Pathophysiology and Risk Stratification of Sudden Cardiac Death in Ischemic Heart Disease.

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Abstract
Sudden cardiac death accounts for approximately 360,000 annually in the United States and is the cause of half of all cardiovascular deaths. Ischemic heart disease is the major cause of death in the general adult population. Sudden cardiac death can be due to arrhythmic or non-arrhythmic cardiac causes, for example, myocardial rupture. Arrhythmic sudden cardiac death may be caused by ventricular tachyarrhythmia (ventricular tachycardia/ventricular fibrillation) or pulseless electrical activity/asystole. The majority of research in risk stratification centers on ventricular tachyarrhythmias simply because of the availability of a successful management strategy, the implantable cardioverter/ defibrillator. Currently the main criterion of primary defibrillator prophylaxis is the presence of organic heart disease and depressed left ventricular systolic function assessed as left ventricular ejection fraction. However, only one third of eligible patients benefit from the implantable defibrillator, resulting in significant redundancy in the use of the device. The cost to the health care system of sustaining this approach is substantial. Further, the current low implantation rate among eligible population probably reflects a perceived low benefit-to-cost ratio of the device. Therefore, attempts to optimize the selection process for primary implantable defibrillator prophylaxis are paramount. The present report will review the most recent pathophysiology and risk stratification strategies for sudden cardiac death beyond the single criterion of depressed ejection fraction. Emphasis will be placed on electrophysiological surrogates of conduction disorder, dispersion of repolarization, and autonomic imbalance, which represent our current understanding of the electrophysiological mechanisms that underlie the initiation of ventricular tachyarrhythmias. Further, factors that modify arrhythmic death, including noninvasive risk variables, biomarkers, and genomics will be addressed. These factors may have great utility in predicting sudden cardiac arrhythmic death in the general public.

Introduction

Sudden cardiac death (SCD) is a major public health problem both at the US and worldwide. It is estimated that each year in the US 360,000 persons die of unexpected SCD in Emergency Departments or before reaching a hospital.[1] The current management of SCD is directed at a relatively small percentage of the total population at risk and primarily at those patients already known to be at increased risk by conventional criteria. Pharmaceutical strategies to prevent SCD have been largely ineffective. Because device therapy [implantable cardioverter-defibrillator (ICD)] is designed to rescue patients once an event has already occurred, primary SCD prevention has become one of today's most critical public health challenges. Current conventional risk stratifiers for SCD have shown low positive predictive power either alone or in different combinations. As of 2005, the main criterion for primary ICD prophylaxis for SCD has been the presence of organic heart disease and depressed left ventricular ejection fraction (LVEF). Unfortunately, depressed LVEF may be a good marker for total cardiac mortality but is not specific for SCD, resulting in a significant redundancy of this strategy. The cost to the health care system of sustaining this approach would be substantial. For the immediate future, attempts to optimize the selection process for primary ICD prophylaxis that goes beyond depressed LVEF must continue.
The present chapter will review the most recent pathophysiology and risk stratification of SCD in ischemic heart disease, and its management beyond the current single criterion of depressed LVEF.

Pathophysiology of SCD in Ischemic Heart Disease

SCD is a worldwide leading cause of all death (15%-20%). The majority of SCD occurs in patients with atherosclerotic coronary artery disease (CAD) (65–85%).[2] However, there is considerable evidence that traditional markers of CAD, such as hypertension, obesity, smoking, diabetes, and lipid abnormalities, are not specific enough to identify patients at high risk for SCD.[3] Patients with similar risk factors for CAD may suffer from SCD or nonfatal ischemic events. The reason for this difference is not clear.
Arrhythmic SCD can be due to ventricular fibrillation (VF)/ventricular tachycardia (VT) or asystole/pulseless electrical activity events. The largest experience on the incidence of VT/VF during an acute ST elevation myocardial infarction (STEMI) in the thrombolytic era comes from the GUSTO-1 trial of 40,895 patients who were treated with thrombolytic therapy.[4] The overall incidence of sustained VT/VF was 10.2%: 3.5% developed VT; 4.1% developed VF; and 2.7% developed both

VT and VF. Approximately 80-85% of these arrhythmias occurred in the first 48 hours. However, in the era pf primary percutaneous cardiac intervention, the incidence of ventricular arrhythmias appears to be lower.[5]

Sustained VT/VF are less common in patients with an acute non-ST elevation MI or unstable angina as illustrated in a pooled analysis of four major trials of over 25,000 such patients.[6] VT/VF occurring 24-48 hours of acute MI are thought to be epiphenomena of the MI and are not associated with worse prognosis after hospital discharge.

