123I-mIBG assessed cardiac sympathetic activity: standardizing towards clinical implementation
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General introduction and outline thesis
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CHRONIC HEART FAILURE

Heart failure (HF) is a life-threatening disease affecting approximately 26 million people worldwide. The incidence of HF in the Netherlands ranges between 28,000 and 44,000 cases per year and increases with age; the majority of HF patients are older than 75 years. Currently, there are between 100,000 and 150,000 patients with HF in the Netherlands. It is the only cardiovascular disease with both growing incidence and prevalence. Reasons for this trend are related to increased life expectancy, improvement of survival after myocardial infarction and better treatment options for HF (Figure 1). It is expected that the total number of HF patients in the Netherlands will increase to 275,000 in 2040. As a consequence, the costs related to HF care will increase: in 2007 these costs were 455 million euro which rose to 940 million in 2011. For 2025, these costs are estimated at 10 billion euros.

Despite the successful introduction of treatment with a combination of beta-blockers and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers together with loop diuretics, the prognosis of chronic HF (CHF) remains unfavourable. The most recent European data (ESC-HF pilot study) demonstrate that 12-month all-cause mortality rates for hospitalised and stable/ambulatory HF patients were 17% and 7%, respectively. The majority of these deaths are caused by progression of HF, lethal arrhythmia and sudden cardiac death. The use of implantable devices such as implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) has improved the overall survival of CHF patients. Current European guidelines recommend ICD for primary prevention of fatal arrhythmias in CHF subjects with an ejection fraction <35% and symptomatic HF NYHA class ≥ 2 under optimal pharmacological therapy. In addition, CRT is recommended in CHF patients who remain symptomatic in NYHA class ≥ 2 under optimal pharmacological therapy, with a left ventricular ejection fraction (LVEF) < 35% and wide QRS complex (≥ 130 ms).

ICDs applied for primary or secondary (i.e. already proven ventricular arrhythmias) prevention reduce the relative risk of death by 20%. However, the MADIT II (Second Multicenter Automated Defibrillator Implantation Trial) has shown that the absolute reduction of fatal events was only 5.6% (mortality was 19.8% in the control group and 14.2% in the ICD group during a mean follow-up of 20 months). In addition, the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study showed that the annual number of ICD shocks was 7.1% of which 5.1% were appropriate in the first year rising to 21% in the 5th year post-implantation. However, three years after ICD implantation for primary prevention, a remarkably high percentage of 65% had never received appropriate ICD therapy. Moreover, there is also a risk of malfunction and operative complications, e.g. inappropriate shocks, infection.
Last but not least is the relative high cost of these devices. Therefore, it is essential, not only from a clinical but also from a socioeconomic point of view, to optimise the current selection criteria for CRT and ICD for primary prevention aimed at better identification of patients who will benefit from implantation.

Currently one of the selection criteria for CRT and ICD implantation for primary prevention is an LVEF < 35%. However LVEF assessed by cardiovascular magnetic resonance imaging (CMR) is significantly lower compared with echocardiography. Therefore CMR would significantly increase the number of CHF patients eligible for CRT or ICD implantation. This illustrates that the method to assess LVEF has substantial impact on the selection of ‘appropriate’ patients for CRT and ICD implantation. The lack of uniformity among imaging modalities to assess LVEF raises the question if other parameters may be useful to better identify those patients who will benefit from CRT or ICD implantation. One of those alternative parameters might be cardiac sympathetic hyperactivity, which is related to poor prognosis and fatal arrhythmias in CHF.
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Figure 2. Schematic representation of the sympathetic synapse. Norepinephrine is synthesised within neurons by an enzymatic cascade. Dihydroxyphenylalanine (DOPA) is generated from tyrosine and subsequently converted to dopamine by DOPA decarboxylase. Dopamine is transported into storage vesicles by the energy-requiring vesicular monoamine transporter (VMAT). Norepinephrine is synthesised by dopamine β-hydroxylase within these vesicles. Neuronal stimulation leads to norepinephrine release through fusion of vesicles with the neuronal membrane (exocytosis). Apart from neuronal stimulation, release is also regulated by a number of presynaptic receptor systems, including α2-adrenergic receptors, which provide negative feedback for exocytosis. Most norepinephrine undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter (NET) and is re-stored in vesicles (following uptake by vesicular amine transporter 2 (VMAT2)) or is metabolised in cytosol dihydroxyphenylglycol (DHPG) by monoamine oxidase (MAO).
CARDIAC SYMPATHETIC ACTIVITY

