Risk stratification for ventricular arrhythmias in ischemic cardiomyopathy:

de Haan, S.

2016

Summary and future perspectives

Nederlandse samenvatting en toekomst perspectief voor onderzoek

SUMMARY AND FUTURE PERSPECTIVES

Patients with an ischemic cardiomyopathy are at increased risk of sudden cardiac death. ICDs have been shown to reduce mortality in this patient category. However, the majority of patients does not have any benefit of the ICD, but they are at risk of ICD-related complications. Therefore, risk stratification for ventricular arrhythmias in these patients is beneficial, since it could cause a reduction in implantations of ICDs and a concomitant reduction in ICD-related complications and costs. Imaging parameters might be important tools in the risk stratification process.

In this thesis, the aim 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 evaluate the value of different imaging parameters for risk stratification for ventricular arrhythmias.

Chapter 2

An overview was provided of the imaging parameters that have proven to have predictive value for the occurrence of ventricular arrhythmias in ischemic cardiomyopathy. Imaging parameters derived from echocardiography, cardiac magnetic resonance imaging and nuclear imaging were discussed. The imaging modality-based risk stratification parameters are promising, but insufficiently developed to be implemented in daily clinical practice.

Chapter 3

In this chapter a possible technical advancement for risk stratification was evaluated. It was shown that the proposed method enables calculation of parametric perfusable tissue index images based solely on a single myocardial ^{15}O-H_2O scan and a low dose CT scan, instead of a myocardial ^{15}O-H_2O scan, a ^{15}O-CO blood-pool scan and a transmission scan using ^{68}Ge sources. This is a possible improvement in risk stratification as this method reduces scan duration, radiation dose and risk of patient motion between scans and it enables simultaneous and quantitative assessment of both myocardial perfusion and viability, both possible risk stratification parameters, with a 10-min scanning protocol.

Chapter 4

Another potential technical improvement was assessed in this section. A reversible two-tissue compartment model best described ^{11}C-HED kinetics, however, a single-tissue compartment model is preferred for routine clinical studies, as it is more robust at clinically relevant noise levels and, at the same time, provides volume of distribution results that are highly correlated with those obtained with the two-tissue compartment model. Simplified measures, such as retention index and standardized uptake value, showed good correlation with fully quantitative results and may be used to detect regions of denervation. The non-linear relationship of the retention index and standardized uptake value with the volume of distribution will limit their application in, for example, monitoring response to treatment.

Chapter 5

This study was conducted to validate the use of a parametric myocardial viability imaging technique using ^{15}O-H2O PET/CT, since this gives the advantage of assessing myocardial perfusion and viability in a single scanning session. It was shown that both parametric perfusable tissue fraction and perfusable tissue index imaging were in good agreement with late gadolinium enhancement on CMR, a marker of myocardial viability. Therefore, as parametric perfusable tissue fraction and perfusable tissue index imaging and myocardial perfusion imaging are obtained simultaneously, both myocardial viability and ischemia can be evaluates in a single scanning session.

Chapter 6

Feasibility of assessment of both cardiac innervation and perfusion by PET with ^{11}C-HED and ^{15}O-water, respectively, in humans was demonstrated in this chapter. Furthermore, mismatch between cardiac innervation and perfusion was shown to correlate with heterogenic scar size assessed with late gadolinium enhanced CMR, both risk markers for ventricular arrhythmias. Though heterogenic scar size and innervation and perfusion mismatch were not shown to be related to inducibility of monomorphic ventricular tachycardias.

Chapter 7

Left ventricular ejection fraction is an important criterion for ICD implantation in primary prevention and is in many instances assessed by 2D echocardiography. This study showed a systematic overestimation of left ventricular ejection fraction by 2D echocardiography compared with CMR in heart failure patients with a severely depressed left ventricular ejection fraction. This indicates that the two imaging modalities are not interchangeable in this patient population. The discrepancy may significantly impact clinical decisions for individual patients in eligibility for device therapy. Since CMR has better inter- and intraobserver variability, it would be the preferred method for assessment of left ventricular ejection fraction in case of eligibility for device therapy. However, this study and previous work point towards the necessity for resetting cut-off values when CMR is used for assessment of left ventricular ejection fraction.

