CHAPTER 1

General Introduction and Outline of the Thesis

Mischa T. Rijnierse

GENERAL INTRODUCTION

Sudden cardiac death

Sudden cardiac death (SCD) is an important cause of mortality with an annual incidence of 100 per 100.000 in the Western world and accounts for approximately 50% of total cardiac mortality.[1, 2] Among patients who suffered from SCD, ischemic heart disease is the most frequent underlying etiology, being responsible for 75% of the cases. In the remaining cases of SCD, cardiomyopathies (dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy) and primary electrical disorders related to channelopathies are frequently observed (figure 1). In the majority, ventricular arrhythmia (VA) such as ventricular tachycardia (VT) or ventricular fibrillation (VF) is the initial rhythm resulting in SCD, irrespective of underlying etiology.[1]

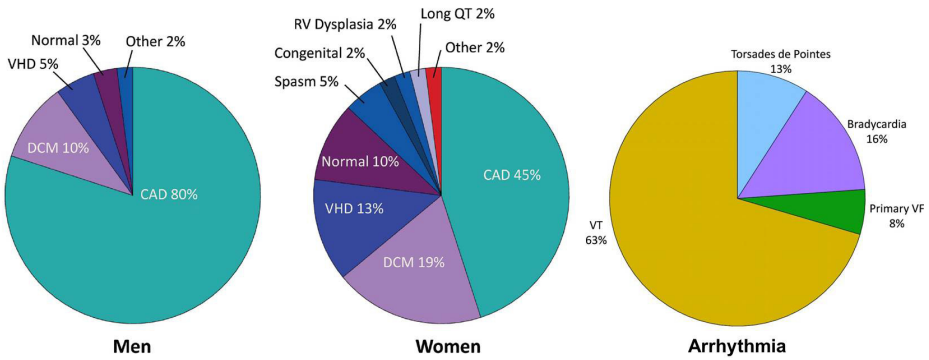

Figure 1. Proportions of underlying cardiac disease men and women who survive out-of-hospital cardiac arrest (A and B) and proportion of first cardiac rhythm documented at time of sudden arrhythmic death (C). Reprint with permission from Deo et al.[1]

Implantable cardioverter-defibrillator

The implantable cardioverter-defibrillator is a device that can effectively detect and terminate sustained VT or VF by delivering anti-tachycardia pacing (ATP) or a defibrillation shock. Until the development of the implantable cardioverter-defibrillator (ICD) in 1980, anti-arrhythmic drugs were the only available treatment options to prevent SCD in patients who survived life-threatening ventricular arrhythmia (VA).[3] Multiple randomized controlled trials were conducted to evaluate if the ICD could reduce mortality in survivors of cardiac arrest or sustained VA. These studies revealed that ICDs were superior to amiodarone or other anti-arrhythmic drugs for secondary prevention of SCD, although statistical significance was reached in one trial.[4-6] Soon after publication of the secondary prevention trials, the first randomized studies were performed to explore

whether the ICD might also improve mortality in patients with increased risk of SCD but without a history of sustained VA.[7-9] As it was previously demonstrated that patients with a left ventricular ejection fraction (LVEF) below 40% are at increased risk of 1-year cardiac mortality after myocardial infarction, this LVEF cutoff value was considered a valid approach to separate patients into high- and low risk groups.[10] Consequently, primary prevention ICD trials included patients with ischemic- and/or non-ischemic dilated cardiomyopathy and LVEF of ≤30-40%.[7-9, 11, 12] Most of the primary prevention studies demonstrated that the ICD was superior over conventional anti-arrhythmic drugs and placebo in reducing both SCD and all-cause mortality.[7, 8, 11] As a result, the ACC/AHA/ESC 2006 guidelines adopted ICD implantation not merely for secondary prevention of SCD, but also for the primary prevention of SCD in patients with LVEF ≤30-40%, depending on cardiomyopathy etiology and heart failure symptoms.[13] In the recent update of ESC 2015 guidelines, ICD implantation for primary prevention is considered a class I indication in patients with LVEF ≤35% and heart failure symptoms, regardless of cardiomyopathy etiology.[14]

