123I-mIBG assessed cardiac sympathetic activity: standardizing towards clinical implementation
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Chapter 13

Summary, general discussion, future perspective and conclusions
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SUMMARY

The cardiac sympathetic system is one of the neurohormonal compensation mechanisms that plays an important role in the pathogenesis of chronic heart failure (CHF). Patients with CHF have increased cardiac sympathetic activity with increased exocytosis of norepinephrine (NE) from the presynaptic vesicles and impaired NE re-uptake via the norepinephrine transporter (NET) in the sympathetic terminal nerve axons. This results in increased levels of NE in the synaptic cleft. Initially, β-adrenergic receptor (AR) stimulation by increased synaptic NE levels helps to compensate for impaired myocardial function. However, long-term NE excess has detrimental effects on myocardial structure and gives rise to a down regulation and availability of post-synaptic β-AR. This leads to left ventricular remodeling and is associated with increased mortality and morbidity in CHF.

Cardiac sympathetic activity can non-invasively be visualized by nuclear medicine techniques. The most commonly used SPECT tracer is the NE analogue $^{123}$I-meta-iodobenzylguanidine ($^{123}$I-mIBG). The most commonly used semi-quantitative measurements of myocardial $^{123}$I-mIBG uptake are the early heart-to-mediastinum (H/M) ratio, derived 15 minutes post injection (p.i.) of $^{123}$I-mIBG, late H/M ratio, derived 4 hours p.i. of $^{123}$I-mIBG and the $^{123}$I-mIBG washout (WO), calculated as the difference between early and late H/M ratio and expressed as a percentage of the early HM ratio.

Although a large number of studies on $^{123}$I-mIBG assessed cardiac sympathetic activity in CHF have been published, the lack of standardization between different institutions have hampered wide scale clinical implementation. In this thesis further standardization of cardiac $^{123}$I-mIBG scintigraphy is validated (part I). The prognostic value of cardiac $^{123}$I-mIBG scintigraphy in CHF was studied and thereby provided further evidence for clinical implementation of cardiac $^{123}$I-mIBG scintigraphy (part II). In addition the use of cardiac $^{123}$I-mIBG scintigraphy in populations other than CHF are discussed (part III).

PART I

A collimator is a pivotal part of a gamma camera and constitutes of a thick sheet of lead, with thousands of adjacent parallel holes through it and corresponding septa. These septa allow only those photons traveling parallel to the septa to pass through and be recorded by the crystal. Photons not traveling parallel to the septa are filtered out by the septa. In addition to the main photopeak of 159 keV $^{123}$I emits a low-abundance of high-energy photons. These high-energy photons leads to penetration of collimator septa and subsequent degrade the image quality and affects estimation of the H/M ratio. Therefore, the thickness of the collimator septa is a major determinant of this
high energy photon-penetration. Consequently collimator choice is one of the most important factors causing variation in myocardial $^{123}$I-mIBG-derived parameters among institutions and published scientific studies. In chapter 2 the influence of differences between collimators on the planar cardiac $^{123}$I-mIBG-derived parameters is evaluated (i.e. early and late H/M ratio) in 53 patients with CHF. Parameters calculated using a low energy high resolution (LEHR) collimator were significantly lower compared with those from a medium energy (ME) collimator (late H/M ratio 1.41 ± 0.18 vs. 1.80 ± 0.41, $p < 0.001$). Interestingly with increasing H/M ratio the difference between the ratios increased in favour of the ME collimator. This difference could be explained by septal penetration of high-energy photons from both liver and lungs in mediastinum and myocardium, being the lowest when using the ME collimator. These results strengthen the importance of the recommendation to use ME collimators in cardiac $^{123}$I-mIBG scintigraphy.

Although the H/M ratio is a simple method to correct for background, standardization of acquisition and analysis is needed. The lack of standardization between different institutions is one of the factors that have hampered the wide scale clinical implementation of planar cardiac $^{123}$I-mIBG scintigraphy. As already mentioned differences in collimators cause variation among institutions and studies. In chapter 3 the results of a European phantom cross-calibration study of planar cardiac $^{123}$I-mIBG scintigraphy are described. Based on the results of this phantom study, a conversion coefficient for each gamma camera-collimator combination was calculated. With these conversion coefficients various conditions can be converted to standardized H/M ratios. This cross-calibration enables a better comparison between institutions which is important for identifying appropriate thresholds for differentiating high and low risk heart failure patients.