However, not all SCDs are due to arrhythmia. Non-arrhythmic causes are found by autopsy in 50% of SCD cases in patients with recent MI, and there is autopsy evidence of acute coronary events in 54% of SCD cases with CAD and even in 5% of SCD cases in patients without CAD.[7] In 97% of cases, AMI was not diagnosed clinically ante-mortem. Post-mortem magnetic resonance imaging (MRI) results in in a higher diagnosis of pre-acute infarction as possible cause of SCD.[8,9]

It is important to understand the cascade that relates the distal events of atherosclerosis to the proximal event of SCD **(Figure 1).** Risk markers for SCD in CAD are likely to cluster under factors that may directly facilitate the development of acute coronary syndromes, specifically those factors that may facilitate transient triggering events, including plaque rupture, enhanced thrombogenesis, and coronary artery spasm.[10,11] There is significant data showing correlation between SCD and:

1) Markers of plaque vulnerability, such as heritable alterations of specific matrix metalloproteinases.[12]

2) Markers of enhanced thrombogenesis, such as increased D-dimer, increased apo-B, and decreased apo-A1.[13]; as well as polymorphism in platelet glycoprotein receptors[14];

3) Genetic variations that predispose to vasospasm, such as variations in the vascular endothelial nitric oxide synthetase (eNOS) system;[15,16]

4) Markers of inflammatory response, such as C-reactive protein (CRP).[17]

Acute coronary syndrome can result either in early electrophysiological vulnerability leading to fatal ventricular tachyarrhythmia and SCD (unless the patient has a prior ICD) or in nonfatal MI. In patient who survive a nonfatal MI the heart undergoes a complex post-MI remodeling process that in the long run results in increased electrophysiological vulnerability, fatal ventricular tachyarrhythmia, and SCD or in progressive deterioration of ventricular systolic function, ischemic cardiomyopathy, congestive heart failure, and non-SCD**.**