Chapter 8

Myocardial scar tissue characteristics assessed by late gadolinium enhanced CMR are shown to be predictors of ventricular arrhythmias in patients with ischemic cardiomyopathy. Several methodologies to quantify myocardial scar are used and these were evaluated. The quantity of total scar size estimation and its predictive value are relatively independent of the methodology used. Additionally, analysis of scar core and peri-infarct zone does not appear to improve the predictive value over the quantification of total scar size alone. Finally, considerable overlap in scar size between patients with and without documented ventricular arrhythmias exits, which may limit risk stratification. However, in each of the methodological approaches a lower threshold could be identified beyond which no ventricular arrhythmias could be detected.

Chapter 9

The relation of rest and hyperaemic myocardial blood flow, assessed with ^{15}O-water PET, and CMR parameters with inducibility of ventricular arrhythmias was evaluated. Impaired global hyperaemic myocardial blood flow and coronary flow reserve were revealed to be associated with inducibility of ventricular arrhythmias in patients with ischemic cardiomyopathy. The relation of CMR-assessed left ventricular ejection fraction, scar burden, and border zone with inducibility of ventricular arrhythmias was shown to be of less significance. These results suggest that impaired hyperaemic myocardial blood flow might contribute to electric instability or acts as a marker of electric instability and suggests that it has a potential important role in risk stratification for ventricular arrhythmias in patients with ischemic cardiomyopathy.

Chapter 10

In this chapter, several potential imaging parameters, including PET-assessed myocardial perfusion, sympathetic innervation and innervation-perfusion mismatch and CMR-assessed left ventricular volumes and scar parameters, and their relation with inducible ventricular arrhythmias were investigated in patients with ischaemic left ventricular dysfunction. Impairment in global hyperaemic perfusion was shown to be the only independent predictor for inducibility of ventricular arrhythmias. Other previously validated approaches to evaluate the arrhythmic substrate including the PET-assessed sympathetic denervation, innervation-perfusion mismatch as well as scar characteristics assessed by late gadolinium enhanced CMR appeared to have less predictive value. Additionally, a combined approach of different imaging variables was not shown to have incremental value in predicting inducibility of ventricular arrhythmias.

FUTURE PERSPECTIVES

Several imaging parameters have been shown to be useful in risk stratification for ventricular arrhythmias in patients with ischemic cardiomyopathy. Furthermore, multiple studies have shown that those imaging parameters are stronger predictors of ventricular arrhythmias than left ventricular ejection fraction. Echocardiographic, cardiac magnetic resonance imaging and nuclear imaging parameters have proven their risk stratification value. Nonetheless, work should be put into further exploration of the predictive value of those imaging parameters. The full potential has not been fully elaborated so far, because data on head-to-head comparisons of the imaging parameters is scarce. Head-to-head comparisons of the different imaging parameters are important, since these comparisons will not only reveal which imaging parameters are the strongest predictors of ventricular arrhythmias, but will also show if there is incremental value if one combines them. Combination of several imaging parameters might give the best risk stratification and studies combining several imaging parameters might demonstrated that one parameter, such as for example hyperaemic myocardial blood flow, represents the combination of various imaging parameters or multiple processes underlying the occurrence of ventricular arrhythmias. Head-to-head comparison might even reveal a clinical risk score, such as the CHA2DS2-vasc score, for benefit of ICD therapy.