In chapter 4 the impact of mediastinal ROI definition on intra- and inter-observer variability in relation to collimator type was assessed. An observer-defined mediastinal ROI was compared to a predefined mediastinal ROI. Substantial agreement was found between all 3 observers using predefined mediastinum ROI for both LEHR and ME collimator use. However, an observer-defined mediastinal ROI resulted in a poor to moderate agreement independent of collimator choice. In addition, intra-observer analysis using a predefined mediastinal ROI showed substantial agreement. Lin’s concordance coefficient did not differ significantly between LEHR and ME collimators (i.e. 0.97 and 0.96 respectively). A predefined mediastinal ROI is therefore to be preferred over observer defined mediastinal ROIs.

The NET, encoded by the solute carrier family 6 (SLC6A2), is responsible for reuptake of NE into the presynaptic nerve terminals and is a regulator of NE homeostasis. $^{123}$I-mIBG shares the same presynaptic uptake, storage and release mechanism as NE. Although polymorphism of the SLC6A2 gene has been reported, the effect on cardiac $^{123}$I-mIBG uptake is unknown. In chapter 5 the influence of SLC6A2 single-
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Nucleotide polymorphisms (SNP) on $^{123}$I-mIBG parameters (i.e. early and late H/M ratio and $^{123}$I-mIBG washout) in 49 CHF patients eligible for ICD implantation for primary prevention was examined. Six different SLC6A2 SNPs were found, but none (of them) were functional. Consequently polymorphisms of the SLC6A2 gene in this study cohort were not associated with any $^{123}$I-mIBG myocardial parameter.

For the quantification of cardiac $^{123}$I-mIBG uptake, the mediastinum is used as a reference region reflecting nonspecific background activity. However, variations in the quantity of vascular structures in the mediastinum and renal clearance rate of $^{123}$I-mIBG from the blood pool may contribute to increased inter-individual variation in $^{123}$I-mIBG uptake. In chapter 6 the relationship between changes in H and M counts and the change in vascular $^{123}$I-mIBG activity, including the effect of renal function was examined. Changes in region of interest (ROI) activity ratios between early (15 minutes p.i.) and late (4 hours p.i.) planar images could not be explained by blood activity, vascular clearance, or renal function. The change in measured H and M counts between early and late planar $^{123}$I-mIBG images was unrelated to intravascular levels of the radiopharmaceutical. This suggests that changes in M counts are primarily due to decrease in soft tissue activity and scatter from the adjacent lungs.

$^{123}$I-mIBG is primarily cleared via the kidneys. In addition patients with CHF tend to have a reduced kidney function. It is therefore logical to assume that a reduced glomerular filtration rate (GFR) is associated with a reduced blood clearance of $^{123}$I-mIBG and thereby could influence the $^{123}$I-mIBG-derived parameters (i.e. early and late H/M ratio and $^{123}$I-mIBG WO). In chapter 7 it was explored whether renal function expressed as the estimated glomerular filtration rate (e-GFR) could explain variability of $^{123}$I-mIBG assessed myocardial sympathetic activity in a CHF population. In addition, renal function was compared to $^{123}$I-mIBG-derived parameters as predictors of cardiac death in CHF. $^{123}$I-mIBG-derived parameters were independent from renal function. Furthermore, $^{123}$I-mIBG assessed cardiac sympathetic activity was found to be superior to renal function in the prediction of prognosis in patients with CHF.