Figure 1: CAD and SCD Cascade

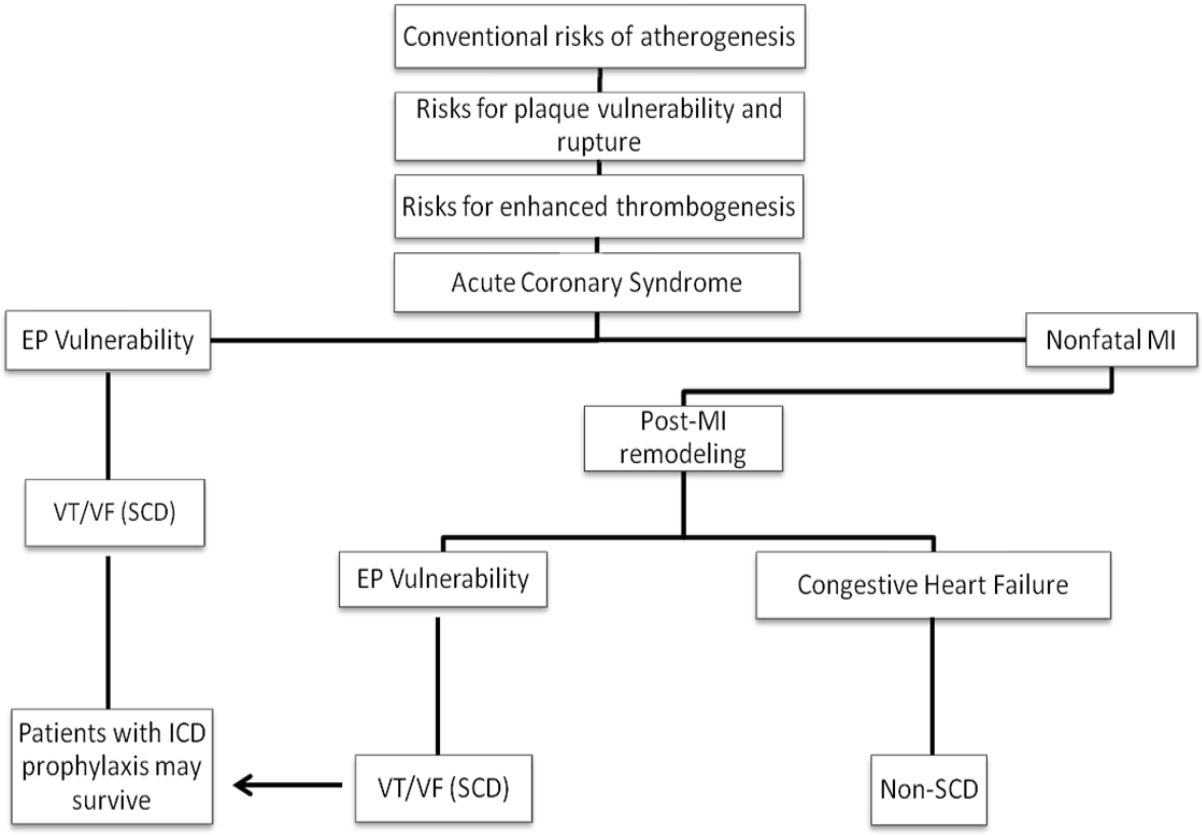

Figure 1: CAD and SCD cascade. (Abbreviations: CAD, coronary artery disease; EP, electrophysiological; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; SCD, sudden cardiac death; VT/VF, ventricular tachycardia/ventricular fibrillation).

Post-MI Remodeling and SCD

Patients who suffer from a nonfatal MI as well as those who survive SCD in the setting of acute MI later undergo post-MI remodeling. Post-MI remodeling is a complex time-dependent process that involves structural, biochemical, neurohormonal and electrophysiological alterations. The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote non-infarcted myocardium.[18] Post-MI remodeling is associated with time-dependent dilatation, distortion of ventricular shape, and hypertrophy of the non-infarcted myocardium. Following a variable period of compensatory hypertrophy, deterioration of contractile function may develop resulting in congestive heart failure. The role of continuous loss of cardiomyocytes to apoptosis in the non-infarcted myocardium; the negative consequences of remodeling of the interstitial matrix, the downregulation of

the beta-adrenergic receptor-G protein-adenylyl cyclase pathway and the L-type calcium current, and the alterations in calcium regulated excitation-contraction coupling are some of the major mechanisms involved in the transition to decompensated congestive heart failure (CHF) of the post-MI heart.

In recent years, the understanding of the signal transduction pathways for cardiac remodeling in the post-MI heart[19,20] has provided opportunities for novel therapeutic interventions. **Figure 2** illustrates a proposed scheme for post-MI signaling pathways.[21,22] Many of these pathways were shown to be activated either in response to ischemia/reperfusion stimuli or to a stretch stimulus using different experimental models and sometimes non-cardiac cell systems. However, cell membrane receptors and intracellular signaling proteins are highly conserved between mammalian species and the triggering events for cellular hypertrophy in humans are likely to resemble closely those in the various animal models used. The diagram shows that a cascade of successive transduction steps allows signal enhancement and diversification at branching points and thus permits combinatorial interactions between multiple pathways. Although multiple signaling pathways may act in synergistic, antagonistic, or permissive ways, some key pathways may play a dominant role.

