Risk stratification for ventricular arrhythmias in ischemic cardiomyopathy:

de Haan, S.

2016

CHAPTER 1

General Introduction

Stefan de Haan

Cardiovascular mortality has declined over the last decades in Western countries.[1] However, still about 17 million people die due to cardiovascular diseases in the world each year, of which approximately 25% is sudden cardiac death.[2] Patients with a heart disease are known to be at increased risk of sudden cardiac death, although in about half of the cases of sudden cardiac death the individual is without a known heart disease.[3] On the contrary, only a relative small proportion of patients with a heart disease will die of a sudden cardiac death. It is beneficial to identify patients who are at increased risk of sudden cardiac death, as an implantable cardioverter defibrillator (ICD) can prevent sudden cardiac death.[4]

Patients with an ischemic cardiomyopathy compose one of the patient groups with a heart disease that are at increased risk of sudden cardiac death. Randomized clinical trials have shown that an ICD reduces mortality in this patient category when the left ventricular ejection fraction is below 30-35%.[4,5] After 5 years mortality was reduced by 7% in these patients.[6] Although this is an important and substantial benefit, the majority of the patients does not have any benefit of the ICD. Nonetheless, these patients suffer from the risk of complications related to implantation, device infections and inappropriate shocks. Furthermore, the majority of the appropriate therapies of the ICD are not "life-saving", as approximately 35% of patients with an ICD receives appropriate therapy during the first 3 years of follow up, which is substantially higher than the previously mentioned mortality benefit.[7] Additionally, ICD therapy and follow up is quite expensive. Therefore it is beneficial to use better risk stratification to select those patients who benefit most from the ICD. As to reduce the proportion of patients who do not benefit from the ICD, but who are at risk of complications, and to reduce the costs.

The occurrence of ventricular arrhythmias is based on abnormalities in impulse formation (abnormal automaticity and triggered activity) in which abnormal ionic currents have a major part or abnormalities in impulse conduction (re-entry) in which abnormal depolarization pathways play an important role.[8] In most cases a complex interaction between both mechanisms is responsible for

the occurrence of ventricular arrhythmias. Several pathological processes may contribute to these prerequisites for ventricular arrhythmias. Scar tissue as a result of myocardial infarction may constitute an area of conduction block and the scar tissue comprises residual viable myocytes, which are characterized by slow propagation of electrical impulses.[9] Both are essential for a re-entry circuit. Patients with large myocardial scar due to a myocardial infarction tend to be at increased risk of ventricular arrhythmias, therefore, the presence of re-entry circuits appears to be related to the amount of myocardial scar.[10] Myocardial perfusion abnormalities might induce myocardial ischemia, stunning and hibernation. These conditions modulate myocyte automaticity, excitability, and refractoriness, which might result in dispersion of repolarization and enhanced susceptibility for ventricular arrhythmias.[11] The connection between perfusion impairment and the occurrence of ventricular arrhythmias has been recognized previously.[12,13]

The peri-infarction zone might also have an important role in the occurrence of ventricular arrhythmias. During the infarction, there is only limited ischemia in this border zone and, as a consequence, a relatively large amount of myocytes are preserved. Due to composition of both fibrosis and preserved myocytes, this zone is characterized by inherent conduction abnormalities. Furthermore, these areas might suffer from persisting impaired perfusion. The size of the border zone is a predictor of ventricular arrhythmias, therefore this zone seems to function as a substrate for ventricular arrhythmias.[14] These border zones might also lack innervation. Nerve endings are more vulnerable to ischemia than myocytes, which has been demonstrated by the fact that the area of denervation is commonly larger than the scar size after a myocardial infarction.[15] Denerved myocardium has been shown to have significantly longer refractory periods and might, consequently, be more prone to instigate ventricular arrhythmias.[16] Furthermore, animal experiments have demonstrated that the existence of areas of mismatch between innervation and perfusion, i.e. denerved viable myocardium, is related to inducibility of ventricular tachycardias and the induced ventricular tachycardias seem to originate from the mismatch areas.[15]

