dilated NIDCM. On multivariate analysis, these investigators identified SDNN as an independent predictor of cardiac death or heart transplant. Yi et al. [54] also showed

that reduced heart rate variability had independent predictive value for death from progressive HF in a cohort of 64 patients with dilated cardiomyopathy. In a large prospective multicenter study, Nolan et al. [55] investigated the prognostic value of heart rate variability in 433 outpatients with HF. In that study, SDNN was associated with death from progressive HF, but not with sudden cardiac death. In the DEFINITE (Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation) trial, Rashba et al. [56] showed that patients with NIDCM and preserved HRV have an excellent prognosis and may not benefit from prophylactic ICD placement. These results appear to contradict those of Grimm et al. [24], where findings did not support the use of HRV to select patients with NIDCM for prophylactic ICD therapy.

Based on the data presented above, patients with NIDCM have decreased heart rate variability. However, this decrease is associated with systolic ventricular function, and does not correlate with increased risk of ventricular arrhythmias. The weight of the evidence suggests that due to the poor positive predictive value of HRV, this test has little role to play in risk stratification for sudden death of patients with NIDCM.

### Heart rate turbulence

Following a ventricular premature complex (VPC) with a compensatory pause, there is known to be an initial acceleration, and a later deceleration, of sinus rhythm. This sequence is termed heart rate turbulence (HRT), and it is thought to be a measure of the autonomic response to perturbations of arterial blood pressure invoked by a VPC [57]. HRT parameters included turbulence onset (TO) and turbulence slope (TS). TO was calculated as the percentage change between the mean of the first two sinus RR intervals after a VPC and the last two sinus rhythm RR intervals before the VPC. These measurements were performed for each single VPC and subsequently averaged. The TS was calculated as the maximum positive slope of a regression line assessed over any sequence of five subsequent RR intervals within the tachogram [57].

Grimm et al. [58] investigated the prognostic significance of HRT in 242 NIDCM patients who were enrolled in the Marburg Cardiomyopathy database. In this study, HRT onset was found as a significant predictor of transplant-free survival, in the same way as LV size and NYHA class. However, only LVEF remained a significant risk predictor on multivariate analysis for arrhythmia risk stratification.

In the Muerte Subita e Insuficiencia Cardiaca (MUSIC; Sudden Death in Heart Failure) study, 576 patients with HF and sinus rhythm enrolled in a study designed to assess risk predictors of sudden cardiac death in patients with HF in NYHA classes II and III [59]. Both HRT parameters, but especially turbulence slope, were significantly correlated with clinical indices of HF (the third heart sound, peripheral edemas, jugular distension, and pulmonary congestion). Patients in NYHA class III had significantly lower turbulence slopes and greater turbulence onset values than those in class II. Abnormal HRT parameters were associated with longer QRS duration, higher mean heart rate, more frequent ventricular arrhythmias and progressively decreasing parameters of heart rate variability. Abnormal HRT parameters were found as independent predictors of HF severity on multivariate analyses [59].

Miwa et al. [57] assessed 375 consecutive patients with dilated cardiomyopathy including ischemic ( $n = 241$ ) and nonischemic causes ( $n = 134$ ). HRT was considered positive when both TO was  $\geq 0\%$  and TS was  $\leq 2.5$  ms/R-R interval. The primary endpoint was defined as cardiac mortality and the secondary endpoint as occurrence of hemodynamically stable sustained ventricular tachyarrhythmias. HRT positivity was significantly associated in both the ischemic and NIDCM patients with both the primary endpoint and with combined endpoints [57].

Klingenheben et al. [60] evaluated the predictive value of heart rate turbulence with those of conventional autonomic risk markers for ventricular tachyarrhythmic events in 114 patients with NIDCM. Determinate test results were obtained for heart rate variability in 98%, for BRS in 90%, and for heart rate turbulence in 75% of patients. During a follow-up of  $22 \pm 17$  months, an end point event occurred in 15 patients. BRS was found as a significant predictor of arrhythmic events both on univariate and multivariate analysis, whereas HRT did not yield predictive power in these patients.

### Baroreceptor sensitivity testing

Baroreceptor sensitivity is a marker of the capability of reflexes to increase vagal activity and to decrease sympathetic activity in response to a sudden increase in blood pressure. Phenylephrine ( $2-4 \mu\text{g}/\text{kg}$ ) is given intravenously by at least three bolus injections at intervals of 10 minutes to raise systolic arterial pressure by 15–40 mm Hg.

Mortara et al. [61] focused on the prognostic value of BRS testing in 282 patients with HF. They found a significantly higher mortality among pa-

tients with greatly reduced baroreflex sensitivity ( $< 1.3$  ms/mm Hg) compared to those with more preserved reflex activity. However, half of the patients in that study were suffering from CAD. In the Marburg Cardiomyopathy Study, Grimm et al. [24] reported no correlation between BRS results and sudden death during the follow-up.

The evidence suggests that BRS is not a reliable risk stratification method for SCD in NIDCM, and may not have additional benefit over other markers of autonomic tone, such as HRV. In the ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, the use of ECG techniques (SAECG, HRV, HRT and BRS) is recommended as possibly useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias (Class II, Level of Evidence: B) [5].

