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Sudden Cardiac Death Risk Stratification in Heart Failure Patients

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Abstract

Sudden Cardiac Death (SCD) remains a major public health burden. There are numerous invasive and noninvasive techniques to identify patients at risk for SCD. The most commonly used parameter for assessment is Left Ventricular Ejection Fraction (LVEF) but there is considerable interest in using cardiac biomarkers that reflect arrhythmogenic substrates more directly and hence enrich the prediction of SCD events. This reasoning results from community-based studies demonstrating that 70%-75% of all SCD cases have either normal or mild to moderately decreased Left Ventricular (LV) systolic function. Thus, there is a critical need for novel biomarkers to be identified and utilized. The complex nature of a SCD phenotype demands an integrated and interdisciplinary approach for identification of early risk predictors. The newer tools should be adequately innovative either to complement or to replace the currently available tools like invasive electrophysiological testing which is often used to identify patient populations with Ischemic Heart Disease (IHD) who are at an increased risk for SCD and therefore may benefit from Automatic Implantable Cardioverter Defibrillator (AICD) therapy. Here in this mini-review, we provide a brief synopsis of the progress made in SCD risk stratification.

Keywords: Heart failure; SCD risk stratification; Public health; Ischemic heart disease

Introduction

SCD is defined as an unexpected death without an obvious extra-cardiac cause that occurs as a witnessed rapid collapse or within 1 hour of the onset of symptoms [1-4]. SCD is a major public health problem that accounts for 15% of all deaths and 50% of all cardiac deaths. However, the underlying pathophysiology of SCD remains uncertain and controversial, which makes it necessary to develop newer tools to enhance SCD risk stratification. The novel cardiac biomarkers such as Galectin-3 (Gal-3) and soluble ST2 (sST2) need to be studied in more detail and utilized in the near future [5]. Additionally, Cardiac Magnetic Resonance Imaging (cMRI) is a rapidly evolving diagnostic tool that provides prognostic information in patients with Non-Ischemic Cardiomyopathy (NICM). It can quantify cardiac structure, function, presence and extent of myocardial fibrosis as well as ischemia. Positron Emission Tomography (PET) provides measurements of cardiac sympathetic function. These sophisticated imaging techniques are promising; however, we need to develop approaches that involve a combination of novel biomarkers, genomics and new cardiac imaging methods to have an impact on SCD risk stratification [6].

Evolution of SCD Risk Stratification Modalities

With advancements in Cardiopulmonary Resuscitation (CPR) and post-resuscitation care, survival rates have improved after cardiac arrest, however 90% of patients will not survive to be discharged from the hospital. Amongst the patients who survived, around 20% remain with severe neurological and physical disabilities [7]. Additionally, the majority of SCDs do not occur in public places where Automatic External Defibrillators (AEDs) and rapid defibrillation have the greatest impact. This has led to a renewed focus in the field of optimizing risk stratification in order to identify the candidate suitable for prophylaxis devices like AICDs and other cardiac assist devices. The highest prevalence of SCD is seen among asymptomatic individuals, despite Coronary Artery Disease (CAD) being present in the majority of SCD cases. Therefore, it is reasonable to develop risk stratification tools that can be applied to the general population and which involve components beyond clinical risk factors. The presence of structural heart disease and inherited arrhythmia syndromes increase the risk for SCD, besides the traditional risk factors such as diabetes mellitus, dyslipidemia, hypertension and obesity. The association between blood lipid levels and CAD development has been widely accepted but not proven. A prospective case-control study of 8000 British middle-aged men by Wannamethee et al. tried to determine such association, but lack of adequate data merits further investigation.

LVEF has long been recognized as the risk stratification tool for SCD, however it has been shown in studies such as SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) and other community-based studies that up to 70% of patients with SCD had preserved LVEF prior to the arrest. Prophylactic AICD placement is established as the major primary prevention modality and its use has been based on LVEF (usually placed when LVEF is below 35%). But, the vast majority of SCD patients do not have severely reduced LVEF and therefore cannot be risk stratified based on this criterion. Animal and human studies

have shown that myocardial fibrosis is associated with worsening LV systolic function, increased ventricular stiffness and abnormal cardiac remodeling. Additionally, it is well established that myocardial scar is associated with a 2.5-fold increased risk of all-cause mortality and a near 5-fold increased rate of ventricular tachyarrhythmias. The underlying mechanism for development of heart failure (HF) and thereafter SCD is secondary myocardial fibrosis. In cases with unknown etiology of SCD, primary myocardial fibrosis was seen on autopsies. Studies have also shown LV fibrosis as a major cause of SCD in young athletes.