Figure 2

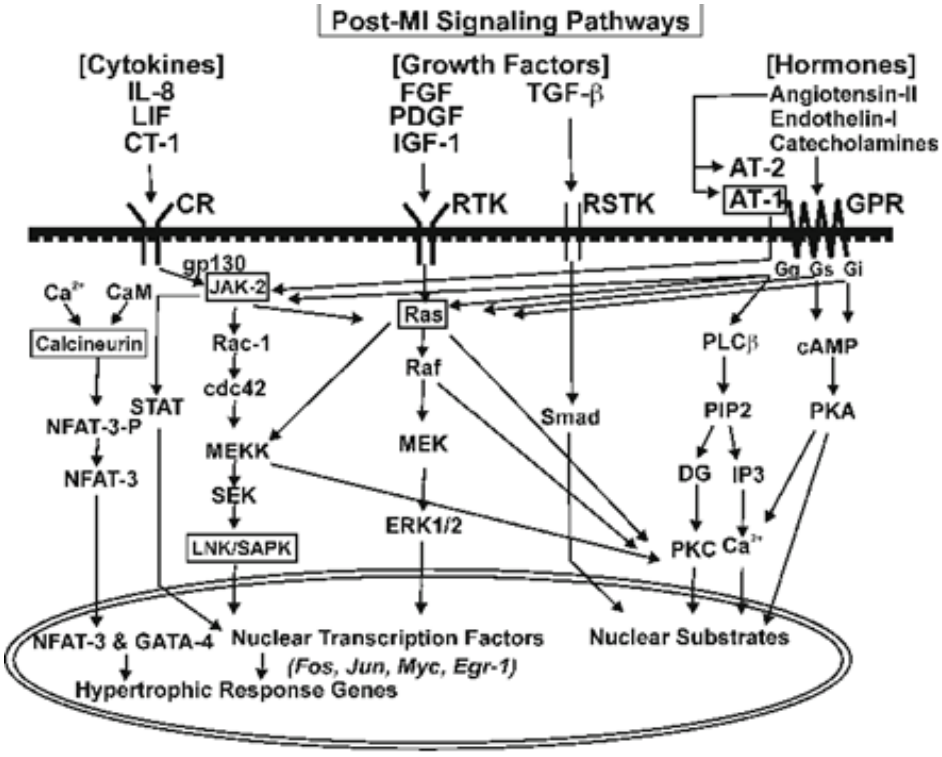

Figure 2. Post-MI signaling pathways. (Modified from ref#22), with permission of Elsevier.

There is a plethora of experimental and clinical evidence showing that the renin-angiotensin system (RAS) and the B-adrenergic system play major roles in post-MI remodeling.[22] This explains the beneficial role of ACE inhibitors, AT-1 receptor antagonists, and beta-blockers in the post-MI period. More recently, other signaling pathways, for example, the calcineurin pathway,[23] and the Janus kinase/signal transducer and activator of transcription (JAK-STAT)[24] signaling pathway were also found to play a significant role in post-MI remodeling. Pharmaceutical agents that can block these pathways may provide new therapeutic modalities in the post-MI period.

Current Risk Stratification of SCD in Ischemic Heart Disease

Current risk stratification of SCD in ischemic heart disease could be grouped into the following three categories (see Table 1):

1. Electrophysiological surrogates;
2. Functional/contractile surrogates;
3. Modifiers of arrhythmic death that includes biomarkers, genomics, and several noninvasive clinical variables.

The electrophysiological surrogates include measures of conduction disorders, measures of dispersion of repolarization, and measures of autonomic imbalance. These three categories represent the current understanding of the electrophysiological mechanisms that underlie the initiation of VT/VF.

There are, at least, two shortcomings in the application of risk stratification of SCD.[25] One, is that most of the risk stratifiers are applied in a dichotomous fashion while the risk of a complex electrophysiological entity like VT/VF is continuous. Second, many of the risk stratifiers are not fixed and can change over time. For example, in both the REFINE and CHARISMA studies, measures of impaired autonomic function assessed within the first month after MI were poorly predictive of SCD. These measures became predictive when measured at 2 to 4 months.[26,27]