Large infarctions of the left ventricle will lead to diminishing of contractile function and, consequently, will lead to negative remodelling and heart failure. Due to the remodelling process the regional wall stress will be inhomogeneously distributed, which in turn will lead to an increase in adrenergic drive. As a result, intracellular processes of the myocytes are altered, for example intracellular calcium levels increase and the expression of connexions is altered.[17] These intracellular changes have been shown to have arrhythmogenic effects. Left ventricular ejection fraction is a parameter used to express the degree of left ventricular remodelling and heart failure. As it reflects left ventricular remodelling, it also reflects the alterations in the intracellular processes in the myocytes. Accordingly, decreased left ventricular ejection fraction has been proved to be an important predictor of sudden cardiac death.[18]

Imaging modalities including nuclear imaging, cardiac magnetic resonance imaging and echocardiography, are able to visualize and assess these pathophysiological processes. As they are capable to capture these processes, they can be applied in risk stratification for ventricular arrhythmias.

OUTLINE OF THESIS

The aim of this thesis was to improve risk stratification for the occurrence of ventricular arrhythmias in patients with ischemic cardiomyopathy with different imaging parameters. For this purpose patients with ischemic cardiomyopathy underwent multiple imaging modalities, including echocardiography, cardiac magnetic resonance imaging with late gadolinium enhancement and PET with ^{15}O-water and ^{11}C-meta-hydroxyephedrine, to discover and assess different imaging parameters and to evaluate their value for risk stratification for ventricular arrhythmias.

Chapter 2

In this chapter, previously investigated imaging parameters for risk stratification are reviewed. Several nuclear imaging, echocardiography and cardiac magnetic resonance imaging parameters and their predictive value for ventricular arrhythmias are discussed.

Chapter 3

In this study we evaluated if perfusable tissue index, a marker of myocardial viability, could be obtained from a single ^{15}O-H_2O PET/CT scan without an additional ^{15}O-CO scan. Because this method reduces scan duration, radiation dose, and risk of patient motion between scans and enables simultaneous and quantitative assessment of both myocardial perfusion and viability with a 10-min scanning protocol.

Chapter 4

Cardiac innervation might play an important role in the occurrence of ventricular arrhythmias. Previous imaging studies used semi-quantitative measurements to assess cardiac innervation, whereas actual quantification might enhance the predictive value of cardiac innervation for ventricular arrhythmias. In this study the optimal tracer kinetic model for ^{11}C-meta-hydroxyephedrine was determined for the quantification of cardiac innervation.

Chapter 5

Imaging parameters such as myocardial viability can be assessed with different imaging modalities. Myocardial viability can be evaluated with PET by measuring the perfusable tissue index and by late gadolinium enhanced cardiac magnetic resonance imaging. We compared the perfusable tissue index with late gadolinium enhancement on cardiac magnetic resonance imaging.

Chapter 6

Various imaging parameters have predictive value for ventricular arrhythmias. Several of these imaging parameters characterize a different entity, but they might represent the same underlying pathology. In this study the innervation and perfusion mismatch and heterogenic scar zone were compared, both originating in the peri-infarction zone.

Chapter 7

Echocardiography is an important imaging modality for the assessment of left ventricular ejection fraction as it is widely available and easy to use. Furthermore, left ventricular ejection fraction assessed with echocardiography has been used in numerous studies as inclusion criterion. Cardiac magnetic resonance imaging, however, has better intra- and interobserver variabilities and might, therefore, be the imaging modality of choice to assess left ventricular ejection fraction. We investigated if left ventricular ejection fraction assessed with 2-dimensional echocardiography is comparable to left ventricular ejection fraction assessed with cardiac magnetic resonance imaging in patients with severely reduced left ventricular ejection fraction.

