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SUDDEN CARDIAC DEATH- CAUSES AND PREVENTION

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Abstract:

Introduction: *Sudden Cardiac Death (SCD) is a major cause of death (15%-20% of all mortality). Its high incidence led to consider it as a major public health problem worldwide. In the United State, it has been estimated that 360,000 death per year has resulted from SCD whether in emergency departments or even before reaching hospitals. The primary prevention of SCD is a public health challenge. This has resulted for many reasons: (a) the current management of SCD is directed toward a small percentage of the population at risk; (b) ineffectiveness of pharmaceutical strategies; (c) The device therapy (implantable cardioverter-defibrillator (ICD) is designed to rescue patients after the occurrence of the event. In addition, different approaches and combinations to risk stratification have failed to produce an acceptable positive predictive value. The presence of organic heart disease and decreased left ventricular ejection fraction (LVEF) were the main criteria to use ICD as primary prophylaxis against SCD. However, a lower LVEF could be a good indicator for total cardiac mortality but it is not specific for SCD; thus, this strategy has resulted in a significant redundancy and hence cost burden. Developing better criteria to use ICD as prophylaxis becomes a priority.*

The aim of work: *In this review, we will discuss Sudden cardiac death- causes and prevention*

Methodology: *We did a systematic search for sudden cardiac death- causes and prevention in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *The future goals to risk stratification and management of SCD especially post-MI could be summarized as the following: (1) Identification of novel clinical, electrophysiological, biochemical, and genetic markers for SCD, this includes the assessment of functional consequences of sequence variants identified in human genetic studies as well as relevant environmental-genetic interactions; (2) Identification of a relatively limited number of incrementally low to intermediate cumulative risk variants and development of a "signature" combination of risk markers. (3) Reducing the redundancy and enhance the criteria for ICD implantation usage that is currently based on reduced LVEF. This should be done by identifying more eligible patients for ICD with either very low or a very high noninvasive clinical risk variable. (4) Development of novel pharmacological, non-pharmacological, and behavioral approaches for risk modification and prevention of SCD; (5) A wider collaboration among different academic and industrial institutions. This could be achieved by sharing research results as well as resources including clinical data, blood and other tissues from biorepository centers. The ultimate goal is not only to change the current management strategy of SCD by reducing the use of ICD, but by identifying novel methods for risk stratification, risk modification, and prevention of SCD that could be generalized.*

Keywords: *sudden cardiac death, causes, presentation, management, and prevention.*

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INTRODUCTION:

Sudden Cardiac Death (SCD) is a major cause of death (15%-20% of all mortality). Its high incidence led to consider it as a major public health problem worldwide. In the United State, it has been estimated that 360,000 death per year has resulted from SCD whether in emergency departments or even before reaching hospitals. [1] The primary prevention of SCD is a public health challenge. This has resulted for many reasons: (a) the current management of SCD is directed toward a small percentage of the population at risk; (b) ineffectiveness of pharmaceutical strategies; (c) The device therapy (implantable cardioverter-defibrillator (ICD) is designed to rescue patients after the occurrence of the event. In addition, different approaches and combinations to risk stratification have failed to produce an acceptable positive predictive value. The presence of organic heart disease and decreased left ventricular ejection fraction (LVEF) were the main criteria to use ICD as primary prophylaxis against SCD. However, a lower LVEF could be a good indicator for total cardiac mortality but it is not specific for SCD; thus, this strategy has resulted in a significant redundancy and hence cost burden. Developing better criteria to use ICD as prophylaxis becomes a priority.

We aim to 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. We will spotlight the most recent evidence regarding sudden cardiac death-causes and prevention.

METHODOLOGY:

We did a systematic search for sudden cardiac death-causes and prevention in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: sudden cardiac death, causes, presentation, management, and prevention

PATHOPHYSIOLOGY OF SUDDEN CARDIAC DEATH IN ISCHEMIC HEART DISEASE

Although the majority of SCD occur in patients with atherosclerotic coronary artery disease (65%–85%), the evidence suggests that traditional association of CAD (hypertension, obesity, smoking, diabetes, and lipid abnormalities) are not specific enough to identify patients with high risk to have SCD. [2] Patients with these risk factors may develop an SCD or nonfatal ischemia. The reason for this is not clear.