Surrogate Measures of Conduction Disorders

Reduced left ventricular systolic function assessed as LVEF, as well as wall motion abnormalities, are crude markers of myocardial scar. Nevertheless, reduced LVEF remains the main criterion for prophylactic ICD, with the current understanding that it is a better assessor of total cardiac mortality than arrhythmic death. On the other hand, there are several ECG-derived criteria that can better assess myocardial scarring. Prolonged QRS duration can reflect the presence of area of slow conduction and has been associated with the risk of SCD in the general population.[28,29] Fractionation of the QRS complex of the electrocardiogram (ECG) is another marker of myocardial scar and may be useful for risk stratification for SCD-VT/VF.[30] In a cohort of 361 ICD recipients with LV dysfunction, a fragmented QRS was a strong predictor

of ventricular arrhythmias, whereas QRS duration was a better predictor of overall mortality.[31]

Table 1

Risk Stratification of SCD

Electrophysiological Surrogates

A) Measures of Conduction Disorders

(ECG-derived):

- QRS duration, QRS fractionation, Signal Average ECG
- Myocardial scan assessment (MRI, SPECT, PET)

B) Measures of dispersion of repolarization

(ECG-derived):

- QT dispersion/variability
- QRS-T angle
- T peak-end interval, T peak-end/QT ratio
- Early repolarization
- T-wave alternans

C) Measures of autonomic system

(ECG-derived):

- Heart Rate Variability
- Heart Rate Turbulence

(Imaging):

- SPECT (MIBG)
- PET (^{11}C-*meta*-hydroxyephedrine)

D) Others

- Ambulatory ECG monitoring
- Electrophysiological study

Functional/Contractile Surrogate

- NYH class
- LVEF

Modifiers of Arrhythmic Risk

A) Biomarkers

- C-reactive protein
- Interleukin-6
- Tumor necrosis factor - α receptor II
- Pro-BNP
- Cardiac troponin T

B) Genomics

- Heritability of SCD, familial aggregation
- Genetic risk variants of CAD
- Genetic susceptibility to ischemic VF:
  - Common variants with modest effect
  - Rare variants with strong effect

C) Noninvasive Clinical Variables

- Age > 70 years
- Renal Insufficiency
- Diabetes
- Obesity
- AF
- LVEF ≤ 20%
- NYHA Class III

The Signal-Averaged (SA) ECG is more sensitive in detecting late ventricular activation from areas of heterogeneous scar.[32] In an early study, serial recording of the SA ECG was obtained from 156 patients with acute MI up to 5 days (phase 1), 6 to 31 days (phase 2), and 31 to 60 days (phase 3) after the infarction. The

study showed that a positive SA ECG in phase 2 has the most significant relation to arrhythmic events in the first year post-MI.[33] However, the positive predictive value of an abnormal SA ECG has generally been insufficient for risk prediction in patients with ischemic heart disease.[34]

Imaging and Quantification of Myocardial Scar

Both the scar extent and infarct core have been associated predominantly with monomorphic VT, while the peri-infarction zone has been associated with polymorphic VT. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) can identify myocardial scars by visualizing areas with reversible perfusion defects. On the other hand, cardiac MRI is able to identify myocardial scars by delayed enhancement imaging after gadolinium administration. It has a much greater spatial resolution than SPECT or PET imaging.[35] Cardiac MRI is capable of differentiating heterogeneous scar, which appears as intermediate density delayed enhancement from dense scar.[36] Several studies have shown that the burden of heterogeneous scar is an independent predictor of VT/VF, ICD therapy, and overall mortality.[37,38]

Surrogate Measures of Dispersion of Repolarization

Almost all surrogate measures of dispersion of repolarization are derived from the 12-lead ECG. Dynamic changes in the QT interval including **QT variability** have been associated with SCD and overall mortality.[39]

Tpeak-end (Tp-end) and Tp-end /QT ratio are proposed to represent transmural dispersion of repolarization, and may predict the risk of malignant tachyarrhythmias. A Tp-end >0.1 and Tp-end/QT ratio >0.3 was found to predict ventricular tachyarrhythmias within 24 hours of ST-segment elevation (STEMI) in a prospective case-control study.[40]