Chapter 8

Several studies have shown the prognostic value of scar characteristics assessed by cardiac magnetic resonance imaging for ventricular arrhythmias. These studies used, however, different definitions of the scar characteristics. In this study we compared these different definitions of scar characteristics in their ability to predict ventricular arrhythmias.

Chapter 9

Impaired hyperemic myocardial blood flow is associated with increased mortality in ischemic and non-ischemic cardiomyopathy. This increase in mortality might be attributed to electric instability with ventricular arrhythmias as result. We assessed whether hyperemic myocardial blood flow impairment might be related with inducibility of ventricular arrhythmias in patients with ischemic cardiomyopathy.

Chapter 10

Various non-invasive imaging parameters have predictive value for ventricular arrhythmias. Head-to-head comparison of the various imaging parameters is scarce. In this study we assessed the predictive role of myocardial perfusion, sympathetic denervation and scar size on the inducibility of ventricular arrhythmias in patients with ischemic cardiomyopathy.

REFERENCES

1. Niemeijer MN, van den Berg ME, Leening MJ, Hofman A, Franco OH, Deckers JW, Heeringa J, Rijnbeek PR, Stricker BH, Eijgelsheim M. Declining incidence of sudden cardiac death from 1990–2010 in a general middle-aged and elderly population: the Rotterdam Study. *Heart Rhythm* 2015;12:123–129.
2. Mendis SPP, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. *Geneva: World Health Organization,* 2011.
3. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992;85:I2–10.
4. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
6. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole JE, Mark DB, Lee KL, Bardy GH. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009;120:2170–2176.
7. Moss AJ, Greenberg H, Case RB, ZarebaW, Hall WJ, Brown MWet al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;110:3760–5.
8. de Bakker J, van Rijen H. Mechanisms of ventricular tachycardia: underlying pathological and physiological abnormalities. In Wang P, Al-Ahmad A, Hsia H, eds. Ventricular Arrhythmias and Sudden Cardiac Death. *Malden: Blackwell Publishing;* 2008:18–27.
9. Lo R, Hsia HH. Ventricular arrhythmias in heart failure patients. *Cardiol Clin* 2008; 26:381–403.
10. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol* 2005;45:1104–8.
11. Luqman N, Sung RJ,Wang CL, Kuo CT. Myocardial ischemia and ventricular fibrillation: pathophysiology and clinical implications. *Int J Cardiol* 2007;119:283–90.
12. Elhendy A, Sozzi FB, van Domburg RT, Bax JJ, Geleijnse ML, Roelandt JR. Relation among exercise-induced ventricular arrhythmias, myocardial ischemia, and viability late after acute myocardial infarction. *Am J Cardiol* 2000;86:723–9.
13. Margonato A, Mailhac A, Bonetti F, Vicedomini G, Fragasso G, Landoni C et al. Exercise-induced ischemic arrhythmias in patients with previous myocardial infarction: role of perfusion and tissue viability. *J Am Coll Cardiol* 1996;27:593–8.
14. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation* 2007;115:2006–14.
15. Sasano T, Abraham MR, Chang KC, Ashikaga H, Mills KJ, Holt DP et al. Abnormal sympathetic innervation of viable myocardium and the substrate of ventricular tachycardia after myocardial infarction. *J Am Coll Cardiol* 2008;51:2266–75.
16. Calkins H, Allman K, Bolling S, Kirsch M, Wieland D, Morady F et al. Correlation between scintigraphic evidence of regional sympathetic neuronal dysfunction and ventricular refractoriness in the human heart. *Circulation* 1993;88:172–9.
17. Jin H, Lyon AR, Akar FG. Arrhythmia mechanisms in the failing heart. *Pacing Clin Electrophysiol* 2008;31:1048–56.
18. Bailey JJ, Berson AS, Handelsman H, Hodges M. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. *J Am Coll Cardiol* 2001;38:1902–11.