Arrhythmic SCD can be due to ventricular fibrillation (VF) and/or ventricular tachycardia (VT) or asystole/pulseless electrical activity. The incidence of VT/VF during an acute ST-segment elevation myocardial infarction (STEMI) was higher with thrombolytic approaches than percutaneous coronary intervention (PCI) approaches. In a large thrombolytic therapy trial (GUSTO-1 trial), the overall incidence of sustained VT/VF was 410.2% with the majority of events occurred in the first 48 hours. [3] In contrast, the incidence of these arrhythmia seems to be lower with PCI.5 A pooled analysis of 4 large trials included 25,000 patients showed that sustained VT/VF is less common in patients with an acute non-ST elevation myocardial infarction (NSTEMI) or unstable angina.6 It is believed that VT/VF occurring within 24 to 48 hours of acute MI are epiphenomena and are not associated with worse prognosis after hospital discharge.

An autopsy showed that 50% of cases with a recent MI had had non-arrhythmic causes of SCD. In addition, there is evidence of acute coronary events in 54% of SCD cases with coronary artery disease (CAD) and in 5% of SCD cases in patients without CAD.7 Postmortem MRI revealed high percent of pre-acute MI as a possible cause of SCD. [4]
It is important to understand the cascade that relates the distal events of atherosclerosis to the proximal event of SCD.
Factors that accelerate the development of acute coronary syndromes in patients with coronary artery disease could be a risk marker for SCD. [5] These

factors include:
(a) Plaque vulnerability to rupture, as in the case of heritable alterations its matrix
Metalloproteinases; (b) Enhanced thrombogenesis, as seen in case of increased D-dimer, increased apolipoprotein-B, and decreased apolipoprotein-A1, and polymorphism in platelet glycoprotein receptors; (c) Genetic predisposition to vasospasm as in vascular endothelial nitric oxide system variation; (d) Markers of the inflammatory response, such as C-reactive protein. [6]

REMODELING AFTER MYOCARDIAL INFARCTION AND SUDDEN CARDIAC DEATH

Survivors of non-fatal MI that escaped SCD experience a complex and time-dependent post-MI cardiac remodeling. This process involves structural, biochemical, neurohormonal, and electrophysiological alterations on the level of an infarcted and remote zone of the myocardium. [7] Distortion of ventricular shape in the form of time-dependent dilatation and compensatory hypertrophy of the non-infarcted myocardium is the core if this process. However, congestive heart failure may develop due to the deterioration of contractile function. The continuous loss of cardiomyocytes by apoptosis, the negative consequences of remodeling of the interstitial matrix, the downregulation of the beta-adrenergic receptor, G protein–adenylyl cyclase pathway, 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.
The recent discovery of signaling pathways was found to play an important role in post-MI remodeling. The calcineurin pathway and the Janus kinase-signal transducer and activator of transcription are major examples. [8]
Understanding these changes and pathways have aided the development of novel therapeutic interventions. [9]

Many studies have demonstrated the major remodeling role of renin-angiotensin system and the Beta-adrenergic system post-MI. [10] This explains the beneficial role of angiotensin-converting enzyme inhibitors (ACE inhibitor), angiotensin II type-1 receptor antagonists, and beta-blockers in post-MI patients.

CURRENT RISK STRATIFICATION OF SUDDEN CARDIAC DEATH IN ISCHEMIC HEART DISEASE

Contemporary risk stratification of sudden cardiac death in ischemic heart disease could be classified into 3 categories: (1) Electrophysiological surrogates; (2) Functional/contractile surrogates; (3) Modifiers of arrhythmic death that includes biomarkers, genomics, and several noninvasive clinical variables.

The first surrogates include measures of conduction disorders, dispersion of repolarization, and autonomic imbalance. These represent an up-to-date understanding of the electrophysiological mechanisms of VT/VF initiation.