Concerns in current clinical practice

The introduction of the ICD for primary prevention of SCD has led to an exponential growth in ICD implantations and concomitant healthcare costs.[15] Although this has resulted in a significant reduction in mortality in patients with impaired left ventricular function, several downsides of patient selection according to LVEF ≤35% as the main eligibility criterion need to be addressed. From an epidemiological point of view, only a small proportion of patients is protected since most cases of SCD in absolute numbers actually occur in patients with preserved LVEF although the relative incidence is higher among patients with impaired LVEF.[16] As a result, a large number of patients that may experience SCD are not eligible for ICD implantation according to current guidelines. In addition, several large observational studies have demonstrated that patients with ICDs implanted for primary prevention experience a low incidence of appropriate ICD therapy (i.e. ATP or shocks) for VA with a documented 3-year incidence ranging from 35% to only 9% in a more recently published study.[17-20] These data suggest that the LVEF has limited sensitivity and specificity for predicting SCD. To complicate matters even further, LVEF can be evaluated using multiple imaging modalities such as echocardiography, radionuclide imaging, cardiovascular magnetic resonance imaging (CMR), and computed tomography. Although current guidelines do not specify the preferred imaging modality to select patients with LVEF ≤35% for ICD implantation, studies have demonstrated that the LVEF as assessed using different imaging modalities may not be interchangeable and could lead to differences in patient selection with potential clinical consequences in follow-up (figure 2).[21-24] As ICD implantation is an invasive therapy which is not infrequently accompanied by major complications[25], a refined patient selection for this therapy is essential and therefore, enhanced risk prediction for VA beyond LVEF is needed.

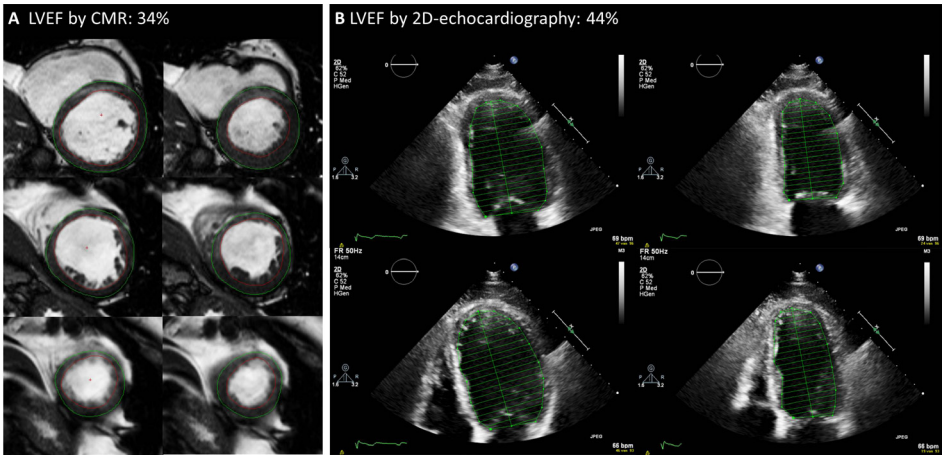

Figure 2. A 67-year old patient with ischemic cardiomyopathy who was screened for ICD implantation for primary prevention of sudden cardiac death. No arrhythmias were documented and the patient did not show signs of heart failure. Both 2D echocardiography and CMR were performed, which yielded a difference in LVEF of ten percentage points (44 vs. 34%, respectively). Based on echocardiographic analysis, ICD implantation should not have been performed, yet CMR drove the decision to implant the device. To date, two years after implantation, no ventricular arrhythmic events have occurred. Reprint with permission from Rijnierse et al.[26]

Risk stratification

In recent years, much effort has been put into the search for new risk markers that can better identify patients at risk for VA. These risk markers may provide information on different pathophysiological aspects of VA. In general, VAs are assumed to be the result from an interaction between an anatomical or functional substrate and a transient triggering factor leading to abnormalities in impulse formation (automaticity, triggered activity) and impulse conduction (re-entry).[27] Myocardial substrates can be formed by scar tissue, perfusion abnormalities, sympathetic denervation, left ventricular dilation or myocardial stretch, and hypertrophy, whereas triggers can be related with sympathetic activation, acute ischemia, environmental stress, electrolyte flux, and hemodynamic stress.[1]