PART II

Although arrhythmia, lethal cardiac events and prognosis are multifactorial and have several determinants, cardiac $^{123}$I-mIBG scintigraphy alone and more likely in combination with other determinants may be able to better select CHF patients with increased risk. Chapter 8 provides a meta-analysis of original individual late H/M ratio data of 636 CHF patients retrieved from six studies from Europe and the United States of America. The use of $^{123}$I-mIBG parameters to predict all-cause mortality, cardiac mortality, arrhythmic events, and heart transplantation was investigated. Late H/M ratio was a significant predictor of all event categories, but lowest hazard ratios
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(HRs) were for the composite endpoint of any event (HR 0.30 [0.19 – 0.46]), all-cause mortality (HR 0.29, [0.16 – 0.53]), cardiac transplant (HR0.22 [0.10 – 0.49]), cardiac mortality (HR 0.28 [0.14 – 0.55]), and arrhythmia (HR 0.33 [0.16–0.67]). In multivariate analysis, late H/M ratio was an independent predictor for all event categories, except for arrhythmias. Interestingly, in CHF patients, late H/M ratio is not only useful as a dichotomous predictor of events (high vs. low risk), but also has prognostic implication over the full range of the outcome value for all event categories except arrhythmias.

CHF results not only in an increased cardiac sympathetic activity but is also associated with increased myocardial inflammation. In chapter 9 the relationship between severity of heart failure, $^{123}$I-mIBG assessed cardiac sympathetic activity and measures of inflammation in 55 subjects with stable, optimally treated CHF was studied. In addition, the predictive value of $^{123}$I-mIBG parameters and markers of inflammation for cardiac events (i.e. appropriate ICD therapy, progression of CHF and cardiac death) was evaluated. Left ventricular ejection fraction (LVEF) was the only independent predictor of late H/M ratio and NT-proBNP was the only independent predictor of $^{123}$I-mIBG WO. CRP, IL12p40, TNF-α, sE-selectin, MPO, PAI-1, tPA and TNFR2 were not related to late H/M ratio or $^{123}$I-mIBG WO. During median follow-up of 34 months 13 patients experienced a cardiac event. These cardiac events were associated with CRP, NT-proBNP, MPO and late H/M. However, multivariate analysis showed only CRP, NT-proBNP, MPO and IL-12p40 as predictors of cardiac events. Inflammation and cardiac sympathetic activity seem not to be related in stable, optimally treated CHF patients. This is corroborated by the finding that they both provide prognostic information in this specific stable CHF population.

Chapter 10 evaluates whether $^{123}$I-mIBG assessed cardiac sympathetic activity could identify high-risk CHF subjects most likely to experience appropriate ICD therapy. 135 subjects with stable, optimally treated CHF were enrolled in 13 centres in Europe. Conversion coefficients from our cross-calibration study were used to correct for the different gamma camera-collimator used. During follow-up 24 patients experienced a cardiac event (appropriate ICD therapy (n = 12), NYHA functional class progression (n = 6) and cardiac death (n = 6)). The late H/M and LVEF were associated with freedom of appropriate ICD therapy. Therefore $^{123}$I-mIBG assessment of cardiac sympathetic activity enables better identification of the prognosis in stable CHF patients and can be used for better selection of patients who benefit from ICD implantation and therefore helps to constrain the CHF related costs.

PART III

22q11.2 Deletion syndrome (DS) affects catechol-O-methyl-transferase (COMT), which involves the degradation of NE, the neurotransmitter of the cardiac sympathetic system.
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Adults with 22q11.2DS are clinical at increased risk for sudden unexpected death. Although the causes are likely multifactorial, increased cardiac sympathetic activity with subsequent fatal arrhythmia, due to increased levels of NE, should be considered as a possible mechanism. In chapter 11 it was determined whether $^{123}$I-mIBG scintigraphy assessed cardiac sympathetic activity is increased in 22q11.2DS, both at baseline and following an acute NE depletion with alpha-methyl-para-tyrosine (AMPT). For the first time normal cardiac sympathetic activity in adults with 22q11.2DS has been demonstrated. Although there was a small difference in adrenergic drive compared to healthy subjects, this most likely does not explain the increased unexpected death rate in the 22q11.2 DS population.