Limitations to the practical use of risk stratification in SCD include that the most of these risks are applied in a dichotomous way, whereas the risks in an electrophysiological entity like VT/VF is prone to be continuous. The second limitation has emerged from the fact that many of the risk stratifiers are unsteady over time. For instance, the REFINE and CHARISMA studies showed that impaired autonomic function assessed within the first month after MI were poorly predictive of SCD. The predictive value enhanced when measured at 2-4 months. [11]

SURROGATE MEASURES OF CONDUCTION DISORDERS

Declined systolic function of the left ventricle (LV) as assessed by LVEF and wall motion abnormalities is a fundamental marker of myocardial scar. Nevertheless, as we mentioned above, reduced LVEF remains the main criterion for prophylactic ICD. From the other hand, there are several electrocardiography-driven (ECG) criteria that could better assess myocardial scarring. One clear example is a prolonged QRS duration that can reflect the presence of an area of slow conduction and has been associated with the risk of SCD in the general population. [12] Fractionation of the QRS complex is another marker for a myocardial scar that is useful for risk stratification and prediction of arrhythmic SCD. [13]

The signal-averaged (SA) ECG is more sensitive means to detect late ventricular activation from areas of heterogeneous scar.32 Researcher had recorded a serial of the SA ECG from 156 patients with acute MI in three phases, up to 5 days, 6 to 31 days, and 31 to 60 days respectively. The result has shown that a positive SA ECG in the second phase has the most significant relation to arrhythmic events in the first year after a MI.[14] However, the positive predictive value has been insufficient for risk prediction. [15]

IMAGING AND QUANTIFICATION OF MYOCARDIAL SCAR

Single photon emission computed tomography

(SPECT), PET imaging modality and Cardiac MRI can be used to identify myocardial scars. The first two modalities visualize areas with reversible perfusion defects, however, cardiac MRI is able to identify myocardial scars by delayed enhancement imaging after gadolinium administration. Its spatial resolution is much higher than SPECT or PET imaging, and it has the ability to of differentiating heterogeneous scar. [16]

Scar extent and infarcted core have been associated predominantly with monomorphic VT, whereas the peri-infarction zone has been associated with polymorphic VT. Several studies have shown that the burden of a heterogeneous scar is an independent predictor of VT/VF, ICD therapy, and overall mortality. [17]

SURROGATE MEASURES OF DISPERSION OF REPOLARIZATION

Surrogate measure the dispersion of repolarization is derived from the 12-lead ECG mostly. Dynamic changes in the QT interval including QT variability have been associated with SCD and overall mortality. it is proposed that Tpeak-end (Tp-end) and Tp-end/QT ratio represent transmural dispersion of repolarization, and hence may be used to predict the risk of malignant tachyarrhythmia.

Early repolarization (ER) is defined as elevation of the QRS–ST junction above the baseline level by 1 mm (0.1 mV) in 2 inferior or lateral ECG leads.41 ER was thought to be a benign feature of 12-lead ECG. Later on, Haissaguerre and colleagues have linked it to idiopathic.42 The clinical importance of ER in the general population is low, given its high prevalence. However, in acute STEMI and acute post-MI phase (<72 hrs.), ER was found to be associated with an increased risk of ventricular tachyarrhythmia irrespective to LVEF and level of cardiac enzymes. [18]

In addition, mV T-wave alternans (TWA) is an important measure of ventricular repolarization dispersion, especially discordant alternans. However, studying its role in risk stratification for arrhythmic death has turned to have mixed results. Yet, a recent paper has supported its overall predictive usefulness for arrhythmic events.

SURROGATE MEASURES OF AUTONOMIC FUNCTION

Autonomic influences especially increased adrenergic and decreased cholinergic activity, can modulate the liability to SCD following acute MI. Resting heart rate has been shown to be an independent risk factor for SCD in middle-aged men.48 in addition, some data have suggested the heritability of heart rate variation.49 Adrenergic agonists are known to trigger ventricular arrhythmias and their level have similar diurnal patterns as SCD events. [19] Polymorphism of beta-adrenergic receptors that is determined genetically has been associated with increased susceptibility to SCD in ischemic heart disease. Furthermore, an association between plasma non-esterified fatty acids and SCD may be correlated with increased adrenergic. Mental stress is a supportive example of this as it was found cause imbalanced activity in right and left cardiac sympathetic nerves, hence, increased dispersion of repolarization, predisposing to arrhythmia. Recently discovered b-3 adrenergic receptors were found in the human heart. In both failing and post-MI myocardium, b-3 adrenergic receptors stimulation may have protective effects against stimulant of type b-1 and b-2 receptors. This makes these receptors a target for a novel pharmacological therapy and interventional trials.

