The Riddle of Nonsustained Ventricular Tachycardia and Sudden Cardiac Death
Are We Approaching a Solution?

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T
 he graveyard of cardiovascular therapeutics is littered with common-sense ideas. Premature ventricular contractions trigger episodes of ventricular fibrillation; therefore, suppression of premature ventricular contractions should lessen the risk of cardiac arrest and sudden death—and yet it has not.1–2 Sudden cardiac death (SCD), which is responsible for between 184 000 and 450 000 deaths in the United States per year,3–6 remains a conundrum, both in prevention and prediction of those at risk. The epidemiology of SCD presents challenges for clinical care; patients who are in the known highest-risk subgroups, such as those with abnormal systolic left ventricular function, account for the minority of events.7 Even among this high-risk subgroup with a mortality benefit afforded by implantable cardioverter defibrillator (ICD) placement, the majority of implanted patients never require therapy for arrhythmic events from the device.8–9 This actuality emphasizes the need to better identify those at highest risk, even within subpopulations in jeopardy of SCD.

In the prethrombolytic era of therapy for myocardial infarction (MI), ventricular ectopy and nonsustained ventricular tachycardia (NSVT) were known to predict increased mortality post MI.10–12 However, with reperfusion and use of β-blockers, NSVT after MI has not always been demonstrated to be an independent predictor of mortality, especially after ejection fraction (EF) is taken into account, and its prognostic significance is ambiguous.13–16 Moreover, whether NSVT is causative in the genesis of SCD or simply a marker of imperiled substrate or disordered autonomic regulation is unknown. In one of the most simultaneously enlightening and discouraging clinical trials, the Cardiac Arrhythmia Suppression Trial, not only did suppression of ventricular ectopy not result in a decreased risk of SCD, treatment with flecainide was associated with an increased risk of SCD, possibly due to proarrhythmia.1 Subsequent pharmacological trials also have demonstrated the lack of correspondence between the ability to suppress arrhythmia and an improvement in prognosis.2,17–18 Importantly, these studies were largely performed in patients with acute ST elevation MI, rather than the distinct pathology of non-ST elevation acute coronary syndrome (NSTE-ACS). Because of the increasing prevalence of NSTE-ACS and changes in medical management in recent years, the lack of focus on these patients is an important research gap.

In this context of a need to better understand the relationship between NSVT and SCD, and to identify other predictors of SCD risk, Scirica and colleagues19 provide important new information about the epidemiology and implications of NSVT in the NSTE-ACS population. In this issue of Circulation, they report data from seven days of continuous ECG monitoring and the association of ECG findings with SCD in 6345 patients from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial. Although the primary end point of this randomized, placebo-controlled trial of the addition of ranolazine to standard therapy has previously been published (no reduction in a composite end point of recurrent ischemic events, MI, or cardiovascular death), the ECG data provide important new insights.18 The study population was largely white and one third male, the median age at enrollment was 64 years, one-fourth smoked, one third had diabetes mellitus, two thirds had hyperlipidemia and no prior MI, three quarters had hypertension, and less than 10% of subjects for whom an echocardiogram was available had a left ventricular EF (LVEF) of <40%.18 In this observational analysis, the value of ancillary information from a large, well-designed, clinical trial is apparent. In contrast to some prior evidence about the acute MI population,13–15 the authors report that in this NSTE-ACS population, despite modern medical and interventional therapy, NSVT is both common and related to SCD if it occurs more than 48 hours after admission.

Similarly to the results of earlier trials, longer episodes of NSVT were less common than short episodes, although 56.4% of subjects had at least one episode of ventricular tachycardia (VT) >3 beats, 18.4% had an episode lasting four to seven beats, and only 6.8% had an episode ≥8 beats. At 12 months, 121 subjects died of SCD, and no difference in the risk of SCD was seen in those with no episodes of NSVT and those with only triplets. However, the risk of SCD increased substantially in those with VT of four to seven beats (hazard ratio [HR] 2.3, 95% confidence interval 1.5, 3.7, P<0.001) and >8 beats (HR 2.8, 95% confidence interval 1.5, 5.1, P=0.001). This result held in the study population as a whole and in the placebo-only group. Among the 70% of subjects for whom echocardiographic data were available, both LVEF

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Editorial
and VT were independently associated with SCD, with similar increases in hazard ratio (LVEF <40%, HR 2.3, 95% confidence interval 1.4, 4, P=0.002). The increased risk of SCD in patients with VT >4 beats was seen both in high-risk subgroups (prior MI, prior heart failure, QTC >450 ms, B-type natriuretic peptide >80 pg/mL, and LVEF <40%), as well as patients without any high-risk features. A clinically-relevant question raised by these findings is whether the increased risk observed after 48 hours of monitoring warrants prolonged continuous ECG monitoring in excess of current guidelines, particularly in light of similar findings of increased SCD risk associated with NSVT reported by Mäkikallio et al using 24-hour continuous ECG monitoring post MI.16