Early repolarization (ER) is defined as at least 1 mm (0.1 mV) of the QRS-ST junction above the baseline level in at least two inferior or lateral ECG leads.[41] Previously, ER was thought to be a benign feature of 12-lead ECG, but was linked to idiopathic VF by Haissaguerre et al in 2008.[42] The clinical relevance of ER in the general population is low, given the high prevalence and low absolute risk. However, in acute STEMI, ER was found to be associated with a significant increase in risk of ventricular tachyarrhythmias in the acute post-MI phase (<72 hours), irrespective of LVEF and level of cardiac enzymes.[43,44]

Finally, an important measure of dispersion of ventricular repolarization is microvolt **T-wave alternans (TWA),** especially **discordant alternans**. Studies evaluating the utility of TWA in risk stratification for arrhythmic death have produced mixed results.[45,46] However, a more recent position paper that reviewed the different techniques of measuring TWA, has supported its overall predictive utility for arrhythmic events.[47]

Surrogate Measures of Autonomic Function

Autonomic neural influences, especially increased adrenergic and decreased cholinergic activity, can modulate the susceptibility to SCD following MI. Resting heart rate has been shown to be an independent risk factor for SCD in middle-aged men.[48] There are data showing the heritability of heart rate variation.[49] Adrenergic agonists are known to trigger ventricular arrhythmias, and their circulating levels have similar diurnal patterns as SCD events.[50] Genetic polymorphism of β-adrenergic receptors have been associated with increased susceptibility to SCD in ischemic heart disease.[51] The association between plasma non-esterified fatty acids and SCD may be related to increased adrenergic tone or the effect on ion channel and transporters.[52] Further, mental stress was found to be associated with lateralization of mid brain activity resulting in imbalanced activity in right and left cardiac sympathetic nerves and increased dispersion of repolarization, predisposing to arrhythmia.[53] Recently, a third type of β-adrenergic receptors, β-3 adrenergic receptors was found in the human heart.[54] In both failing and post-MI myocardium, β-3 adrenergic receptors stimulation may have protective effects against β-1 and β-2 catecholaminergic stimulation.[55] This makes β-3 adrenergic receptors an attractive target for pharmacological therapy of cardiac arrhythmias related to cardiac sympathetic nerve stimulation.

Heart rate variability (HRV) has been the most extensively investigated measure of autonomic tone. Loss of vagal tone leads to a decrease in the spontaneous variation in heart rate. Assessing the utility of HRV for the prediction of SCD and VT/VF is clouded by the numerous potential techniques used to quantify HRV (time domain indices, frequency domain indices, and nonlinear analyses).[56] Diminished HRV has been associated with both SCD and non sudden death in MI and in chronic LV dysfunction, independent of LVEF.[57] The poor specificity of HRV to predict SCD and VT/VF may limit its use in risk stratification.[25]

Heart rate turbulence (HRT) has been evaluated as another noninvasive and reproducible measure of autonomic function. HRT quantifies the short-term variation in heart rate after a spontaneous ventricular premature beat. HRT has been shown to predict overall mortality, independent of LVEF, after MI.[58] In the REFINE study of patients after MI, HRT was also independently predictive of fatal or nonfatal cardiac arrest.[26] Therefore HRT may be more specific for SCD and VT/VF than HRV.

Imaging of Cardiac Sympathetic Innervation

An estimate of cardiac sympathetic innervation could be obtained using 123-Iodine metaiodobenzylguanidine (MIBG) SPECT planar images. Myocardial uptake relative to mediastinum can be quantified, providing

an estimate of the cardiac sympathetic innervation. A heart-to-mediastinum ratio >1.6 identified a group of heart failure patients at increased risk of VT/VF.[59] Furthermore, on SPECT images, the presence of regional abnormalities in MIBG uptake has been associated with high cumulative rate of ventricular arrhythmia in ICD patients.[60] Advances in SPECT and PET imaging can allow for visualization of cardiac sympathetic function of the LV. Using norepinephrine analogs, both PET and SPECT can identify areas of relative sympathetic denervation. In the prospective PARAPET study of patients with ischemic cardiomyopathy receiving an ICD, the amount of viable, but denervated myocardium was independently predictive of the development of VT or arrhythmic death.[61]