### Heart rate recovery and recovery ventricular ectopy

Heart rate recovery after graded exercise is one of the most commonly used techniques which reflect autonomic activity. Immediately after graded exercise, heart rate normally falls in a biphasic manner, with an initial rapid decline occurring during the first 30–60 s of recovery [62, 63]. Imai et al. [64] demonstrated that this initial steep descent is marked in athletes and attenuated in patients with HF and that it can be eliminated by administration of atropine. Thus, parasympathetic reactivation probably plays a major role in regulating heart rate recovery. Because impaired parasympathetic tone correlates with increased risk of death, it was hypothesized that an attenuated heart rate recovery would similarly predict an increased risk of death [4].

Severe ventricular ectopy during recovery after exercise is predictive of increased mortality in patients with severe HF and can be used as a prognostic indicator of adverse outcomes in HF cohorts [4]. O'Neill et al. [65] assessed 2,123 (49.1% NIDCM) consecutive patients with left ventricular systolic ejection fraction  $\leq 35\%$  who were referred for symptom-limited metabolic treadmill exercise testing. Severe ventricular ectopy was defined as the presence of ventricular triplets, sustained or NSVT, ventricular flutter, polymorphic VT, or VF. The primary end point was all-cause mortality, with censoring for interval cardiac transplantation. Severe ventricular ectopy during recovery was associated

with an increased risk of death. After adjustment for ventricular ectopy at rest and during exercise, peak oxygen uptake, and other potential confounders, severe ventricular ectopy during recovery remained an independent predictor of death.

### Fragmented QRS

Fragmented QRS (fQRS) is defined on the routine 12-lead ECG and includes various morphologies of the QRS wave with or without a Q wave. Fragmented QRS includes the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of  $>1$  R' (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory [66]. Typical BBB pattern (QRS  $> 120$  ms) and incomplete right BBB were excluded from the definition of fQRS. The mechanism of fragmentation in the QRS complex on the surface 12-lead ECG has been explained by inhomogeneous activation of the ventricles because of myocardial scar and/or ischemia. The amount, distribution, and pattern of scar depends on the disease states. Scars in patients with non-ischemic cardiomyopathy are patchy and mid-myocardial or subepicardial. Therefore, different morphologies of fQRS are caused by shifting of the QRS vector during depolarization in and around the areas of scarred or ischemic myocardium, depending on their extent and location in the ventricles [66].

Michael et al. [67] studied arrhythmic events and all-cause mortality in 105 patients with NIDCM who received an ICD for primary and secondary prophylaxis. The combined endpoint of ICD therapy and mortality was also significantly higher in the fQRS group as compared to the non-fQRS group (70% vs 17.6%). Mortality was 24% in the fQRS group and 14% in the non-fQRS group. Event-free survival was significantly decreased in the fQRS group versus the non-fQRS group.

Fragmented QRS on 12-lead ECG might be a predictor of arrhythmic events in patients with NIDCM. Note that fQRS is a nonspecific finding and should only be interpreted in the presence of pertinent clinical evidence.

### Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging is a powerful tool to assess morphology and myocardial function, as well as changes in tissue structure. Myocardial damage, viability, and scarring have been frequently studied in patients with post-myocardial infarction using pathological late uptake of



extracellular MR contrast media by the ventricular myocardium (LGE, late gadolinium enhancement) [68]. Wu et al. [69] examined NIDCM patients with LVEF  $\leq$  35% who underwent CMR before placement of an ICD for primary prevention of sudden cardiac death. After adjustment for LV volume index and functional class, patients with LGE had an eight times greater risk of experiencing the primary outcome. Hombach et al. [70] assessed 141 patients with NIDCM. LGE was detected in 36 patients (26%). The presence of LGE, QRS  $>$  110 ms and diabetes mellitus were found to be significant parameters for a worse outcome.

### Nonlinear dynamics

Clinicians and basic investigators are increasingly aware of the remarkable interest in nonlinear dynamics (Chaos Theory). In linear systems, the magnitude of the output (y) is controlled by that of the input (x) according to simple equations in the familiar form  $y = mx + b$  [71, 72]. Two central features of linear systems are proportionality and superposition. Proportionality means that the output bears a straight-line relationship to the input. Superposition refers to the fact that the behaviour of linear systems composed of multiple components can be fully understood. In contrast, even simple nonlinear systems violate the principles of proportionality and superposition. Nonlinear dynamics include nonlinearity, fractals, periodic oscillations, bifurcations, complexity and chaos [71, 72].

Researchers and clinicians should recognize that arrhythmic cardiac death is a nonlinear and heterogeneous phenomenon. The transitions between rhythms capable of sustaining life and those that lead to death occur via a variety of different scenarios that are amenable to analysis [71, 72]. Although for now it will be necessary to rely on criteria for risk stratification based on large clinical studies, in the future, individualized analyses that combine traditional clinical measures of cardiac risk with genetic and mathematical analyses that offer insight into the pathophysiology of individual patients should provide improved methods of risk stratification [72].

### Conclusions

In conclusion, it appears that a NIDCM patient has a less certain clinical course in terms of SCD compared to similar patients with ischemic cardiomyopathy. Current indications for ICD implantation envisage large numbers of patients at risk of

SCD. Due to the substantial costs of these devices, it would not be feasible to place them in all patients with NIDCM. Most of the current trials of risk stratification for patients with NIDCM are underpowered and non-randomized. Further studies that define the precise role of various risk stratification modalities are needed.

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