Importantly, the prognostic significance of NSVT depends on the timing of occurrence; there was no relationship between the risk of SCD and VT of any length if the VT occurred within the first 48 hours of admission—a finding consistent with trials reported as early as the 1970s. Likewise consistent with prior findings, the Kaplan-Meier SCD curves began to plateau at a substantially lower risk after the first three months, reaffirming in this ACS population that the risk of SCD after MI is highest during this period.7,20–21 The time-dependence of occurrence of SCD post MI has established yet another paradox in the field: overall mortality and risk of SCD is reduced with ICD therapy in post-MI patients with reduced left ventricular function.8–9 However, ICD implantation early after MI does not improve survival, largely due to an increased risk of nonarrhythmic death.22–23 From a risk prediction standpoint, if NSVT is but a marker of increased risk of progressive heart failure, the failure of an ICD to provide a mortality benefit in this population is understandable.

The issue of the significance of NSVT is particularly germane in this population, with most of the subjects having preserved left ventricular function. Prior primary prevention ICD trials have been performed in patients with reduced EF, the most robust indicator of risk of cardiovascular death. However, the majority of SCD events occur in people with normal ventricular function, most of whom have unrecognized coronary artery disease.7 Evidence that ICD therapy is superior in patients with a lesser degree of heart failure24 supports speculation that a subset of patients post MI with normal or near normal EFs may not only benefit from ICD, but be better candidates than those with worse heart failure. Scirica et al provide additional intriguing evidence that NSVT may be a more promising risk marker in this particular population than in patients with heart failure.14,19 The authors report that the association between NSVT and SCD is similar among individuals with EF <40% (HR=2.7 and 3.7) and EF >40% (HR=1.9 and 2.4). Because most people at risk of SCD do not have a low EF, a predictor that identifies high-risk individuals with normal EF is quite valuable. Inclusion of NSVT in their prognostic models improved prediction of SCD over models including only clinical predictors and LVEF. Given the epidemiology of SCD, the normal EF group is an extremely desirable target for intervention. However, in the MERLIN TIMI-36 clinical trial population, even the highest risk group had a SCD rate of only 4.3% at one year. This low rate precludes fiscally-reasonable demonstration of ICD benefit, in the absence of additional hazard. Future risk stratification attempts may benefit from multivariable clinical risk modeling, with the addition of biomarker and genetic information.

Analyses of MERLIN TIMI-36, a drug trial of ranolazine, an antianginal agent that inhibits the late inward sodium current, have repeatedly shown a reduction in cardiac arrhythmia in treated subjects. However, treatment with this agent was not associated with an overall reduction in total mortality or the risk of SCD.18,25 In an exploratory, post hoc analysis presented in this report, there was a nonsignificant reduction in the hazard ratio of SCD in the high-risk group of VT >8 beats treated with ranolazine. Given the lack of association between suppression of ventricular arrhythmias and improved clinical outcome in the literature, this preliminary observation should be viewed as hypothesis-generating. The observations that ventricular arrhythmia is frequently preceded by ventricular ectopy and NSVT, NSVT is associated with increased cardiovascular mortality, and inhibition of NSVT does not improve mortality remain paradoxical. Possible explanations to align these findings include considering NSVT as a risk marker of underlying ischemia, neurohormonal dysfunction, or genetic electric susceptibility. Patients with non-ST-segment elevation MI have long been known to have a similar or worse long-term prognosis compared with ST-segment MI, due to a larger burden of myocardium in jeopardy, which translates to an increased risk of recurrent ischemia and infarction. Both provide substrate and trigger for ventricular arrhythmia and heart failure, yet our understanding of how these factors interrelate in a particular patient is poorly understood. The prognostic significance of NSVT may well be different after NSTE-ACS, due to more heterogeneity of scar and variation in border zone areas in which slowed conduction promotes reentry circuits.26 The greater burden of ischemia may initiate calcium loading and increase triggered activity, or it may promote degradation of a stable ventricular tachycardia circuit to lethal ventricular fibrillation.

Prediction and prevention of SCD remains a major public health challenge. While SCD is not simply a single diagnostic entity, it occurs most commonly in Western populations, in the setting of coronary heart disease. Scirica and colleagues are to be congratulated for shedding light on this difficult puzzle. Future challenges will be to use these data to investigate the potential mechanisms of these associations, incorporating innovations from clinical care,27 genetics,28–29 biomarkers,30–31 cardiovascular imaging,32 and invasive electrophysiological studies.33–34 Because ICD therapy is neither benign nor cheap, assessing which patients truly benefit from device placement is an imperative. Disentangling risk for SCD from risk of nonarrhythmic cardiovascular death has proven to be an enduring problem for the cardiovascular community - one that is absolutely crucial to solve. Abrupt, unanticipated, and heartbreaking, the problem of SCD continues to merit attention and resources.

Disclosures

None.

References


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