As the pathophysiology of VA is complex and multifactorial, it is likely that a combination of risk markers is needed for predicting the risk of VA. Risk markers that evaluate triggers or modulating factors such as the sympathetic tone fluctuate over time and therefore may be challenging to use for risk prediction of spontaneous VA in the ensuing years. However, as markers evaluating the myocardial substrate of VA remain relatively constant in the majority of patients suffering from chronic cardiomyopathy, it is considered to be a promising approach in risk stratification. A more detailed evaluation of the anatomical substrate of VA has therefore been an emerging topic of research over the last decade. Advanced non-invasive cardiac imaging modalities such as cardiovascular magnetic resonance imaging (CMR), positron emission tomography (PET), and single

photon emission computed tomography (SPECT) can adequately evaluate arrhythmic substrates in detail and therefore hold great potential in risk stratification.[28] Typical imaging targets of the arrhythmic substrate include myocardial perfusion abnormalities, scar and heterogenic scar border zone, sympathetic denervation, and the mismatch between innervation and perfusion. For the evaluation of scar and heterogenic scar border zone, CMR with late gadolinium enhancement (LGE) is considered the preferred imaging modality, whereas PET imaging allows for absolute quantification of perfusion abnormalities with high accuracy and reproducibility. In addition, PET is able to assess biological aspects of the arrhythmic substrate such as cardiac sympathetic innervation.

OUTLINE OF THE THESIS

This thesis aimed to evaluate the role of CMR and PET in identifying susceptibility for ventricular arrhythmia in patients with cardiomyopathy to refine patient selection for ICD implantation for primary prevention of SCD.

Chapter 2 provides a detailed overview of the principles and techniques of currently available advanced imaging modalities in identifying the substrate of VA. Advanced cardiac imaging has emerged as a promising approach to assess the risk of sudden cardiac death. In addition, non-invasive identification of the critical sites of arrhythmias may guide ablation therapy. Typical anatomical substrates that can be evaluated by multiple advanced imaging techniques include perfusion abnormalities, scar and its border zone, and sympathetic denervation.

Although 2D echocardiography has been mainly used for patient selection in the primary prevention ICD trials upon which current guidelines are based, CMR is currently considered the preferred technique for LVEF assessment and is frequently performed to screen patients for ICD eligibility. LVEF's assessed using CMR are, however, typically lower as compared to echocardiography, which may lead to higher implantation rates when using a similar cutoff value (LVEF ≤35%) for ICD eligibility. In ***chapter 3***, the clinical consequences of CMR versus echocardiography guided LVEF assessment for patient selection for primary prevention ICD therapy are investigated in a retrospective study design with long-term follow up.

In ***chapter 4***, the relation between the size of the heterogeneous infarct border zone as assessed using CMR and the innervation-perfusion mismatch area evaluated by PET in patients with ischemic cardiomyopathy is investigated. ***Chapter 5*** describes the association between impaired hyperemic myocardial blood flow as quantified by PET and the inducibility of VA during an electrophysiological study in patients with ischemic cardiomyopathy. It was hypothesized that impaired hyperemic perfusion, which is a strong predictor of mortality in various cardiomyopathy etiologies, may relate to the susceptibility of VA.

Impaired sympathetic innervation is also related with a worse prognosis in cardiomyopathy. In ***chapter 6***, the interrelations between impaired sympathetic innervation, impaired perfusion, and contractile function are explored in non-infarcted remote myocardium specifically. This chapter was aimed to gain more insight into factors that are associated with impaired sympathetic innervation in non-infarcted myocardium in patients with ischemic and dilated cardiomyopathy. ***Chapter 7*** provides an overall comparison of the role of impaired perfusion, sympathetic denervation, innervation-perfusion mismatch, and scar size in predicting the susceptibility for VA in patients with ischemic cardiomyopathy. In ***chapter 8***, the potential value of a novel risk marker, left atrial emptying fraction, and scar size as assessed with CMR in predicting appropriate ICD therapy for VA is described in a retrospective study design. It was hypothesized that impaired left atrial function, which is an independent predictor of mortality in heart failure patients, may reflect underlying left ventricular dysfunction with increased wall stress and consequently relate to electrical instability. Finally, the general conclusions and future perspectives of this thesis are discussed in ***chapter 9***.

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