Tako-tsubo cardiomyopathy (TCM) is an increasingly recognized clinical syndrome characterized by acute reversible apical ventricular dysfunction, commonly preceded by exposure to severe physical or emotional stress. In chapter 12 an overview is given of the clinical presentation and treatment of TCM and all various non-invasive imaging techniques with a focus on the potential role of $^{123}$I-mIBG scintigraphy. In addition the possible pathophysiological mechanisms of TCM are discussed. Currently, the dominating hypothesis on the pathophysiology of TCM postulates that high levels of the neurotransmitter epinephrine may trigger a change in intracellular signaling in ventricular myocytes. With significant increasing levels of epinephrine, the predominance of stimulation is shifted from G-stimulating to the G-inhibitor protein coupling, which leads to a negative inotropic effect. Interestingly, this negative inotropic effect is the largest in the apical myocardium where the $\beta_2$AR:$\beta_1$AR ratio is the highest. It has been demonstrated that uptake of NE via the NET is inhibited in the presence of high levels of epinephrine. Therefore, in TCM, decreased uptake of $^{123}$I-mIBG via the NET could be explained as an indirect effect to high circulating levels of epinephrine. Therefore $^{123}$I-mIBG scintigraphy may guide optimization of individual (pharmacological) therapy in TCM. These new insights can be used as starting point for the development of international guidelines of TCM which may increase the awareness, and optimize the treatment of TCM.

CONCLUSION AND FUTURE PERSPECTIVES

Cardiac sympathetic activity can non-invasively be assessed by cardiac $^{123}$I-mIBG scintigraphy. However, the lack of standardisation of acquisition and post-acquisitions analysis have hampered comparison between different institutions and therefore wide scale clinical implementation. In this thesis the influence of several acquisition, post-acquisition and patient related parameters such as collimator choice, mediastinal ROI definition, polymorphism of the SLC6A2 gen, renal function and inflammation, on cardiac $^{123}$I-mIBG scintigraphy outcome were studied. The results showed that
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Standization and validation of these parameters in combination with cross-calibration of gamma camera-collimator results in a good reproducibility with a small inter- and intra-observer variation. Moreover, the standardized cardiac $^{123}$I-mIBG scintigraphy outcomes seem to have good prognostic value. Therefore, major objections for clinical implementation have been overcome. Furthermore, the use of standardized H/M ratios allows development of universal prognostic cut-off values (high vs. low risk). These cut-off values can be calculated by re-analysis of the data of previous published multicentre studies. Finally, it should be stressed that standardization of the H/M ratio is essential for the preparation of adequate risk models.

Despite therapeutic improvements the prognosis of CHF remains unfavorable in part due to sudden cardiac death (SCD). The introduction of implantable cardioverter defibrillators (ICD) has improved the overall survival of CHF. However, a high percentage of CHF with ICD implantation will never receive appropriate ICD therapy. Moreover, there is a risk of malfunction and operative complications of these devices. Furthermore, this therapeutic strategy has a great impact on the healthcare budgets. Therefore, it is essential to optimize the current selection criteria to improve patient selection for ICD implantation. This thesis showed that stable CHF patients with intermediate late H/M ratios are more likely to have appropriate ICD therapy compared to patients with low and high late H/M ratios. These findings are new and may be useful to better identify patients who, most likely, benefit from ICD implantation and therefore helps to constrain the CHF related costs. Recently, the ADMIRE-ICD study has been started. This randomized, multicentre study will evaluate the prognostic value of planar $^{123}$I-mIBG scintigraphy in CHF. Subjects will be randomized to a standard care group receiving an ICD implantation for primary prevention of SCD or a $^{123}$I-mIBG scintigraphy group. Subjects in the $^{123}$I-mIBG scintigraphy group will receive an ICD for primary prevention of SCD based on a predefined late H/M ratio cut-off level of ≤ 1.6. The primary endpoint is all-cause mortality and the secondary endpoint is combined endpoint of hospitalization, cardiac death and ventricular arrhythmia. The first results of this study are expected by the end of 2019. To improve the clinical impact of the ADMIRE-ICD study the use of standardized H/M ratios is strongly recommended.

In conclusion, improving standardization and validation of cardiac $^{123}$I-mIBG scintigraphy will lead to a much more accepted application for individual CHF management. These findings will help to improve the quality of cardiac $^{123}$I-mIBG imaging and to facilitate appropriate use of cardiac $^{123}$I-mIBG imaging.