IMAGING OF CARDIAC SYMPATHETIC INNERVATION

We can estimate cardiac sympathetic innervation by imaging the uptake of 123-iodine metaiodobenzylguanidine using SPECT planar images. The increased heart-to-mediastinum ratio of more than 1.6 indicates a group of heart failure patients with an increased risk of VT/VF.59 In addition, the presence of regional uptake abnormalities has been associated with a high cumulative rate of ventricular arrhythmia in ICD patients. [20] The advancement in these techniques can allow for visualization of the cardiac sympathetic function of the LV. Using norepinephrine analogs, SPECT can identify areas of relative sympathetic denervation. In the prospective PARAPET study, patients with ischemic cardiomyopathy receiving an ICD, the amount of viable yet denervated myocardium was independently predictive of the development of VT or arrhythmic death.

AMBULATORY MONITORING

Ambulatory ECG monitoring is an attractive modality as for risk stratification tool because of its ubiquitous availability and it is relatively easy to interpret. Numerous trials have evaluated interventions to reduce mortality in patients with frequent PVCs or non-sustained VT after an MI or in the presence of LV dysfunction. The majority have shown a reduction in SCD and VT/VF, but without impact on the overall mortality. Thus, the role of ambulatory monitoring in risk stratification of arrhythmic death remains ill-unclear.

ELECTROPHYSIOLOGIC STUDY

The future occurrence of monomorphic VT could be predicted by programmed ventricular stimulation. Yet, it has a limited ability to predict polymorphic VT or VF. MUSTT study has estimated the positive predictive value of electrophysiological testing to be high, but this was not the case for the negative predictive value. Even in non-inducible patients, the rate of cardiac arrest or SCD was relatively high (12% at 2 years). in contrast, the combination of a negative TWA and negative electrophysiological methods in the ABCD study has identified a much lower risk with an event rate of 2.3% at 2 years. though the population was similar to that of MUSTT study.46 Because the nature of electrophysiological testing is invasive, and its modest negative predictive value, its role in the overall stratification of SCD in ischemic heart disease is still limited.

BIOMARKERS

Biomarkers could be a useful tool in refining the risk of SCD and VT/VF in the general population, particularly in individuals at intermediate or high risk of CAD. However, there is still a lack of large comprehensive studies. The PROSE-ICD trial has investigated 5 potential biomarkers in patients with primary prevention ICD to predict appropriate shocks and a surrogate marker for SCD; C-reactive protein, interleukin-6, tumor necrosis factor alpha, receptor II, pro-brain natriuretic peptide (pBNP), and cardiac troponin T. All these markers were associated with a significant increase in all-cause mortality, but only interleukin-6 had an association with predicting appropriate shock therapy in ICD patients.

CONCLUSIONS:

The future goals to risk stratification and management of SCD especially post-MI could be summarized as the following: (1) Identification of novel clinical, electrophysiological, biochemical, and genetic markers for SCD, this includes the assessment of functional consequences of sequence variants identified in human genetic studies as well as relevant environmental-genetic interactions; (2) Identification of a relatively limited number of incrementally low to intermediate cumulative risk variants and development of a "signature" combination of risk markers. (3) Reducing the redundancy and enhance the criteria for ICD implantation usage that is currently based on reduced LVEF. This should be done by identifying more eligible patients for ICD with either very low or a very high noninvasive clinical risk variable. (4) Development of novel pharmacological, non-pharmacological, and behavioral approaches for risk modification and prevention of SCD; (5) A wider collaboration among different academic and industrial institutions. This could be achieved by sharing research results as well as resources including clinical data, blood and other tissues from biorepository centers. The ultimate goal is not only to change the current management strategy of SCD by reducing the use of ICD, but by identifying novel methods for risk stratification, risk modification, and prevention of SCD that could be generalized.

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