Ambulatory Monitoring

Ambulatory ECG monitoring is attractive as a risk stratification tool because of its ubiquitous availability and ease of interpretation. Numerous trials have evaluated interventions, including drug and ICD therapy, to reduce mortality in patients with frequent premature ventricular contractions (PVCs) or nonsustained VT after MI or in the presence of LV dysfunction. The majority has shown a reduction in SCD and VT/VF but no impact on overall mortality.[62,63] Thus, the role of ambulatory monitoring in risk stratification of arrhythmic death remains ill defined.[25]

Electrophysiological Study

Although programmed ventricular stimulation may predict future occurrence of monomorphic VT, it has limited ability to predict polymorphic VT or VF.

In the MUSTT study, the positive predictive value of electrophysiological testing was high, but the negative predictive value was modest. Even in non-inducible patients, the rate of cardiac arrest or SCD was relatively high (12% at 2 years).[64] On the other hand, in the ABCD trial the combination of a negative TWA and negative electrophysiological study identified a low-risk group with an event rate of 2.3% at 2 years in a population similar to the MUSTT population.[46]

Electrophysiological study has recently received a significant boost from the PRESERVE EF study.[65] The study introduced a combined non-invasive/invasive risk stratification approach in post-MI ischemia-free patients, with LVEF ≥ 40%, in a multicenter, prospective, observational cohort study. Patients with at least one positive electrocardiographic non-invasive risk factor (NIRF): premature ventricular complexes, non-sustained ventricular tachycardia, late potentials, prolonged QTc, increased T-wave alternans, reduced heart rate variability, abnormal deceleration capacity with abnormal turbulence, were referred for programmed ventricular stimulation (PVS), with ICDs offered to those inducible. The primary endpoint was the

occurrence of a major arrhythmic event, namely sustained ventricular tachycardia/fibrillation, appropriate ICD activation or SCD. The study screened and included 575 consecutive patients (mean age 57 years, LVEF 50.8%). Of them, 204 (35.5%) had at least one positive NIRF. Forty-one of 152 patients undergoing PVS (27-7.1% of total sample) were inducible. Thirty-seven (90.2%) of them received an ICD. Mean follow-up was 32 months and no SCDs were observed, while 9 ICDs (1.57% of total screened population) were appropriately activated. No patient without NIRFs or with NIRFs but negative PVS met the primary endpoint. The algorithm yielded the following: sensitivity 100%, specificity 93.8%, positive predictive value 22%, and negative predictive value 100%. The study validated the concept of staged evaluation of risk of SCD with NIRFs followed by PVS.[66]

Biomarkers

Biomarkers may be useful in refining the risk of SCD and VT/VF in the general population, particularly in individuals at an intermediate or high risk of CAD. However, large scale comprehensive studies of biomarkers are lacking. Biomarkers for inflammation, neurohumoral activation, and cardiac injury have been studied in patients with primary prevention ICD to predict appropriate shocks, a surrogate marker for SCD, and all-cause mortality. PROSE-ICD investigated five potential biomarkers; C-reactive protein, interleukin-6, tumor necrosis factor-a receptor II, pro-brain natriuretic peptide (pro-BNP), and cardiac troponin T. All markers were associated with a significant increase of all-cause mortality, but only interleukin-6 had an association with predicting appropriate shock therapy.[67]

Genomics

Several studies have demonstrated a familial aggregation of SCD, suggesting a possible influence of genetic factors. The first of these studies was published in 1998 and showed that a family history of MI or primary cardiac arrest was independently associated with an increased risk of primary cardiac arrest.[68] The observational Paris Prospective Study I confirmed that parental SCD is an independent risk factor for SCD in middle-aged men. A family history of SCD on either the paternal or maternal side of family was associated with a nearly 2-fold increased risk of SCD, and if both parents had a history of SCD, there was a 9-fold increased risk of dying suddenly.[69] These two studies did not distinguish between different phenotypes of SCD, i.e. arrhythmic versus non-arrhythmic SCD. On the other hand, the AGNES study was the first to suggest an association between family history of SCD and VF caused by first STEMI.[70] However, little is known about the exact genetic component that increases the vulnerability of VF caused by MI in the general population. The genetic components are likely to involve both common variants with modest effect and