Norepinephrine is the neurotransmitter of the cardiac sympathetic system and is stored in vesicles in the presynaptic nerve terminals (Figure 2). On the basis of tissue norepinephrine content, the heart is characterised by dense sympathetic innervation with a gradient from atria to base of the heart and from base to apex of the ventricles. Via exocytosis, norepinephrine is released into the synaptic cleft. Only a small amount of the released norepinephrine in the synaptic cleft is available to stimulate the post-synaptic \( \beta \)-adrenergic receptors (\( \beta \)-AR) on the myocytes. Most of the norepinephrine undergoes reuptake into the nerve terminals via the uptake-1 mechanism, member of the solute carrier family of transporter SLC6A2. This transport system, i.e. norepinephrine transporter (NET), is sodium and chloride dependent and responsible for approximately 70–90% of the norepinephrine re-uptake from the myocardial synaptic cleft.

The cardiac sympathetic system is one of the neurohormonal compensation mechanisms that plays an important role in the pathogenesis of CHF with impaired LVEF. Patients with CHF have increased cardiac sympathetic activity with increased exocytosis of norepinephrine from the presynaptic vesicles. In addition, the norepinephrine re-uptake via uptake-1 (NET) in the sympathetic terminal nerve axons is decreased resulting in elevated synaptic levels of norepinephrine. Eventually this results in increased plasma and urinary levels of norepinephrine concomitant with the severity of left ventricular dysfunction.\(^{15-17}\) Initially, \( \beta \)-AR stimulation by increased norepinephrine levels helps to compensate for impaired myocardial function, but long-term norepinephrine excess has detrimental effects on myocardial structure and gives rise to a downregulation and decrease in the sensitivity of post-synaptic \( \beta \)-AR.\(^{18,19}\) This downregulation leads to left ventricular remodelling and is associated with increased mortality and morbidity. Increased norepinephrine plasma levels are associated with poor prognosis in CHF.\(^{20}\) However, these levels do not specifically reflect the sympathetic activity at a cardiac level. In addition, these measurements are time consuming and there is a high variability in measurements. However, cardiac sympathetic activity can be non-invasively visualised by nuclear techniques. To date, most commonly used tracers are norepinephrine analogues (\(^{123}\)I-mIBG) for single photon emission tomography (SPECT) and \(^{11}\)C-hydroxyephedrine for positron emission tomography (PET). Both radiotracers are resistant to metabolic enzymes and show high affinity for presynaptic norepinephrine uptake-1 (NET) allowing the visualisation of presynaptic sympathetic nerve function. Other presynaptic PET tracers include \(^{11}\)C-epinephrine, \(^{11}\)C-phenylephrine, and \(^{18}\)F-LMI1195. \(^{11}\)C-CGP12177 is the most commonly used tracer for postsynaptic \( \beta \)-ARs.\(^{20-22}\) However, unlike \(^{123}\)I-mIBG, which can be centrally manufactured and then distributed, most PET agents are labelled with short half-life isotopes and are therefore only available in institutions with an on-site cyclotron. Although the early development of an \(^{18}\)F-labelled compound for sympathetic PET imaging is continuing\(^{20}\), for the foreseeable future \(^{123}\)I-mIBG scintigraphy will remain the only widely
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**Figure 3.** Example of placing a region-of-interest (ROI) over the heart (H) and fixed rectangular mediastinal ROI placed on the upper part of the mediastinum (M) for calculating H/M ratio.