Effective risk stratification requires the availability of tools that can be employed at an early stage in the natural history of the disease when the LVEF is well within the normal range. Moreover, such tools should be inexpensive, cost effective, widely available, easy to use and interpret. Biomarkers fulfill these criteria and might serve as an add-on to the current risk stratification tools with a goal to identify individuals with unidentified, subclinical or acquired risk factors for SCD. As per the NIH consensus document, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic and pathogenic processes or pharmacologic responses to a therapeutic intervention. Plasma biomarkers play an important role in HF patients for SCD risk stratification. Besides that, cardiac imaging such as cMRI plays a vital role in SCD risk stratification [8,9].

Inflammatory Biomarkers

Inflammation plays a central part in the development of vulnerable plaque. Biomarkers reflecting the increased inflammatory activity have been the focus of extensive research in CAD but also in SCD. C-Reactive Protein (CRP), an acute phase reactant, has been studied the most, however whether this biomarker is useful in determining an individual's risk level for CAD remains controversial. Interleukin-6 (IL-6) is another inflammatory marker that has been associated with CAD, but data is insufficient to prove the role of IL-6 in detection of CAD. Three biomarkers have been approved by the Food and Drug Administration (FDA) for assessing prognosis of HF patients: NT-ProBNP, Gal-3 and sST2.

NT-ProBNP and BNP are more traditional markers of HF, released in response to myocardial wall stress. Gal-3 and sST2 are novel and reflect the pathophysiology of HF (myocardial fibrosis) and are associated with increased risk of death from SCD but not pump failure [10]. Gal-3 is a beta-galactosidase-binding lectin and a novel prognostic biomarker of HF. It is known as a mediator of cardiac fibrosis in animal models leading to progressive fibrosis and LV systolic dysfunction and thus plays a role in promoting LV remodeling. Several cohort studies have demonstrated that increased Gal-3 levels are associated with higher incidence of decompensated HF and thus indicate worse prognosis. Gal-3 can assist physicians to identify patients at risk of decompensation, readmission and death. In the future, Gal-3 might also serve as a therapeutic target for intervention as it impacts the progression of HF through cardiac remodeling which has been proven in murine and rat models of heart failure. On the other hand, sST2 is another novel biomarker reflecting cardiac strain. It has a role in the development of immunological tolerance and modulatory responses of T helper type 2 cells. It belongs to the interleukin-1 (IL-1) receptor family and is usually released when cardiac muscle cells undergo a biomechanical strain. Therefore, sST2 is identified as a biomarker of cardiac fibrosis, remodeling and wall stress. There are few studies that have demonstrated the prognostic value of sST2 in predicting mortality in ACS. Additionally, a combination of sST2 and NT-ProBNP have been proven to be a potent marker of cardiovascular risk stratification and prediction of adverse outcomes in studies.

Cardiac Imaging

cMRI is a noninvasive imaging method for heart failure patients and now considered as the gold standard tool for assessment of myocardial anatomy as well as global and regional wall function by detection of wall edema, fibrosis, infiltration, necrosis and wall perfusion. Thus, it plays an important role in diagnosis, monitoring and prognosis of heart failure patients. Additionally, late gadolinium enhancement (LGE) feature of cMRI may further help to identify the regions of myocardial wall fibrosis that have potential to generate life-threatening ventricular tachyarrhythmias.

It is worth to consider here the possibility that the novel biomarkers such as Gal-3 and sST2 might complement LGE-CMR for the detection of myocardial fibrosis and thus for SCD risk stratification in heart failure patients. However, it is necessary to further investigate such a possibility by designing an appropriate prospective randomized clinic study in the near future.

Conclusion

We conclude that SCD is a major public health burden, and it can be prevented with prophylactic measures such as AICD placement. This can be achieved by identifying potential candidates at an early stage of disease progression by using risk stratification tools. LVEF can be combined with the novel biomarkers Gal-3 and sST2 as well as cardiac imaging such as LGE-cMRI for effective risk stratification and prevention of SCD. However, the application of novel biomarkers and cardiac imaging for SCD risk stratification needs to be investigated before taking into consideration for routine clinical practice.

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