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Chapter 1

General Introduction and Outline of the Thesis
Cardiovascular Disease

Although considerable improvements in diagnosis, therapeutic interventions and prog-
nostification of patients with cardiovascular disease have been made over the last several
decades, cardiovascular disease remains one of the foremost challenges of public health
these days.\textsuperscript{1-3}

Based upon National Health Surveys, the World Health Organization (WHO) has reported
that cardiovascular disease affects approximately 17.3 million individuals worldwide, with
an estimated 7.3 million people who are suffering from ischemic heart disease.\textsuperscript{3} The WHO
has stated that 4.6 million Europeans have been diagnosed with cardiovascular disease,
including 2.2 million individuals with ischemic heart disease across European countries.\textsuperscript{3}
Even though the age-adjusted incidence of cardiovascular disease may appear constant over
the last couple of years, its prevalence is expected to grow considerably in the upcoming
years as the population ages over time due to further improvements in early diagnosis,
treatment options along with advances in risk stratification of patients with cardiovascular
disease. Additionally, the world-wide under-recognition and under-treatment of individuals
with risk factors for atherosclerosis will lead to an even further increase in cardiovascular
disease, predominantly ischemic heart disease.\textsuperscript{2}

At present, cardiac imaging has contributed significantly to the currently applied
diagnostic, therapeutic and prognostic algorithms for patients with cardiovascular disease.
Among available cardiac imaging techniques, computed tomography (CT) has emerged as
one of most potent cardiac imaging techniques for non-invasive evaluation of coronary
atherosclerosis. However, despite the presence of highly advanced image acquisition tech-
niques for cardiac CT, the evaluation of coronary artery disease (CAD) is usually based on
a rather simple dichotomous visual approach. Based upon visual analysis of cardiac CT
images, coronary lesions with ≥50% luminal narrowing are usually defined as lesions with
significant coronary stenosis.

Accordingly, the use of automated quantitative algorithms for post-processing of cardiac
CT images may help to improve diagnosis of coronary atherosclerosis by cardiac CT (Part
I). A detailed assessment of coronary atherosclerosis on cardiac CT can be used to guide
patient referral for percutaneous coronary intervention or coronary artery bypass grafting
surgery.

Beyond advances in diagnosis of cardiovascular disease, cardiac imaging has also been
used to improve the selection of patients who will benefit from specific therapeutic inter-
ventions. Cardiac imaging has been applied to guide clinicians in the selection of heart
failure patients for cardiac resynchronization therapy (CRT). Even though several cardiac
imaging techniques are already available in clinical practice, the selection of heart failure
patients who will gain benefit from dedicated cardiac device therapies remains difficult.
Phase analysis on gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS) provides potential important information in patients with heart failure referred for CRT. Novel insights in GMPS with phase analysis may further improve the selection of heart failure patients who will benefit from CRT (Part II).

Finally, cardiac imaging can be used to risk stratify patients with cardiovascular disease for future adverse events. Although significant improvements in prognostification of patients with cardiovascular disease have been made in recent years, appropriate selection of patients at risk for adverse cardiac events remains a main challenge these days. Recent developments in sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine (123-I MIBG) imaging may be used to improve risk stratification of patients with cardiovascular disease (Part III).

**Dedicated Automated Quantitative Computed Tomography in Patients with Coronary Artery Disease (Part I)**

The presence of coronary artery disease can be detected by direct anatomic assessment of coronary atherosclerosis and luminal narrowing using cardiac CT, which has emerged as a potent non-invasive imaging technique since it provides excellent image quality and high diagnostic accuracy for visualization of CAD when compared to invasive coronary angiography.\(^4\)-\(^6\)

Although invasive coronary angiography is primarily restricted to luminography, cardiac CT offers the ability for a comprehensive evaluation of CAD by assessment of location, extent and severity as well as composition of atherosclerotic lesions, rather than the degree of coronary artery stenosis alone.\(^6\) A complete analysis of coronary atherosclerosis may provide important information to identify patients at risk for adverse cardiovascular events\(^7\), and importantly, may be used to guide future therapeutic interventions such as percutaneous coronary intervention or coronary artery bypass grafting surgery. Despite the rapid developments in CT acquisition technology, cardiac CT angiography images are most commonly post-processed and evaluated by an expert CT reader using a rather simple visual and dichotomous approach, in which \(\geq50\%\) luminal narrowing is usually defined as a significant coronary stenosis.

In this perspective, the introduction of new dedicated algorithms for automated quantification of coronary atherosclerosis (Figure 1) may further improve diagnostic accuracy of cardiac CT, and interestingly, may lead to a more time-efficient post-processing of cardiac CT images. Moreover, even though the number of cardiac CT scans with ambiguous or inconclusive results has become considerably smaller with the introduction of modern CT
scanners and image acquisition protocols, the use of dedicated post-processing techniques may result in a further decrease in the number of inconclusive or misinterpreted cardiac CT scans.

Additionally, one should acknowledge that cardiac CT is still hampered by reduced positive predictive values due to image artifacts along with a tendency to overestimate coronary stenosis in calcified lesions. Visual analysis of heavily calcified lesions can lead to (severe) overestimation of luminal narrowing due to blooming artifacts, which in turn, results in false-positive findings on invasive coronary angiography. Accordingly, the development of novel automated quantitative approaches for cardiac CT has gained increasingly interest over the recent years.