**Figure 4.** Example of late $^{123}$I-mIBG SPECT imaging. On the left the conventional short, vertical and horizontal axis, in the middle the corresponding 17-segment model polar map and on the right a 3D reconstruction. There is impaired regional $^{123}$I-mIBG uptake in the inferior wall from the myocardial base until the apex with extension to both inferoseptal and inferolateral regions.
available nuclear imaging method for assessing global and regional myocardial sympathetic innervation. In addition, myocardial $^{123}$I-mIBG scintigraphy is easily implemented in any department of nuclear medicine and thereby readily available for CHF patients.

$^{123}$I-mIBG SCINTIGRAPHY

$^{123}$I-mIBG is a norepinephrine analogue that shares the same presynaptic uptake, storage and release mechanism as norepinephrine. Because $^{123}$I-mIBG is not metabolised, its accumulation over several hours is a measure of neuronal sympathetic integrity of the myocardium. Since the introduction of cardiac $^{123}$I-mIBG scintigraphy, parameters of $^{123}$I-mIBG myocardial uptake and washout have been shown to be of clinical value in many cardiac diseases, especially for the assessment of prognosis.$^{24-27}$

$^{123}$I-mIBG scintigraphy planar acquisition and analysis

To block uptake of free $^{123}$I by the thyroid gland, subjects are pretreated with 250 mg of oral potassium iodide 30 min before intravenous injection of 185 MBq $^{123}$I-mIBG. Fifteen minutes (early acquisition) and 4 hours (late acquisition) after administration of $^{123}$I-mIBG, 10-min planar images are acquired with the subjects in a supine position using a gamma camera equipped with a low energy high resolution or medium collimator. Based on the obtained planar (2D) images, three major outcomes of cardiac $^{123}$I-mIBG uptake can be determined: the early and late heart/mediastinal (H/M) ratio and cardiac washout rate (WO). The H/M ratio is calculated from planar $^{123}$I-mIBG images using a regions-of-interest (ROI) over the heart (Figure 3). Standardised background correction is derived from a fixed rectangular mediastinal ROI placed on the upper part of the mediastinum.$^{28}$ The location of the mediastinal ROI is determined in relation to the lung apex, the lower boundary of the upper mediastinum, and the midline between the lungs. The H/M ratio is calculated by dividing the mean count density in the cardiac ROI by the mean count density in the mediastinal ROI.$^{28}$ The $^{123}$I-mIBG WO can be calculated using early and late H/M ratio (A). There are variations to the WO calculation using the myocardial count densities only, requiring a time-decay correction (factor of 1.21), without (B) or with background correction (C):

\[
\text{(A) WO} = \left( \frac{\text{early H/M ratio} - \text{late H/M ratio}}{\text{early H/M ratio}} \right) \times 100
\]

\[
\text{(B) WO} = \left( \frac{\text{early H} - (\text{late H} \times 1.21)}{\text{early H}} \right) \times 100
\]

\[
\text{(C) WO} = \left( \frac{\text{early H} - \text{early M} \times \text{late H} - \text{late M} \times 1.21}{\text{early H} - \text{early M}} \right) \times 100
\]
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The early H/M ratio predominantly reflects the integrity of sympathetic nerve terminals (i.e. number of functioning nerve terminals and intact uptake-1 mechanism). The late H/M ratio particularly offers information about neuronal function resulting from uptake, storage and release. The $^{123}$I-mIBG WO reflects predominantly neuronal integrity of sympathetic tone/adrenergic drive.29

$^{123}$I-mIBG scintigraphy SPECT acquisition and analysis

Further, compared with the H/M ratio derived from two-dimensional planar images, the results of three-dimensional imaging using SPECT provide a more complete understanding of global dysinnervation.30,31 Preclinical and animal studies suggested that myocardial regions with damaged or dysfunctional neurons but preserved perfusion can be a source of arrhythmias. Therefore, volumetric data such as SPECT may be of added value. The specific SPECT acquisition parameters have been described elsewhere but are largely comparable with those used for myocardial perfusion SPECT imaging.28 Images can be processed and prepared for display and interpretation using the available commercial software packages (e.g. Emory Cardiac Toolbox and Cedar-Sinai Quantitative Perfusion SPECT). While there is no officially established method for scoring $^{123}$I-mIBG SPECT images, analysis can be performed similar to the conventional 17-segment/5-point model used for SPECT myocardial perfusion imaging (MPI) (Figure 4).32 Therefore the $^{123}$I-mIBG SPECT images can easily be compared with MPI SPECT images in order to investigate the difference between regional innervation and possible myocardial perfusion abnormalities.33-35