The use of appropriate end-points in the studies remains a challenge. Most studies on risk stratification for ICD implantation use the occurrence of ventricular arrhythmias as end-point. Although the mortality benefit of the ICD is caused by terminating life-threatening ventricular arrhythmias, the occurrence of ventricular arrhythmias is not directly related to mortality. One of the end-points used is inducibility of ventricular arrhythmias. Inducibility of monomorphic ventricular arrhythmias on electrophysiological testing is correlated to the occurrence of ventricular arrhythmias in real life. This is, however, not a one-on-one relationship and patients with inducibility of monomorphic ventricular arrhythmias on electrophysiological testing have up till now not been shown to have more benefit of an ICD. Therefore the use of inducibility of ventricular arrhythmias as end-point is of limited value. Furthermore, ICD therapy is used is end-point, but much of its value depends on ICD settings. Previous data have shown that patients receive more often ICD therapy than they have mortality benefit. A more aggressive setting of the ICD will result in more treatment of otherwise non-sustained ventricular arrhythmias and ventricular arrhythmias not resulting in death. Nonetheless, less aggressive ICD settings will still lead to more ICD therapies than mortality benefit. ICD therapy is not the perfect surrogate end-point for sudden cardiac death, although one can define a subgroup of low risk of sudden cardiac death when using ICD therapy as end-point, which are the patients who do not receive any ICD therapy. Therefore the occurrence of ICD therapy can be quite a useful end-point. Eventually, actual mortality benefit or lack of mortality benefit is the ultimate end-point.

Mortality should be the end-point in randomized clinical trials on patients receiving ICDs. Randomized trials on all patients who should receive an ICD because of primary prevention according to current guidelines, would be unethical, as patients who are actually at high risk of sudden cardiac death have the chance of being randomized to not receiving an ICD. Randomized trials should first be conducted in patients who are actually at low risk of sudden cardiac death, but who should have an ICD according to the current guidelines. Imaging parameters can be used to identify those patients who are at lowest risk of sudden cardiac death. In that way the predictive potential of the imaging parameters can fully be elaborated.

NEDERLANDSE SAMENVATTING EN TOEKOMST PERSPECTIEF VOOR ONDERZOEK

Patiënten met een ischemische cardiomyopathie hebben een verhoogd risico op plotselinge hartdood. ICD's hebben laten zien de mortaliteit in deze patiëntengroep te reduceren. Hoewel de meeste patiënten geen benefit hebben van de ICD, maar het risico hebben om ICD-gerelateerde complicaties te krijgen. Daarom is risicostratificatie voor ventriculaire aritmieën voordelig, omdat het een afname van ICD-implantaties kan bewerkstelligen en dientengevolge een afname van ICD-gerelateerde complicaties en kosten. Beeldvormingsparameters kunnen belangrijke hulpmiddelen zijn in het proces van risicostratificatie.

In deze thesis was het doel om de risicostratificatie voor het voorkomen van ventriculaire aritmieën in patiënten met een ischemische cardiomyopathie te verbeteren door middel van verschillende beeldvormingsparameters. Voor dit doel hebben patiënten met een ischemische cardiomyopathie verschillende beeldvorming ondergaan, zoals echocardiografie, cardiale MRI met late gadolinium contrastaankleuring en PET met ^{15}O-water en ^{11}C-meta-hydroxyefedrine, om de waarde van de verschillende beeldvormingsparameters voor risicostratificatie voor ventriculaire aritmieën te bepalen.

Hoofdstuk 2

Een overzicht van de beeldvormingsparameters die bewezen hebben voorspellende waarde voor het voorkomen van ventriculaire aritmieën in patiënten met een ischemische cardiomyopathie te hebben, werd gegeven. Beeldvormingsparameters van de echocardiografie, cardiale MRI en nucleaire beeldvorming werden besproken. Risicostratificatie op basis van beeldvormingsparameters is veelbelovend, maar vooralsnog onvoldoende ontwikkeld om te implementeren in de dagelijkse praktijk.

Hoofdstuk 3

In dit hoofdstuk werd een mogelijke technische verbetering voor risicostratificatie geëvalueerd. Er werd aangetoond dat de voorgestelde methode het mogelijk maakt om parametrische perfusable tissue index beelden te berekenen met alleen myocardiale ^{15}O-H_2O scan en een low-dose CT-scan, in plaats van met een myocardiale ^{15}O-H_2O scan, een ^{15}O-CO blood-pool scan en een transmissie scan met ^{68}Ge bronnen. Dit is een mogelijke verbetering voor de risicostratificatie, omdat deze methode de scantijd bekort, de stralingsbelasting en risico op verplaatsing van de patiënt tussen de scans reduceert en het maakt gelijktijdige kwantitatieve analyse of zowel myocardiale perfusie, als vitaliteit mogelijk, beide mogelijke risicostratificatie parameters, in een scanprotocol van 10 minuten.