rare variants with stronger effects.[71] Several studies have examined the association between common and rare genetic variables and SCD (see review by Glinge et al).[72] However, only few of the variants identified in these studies have been replicated, and many do not have yet a clear functional implication. The genetic component of VF and SCD due to MI has been investigated using either candidate gene or genome-wide association studies (GWAS). Some of the reasons of the lack of replication among genetic studies of SCD and VF may have to do with the fact that the effect of the risk of an allele may differ between populations, because of gene-gene interaction or gene-environment interaction.[73] Future research may also needs to incorporate epigenetics for better understanding of the complex phenotype of VF and SCD. Last, but not least, a recent study showed that a score formed by the most significant genetic risk variant for CAD is associated significantly with the occurrence of CAD-related out-of-hospital cardiac arrest.[74]

Noninvasive Clinical Risk variables

A striking finding in the multivariable risk stratification is the degree of consistency among predictor variables.[75] The relative risk variables in the prospective randomized clinical trials (RCT) include atrial fibrillation, age>70 years, New York Heart Association (NYHA) class III, creatinine>1.3 or BUN >26 mg/dl, QRS duration>120 msec, and LVEF< 20%. Ideally a multicenter RCT could be conducted to test a multivariable risk stratification model. However, at least in the USA, such an RCT is unlikely to succeed because currently ICD implantation is Class I guideline for patients with LVEF<35% (73). An alternate method is to conduct a prospective observational comparative study. In such a study patients receiving ICDs for primary prevention of SCD under current guidelines would be characterized by a number of noninvasive risk markers and followed prospectively; their survival would be compared with a group of patients matched for demographic characteristics that do not receive ICDs.[75] Since ICD implantation rate among eligible population can be as low as 7% in one study,[76] it may not be difficult to recruit a matching group. The low implantation rate probably reflects a perceived low benefit to cost ratio for the device.

A sub-analysis of the MADIT-II study helps to explain the value of such a prospective observational study. In MADIT-II, patients with severe renal dysfunction (defined as BUN>50 mg/dL or creatinine >2.5 mg/dL) had very high mortality and did not derive benefit from ICD implantation. When these patients were excluded from subsequent analysis, patients with no risk factors (defined as age>70 years, atrial fibrillation, creatinine >1.3 mg/dL or BUN> 26 mg/dL, NYHA functional class III, and QRS duration>120 msec) had a very low risk of total mortality and did not derive a survival benefit from the ICD. Patient with more than three risk factors had very

high mortality, due primarily to non-arrhythmic death, and also did not derive benefit from the ICD. Only patients with 1- 2 risk factors had the ICD improve their mortality.[77]

Conclusions

The immediate future goals for risk stratification and management of SCD post-MI could be summarized as follows: 1. Identification of novel clinical, electrophysiological, biochemical, and genetic markers for SCD including assessment of the functional consequences of sequence variants identified in human genetic studies as well as relevant environmental-genetic interactions; 2. Identification of a battery of a relatively limited number of incrementally cumulative low-intermediate risk variants and development of a "signature" combination of risk markers of SCD**.** However, we should not be surprised if the positive predictive value of some of the new risk markers, similar to conventional risk markers, will be relatively low, especially if these are applied to large populations who are at low risk; 3. One way of reducing the redundancy in the use of ICD implantation, that is currently based solely on reduced LVEF, is to identify those ICD eligible patient with either very low or very high noninvasive clinical risk variables who may not benefit from ICD implantation; 4. Identification of novel pharmacological, non-pharmacological, and behavioral approaches for risk modification and prevention of SCD; 5. Wider collaboration among different academic and industrial institutions by sharing research results as well as resources such as clinical data, blood and other tissues from Biorepository centers. The ultimate goal is not only to change the current direction of management strategy of SCD away from increased ICD utilization, but primarily to identify novel methods for risk stratification, risk modification, and prevention of SCD that could be applied to the general public at large.

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