$^{123}$I-mIBG scintigraphy and prognosis in CHF

Cardiac sympathetic hyperactivity is reflected by a decreased $^{123}$I-mIBG late H/M ratio and increased WO. Both are associated with increased fatal arrhythmia and cardiac mortality.36-38 Initially $^{123}$I-mIBG scintigraphy assessed cardiac sympathetic activity in CHF has extensively been studied in small, single centre studies. However, the ADMIRE-HF study (ADreView Myocardial Imaging for Risk Evaluation in Heart Failure), a large multicentre, prospective study, reported that decreased late H/M ratio was associated with the composite endpoint of HF progression, ventricular tachyarrhythmia and death.27

AIM OF THIS THESIS

In this thesis several aspects of cardiac $^{123}$I-mIBG imaging and the prognostic value in CHF are discussed. Although a large number of studies on $^{123}$I-mIBG assessed cardiac sympathetic activity has published, methodological and analytical limitations have hampered wide scale clinical implementations of cardiac $^{123}$I-mIBG scintigraphy. Essential for large scale implementation of cardiac $^{123}$I-mIBG imaging is adequate
reproducibility, standardization and validation. The lack of standardisation of acquisition and post-acquisitions analysis have hampered comparison between different institutions. Moreover, most of these data are acquired from single centre experience and do not necessarily allow extrapolation of the obtained results to other institutions. **Part I** of this thesis focusses on the standardization and validation of planar cardiac $^{123}$I-mIBG scintigraphy and describes several factors that could influence the $^{123}$I-mIBG derived parameters. In **Part II** the prognostic value of cardiac $^{123}$I-mIBG imaging in patients with CHF is studied. Finally in **Part III** the use of cardiac $^{123}$I-mIBG scintigraphy in populations other than CHF is discussed.

**OUTLINE OF THIS THESIS**

In **Part I** of this thesis several aspects are studied related to standardization of image acquisition. High-energy photon emission of $^{123}$I leads to penetration of collimator septa and subsequently affects the accuracy of the H/M ratio. It is therefore apparent that differences in collimator, essential in nuclear medicine techniques, influence $^{123}$I-mIBG myocardial derived parameters. To correct for these differences in collimators a European cross-calibration study was performed. 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. Standardizing the post-acquisition processing of planar cardiac $^{123}$I-mIBG scintigraphy is also essential. Therefore the impact of differences in region of interest (ROI) placement (e.g. a fixed mediastinal ROI) on the accuracy were studied. In addition different patient factors such as polymorphism of the SLC6A2 gene encoding for the NE re-uptake, renal function and the relationship between changes in heart (H) and mediastinal (M) counts and the change in vascular $^{123}$I-mIBG activity were studied.

**Part II** evaluates the prognostic value of cardiac $^{123}$I-mIBG scintigraphy in CHF. First, a meta-analysis using individual patient data from 6 different published studies looked at the prognostic value of cardiac $^{123}$I-mIBG scintigraphy. Furthermore the relationship between cardiac sympathetic activity and inflammation in stable CHF and their prognostic value was evaluated. Finally, an European multicentre study was performed to study cardiac $^{123}$I-mIBG scintigraphy in stable CHF patients eligible for ICD implantation for primary prevention with the goal to optimize the current selection criteria for this specific indication.

**Part III** describes $^{123}$I-mIBG scintigraphy assessed cardiac sympathetic activity in patients with 22q11.2 deletion syndrome which affects the degradation of NE, the neurotransmitter of the cardiac sympathetic system. Furthermore we discussed the possible pathophysiology and the potential role of cardiac $^{123}$I-mIBG scintigraphy in Tako-tsubo cardiomyopathy.
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REFERENCES


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