Current preliminary data for quantitative CT have been derived from semi-manual or manually-assisted cardiac CT approaches, rather than automated dedicated algorithms for quantification of coronary atherosclerosis. As compared to intravascular ultrasound (IVUS), these quantitative approaches were limited by substantial variability and large limits of agreement. The use of sophisticated automated post-processing algorithms for quantification of coronary atherosclerosis may lead to improved diagnostic accuracy and reproducibility of cardiac CT. Such quantitative information can be used to improve diagnosis of coronary atherosclerosis, and for this reason, may improve the patient referral

![Figure 1](image-url)

**Figure 1.** Schematic illustration of consecutive processing steps involved in automated quantification using dedicated quantitative post-processing software for cardiac computed tomography (CT).

for percutaneous coronary intervention or coronary artery bypass grafting surgery.
Myocardial Perfusion SPECT for Selection of Heart Failure Patients Referred for Cardiac Resynchronization Therapy (Part II)

Within the last 10 to 15 years, multiple randomized controlled trials have clearly demonstrated the benefits of biventricular pacing on morbidity and mortality rates in patients with moderate-to-severe heart failure who remain symptomatic despite optimal pharmacological treatment. Based on several landmark trials, international guidelines have recommended CRT with a class I indication in patients with symptomatic drug-refractory systolic heart failure. New York Heart Association (NYHA) functional class III and IV, ventricular dyssynchrony (prolonged QRS duration ≥120 ms), reduced LV ejection fraction (LVEF) ≤35% and sinus rhythm.

Although considerable improvements in heart failure symptoms, exercise capacity, mitral regurgitation and LV dimensions have been observed in heart failure patients receiving CRT, a consistent proportion of patients who meet the current selection criteria for CRT fail to respond to CRT. As a consequence, numerous clinical studies have been conducted that were designed to improve current selection of patients referred to CRT by identification of potential determinants for response to CRT. Among the multiple pathophysiologic mechanisms involved in heart failure, the presence of LV systolic dyssynchrony has been identified as one of the major determinants of CRT response. It has been shown that LV systolic dyssynchrony can affect biomechanics and performance of the LV considerably.

At present, many cardiac imaging techniques have been applied in clinical practice to assess the presence and extent of LV systolic dyssynchrony in heart failure patients, wherein echocardiographic techniques such as 2D echocardiography with tissue Doppler imaging (TDI) have been used most widely for detection of LV systolic dyssynchrony. At present however, no consensus exists on the echocardiographic definition of LV systolic dyssynchrony, an issue which can be addressed by nuclear imaging techniques since phase analysis on GMPS allows assessment of mechanical dyssynchrony using an automated and reproducible post-processing algorithm.

Moreover, non-synchrony issues such as location, extent and severity of scar tissue have been identified as (important) determinants affecting the likelihood of response to CRT. Additionally, the relation between LV lead position and site of latest mechanical activation has been shown to play an important role in prediction of CRT response. Accordingly, SPECT may be of interest, since it provides information on cardiac dyssynchrony (by phase analysis of gated SPECT data) along with assessment of presence, location and extent of scar tissue.
As indicated in Figure 2, phase analysis is performed on standard GMPS short-axis images and involves several processing steps. A histogram is generated that provides information on LV systolic (dys)synchrony for the entire ventricle. A total of 5 quantitative parameters for LV systolic dyssynchrony can be derived from the phase histogram, including histogram bandwidth (HBW), phase standard deviation (SD), histogram kurtosis, skewness and peakedness. HBW (including 95% of the phase angles) and phase SD (SD of the phase distribution) have been validated against echocardiographic techniques for assessment of LV systolic dyssynchrony.\textsuperscript{36, 37} Along with LV systolic dyssynchrony, phase analysis can be used for assessment of LV diastolic dyssynchrony by detection of changes in myocardial counts during the diastolic phase of the LV. Additionally, phase analysis on GMPS can be used to

![Figure 2: Phase analysis on gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS) allows integrated assessment of left ventricular (LV) systolic dyssynchrony, myocardial infarction and site of latest mechanical activation. Phase analysis is performed on standard GMPS reconstructed short-axis images and involves several processing steps: (1) detection of maximal counts in 3D for each temporal frame, (2) count-based wall-thickening curves are created from regional count changes during the R-R cycle, (3) approximation of separate sample points into a continuous curve using first Fourier Harmonic function (middle, left panel). As indicated below, the phase polar map (bottom, left panel) shows a considerable phase delay (bright region) at the anterior and apical segments of the LV. Subsequently, the phase histogram (bottom, mid panel) shows the degree of systolic dyssynchrony or synchrony for the entire LV, in which histogram bandwidth (HBW) and phase standard deviation (SD) are the most commonly used indicators of LV (dys) synchrony.](image-url)
identify the site of latest mechanical activation (and whether this region is viable) which may help in selecting the optimal LV lead position. Thus, GMPS with phase analysis is a potent cardiac imaging technique that provides important information in patients with heart failure referred for CRT. In part II, the role of phase analysis on GMPS for selection of heart failure patients for CRT will be addressed.

**Cardiac Sympathetic Nerve Scintigraphy with 123-I Metaiodobenzylguanidine for Risk Stratification of Patients with Cardiovascular Disease (Part III)**

Among patients with cardiovascular disease, the clinical syndrome of heart failure is a common pathophysiologic disorder, with an estimated prevalence of approximately 5.3 million individuals in the United States. The risk for newly diagnosed heart failure is considerably high in the western population, with a life-time risk of 1 out of 5 in patients aged 40 years. Importantly, heart failure patients are suffering from a serious pathophysiologic condition as 20% of patients will die within the first year after the beginning of heart failure. Moreover, heart failure patients also exhibit a considerably high long-term mortality rate, with an estimated 5-year mortality rate of 59% in men and 45% in women.

Even though considerable advances in risk stratification of patients with heart failure have been made in recent years, identification of heart failure patients who will suffer from serious adverse events remains a difficult issue.

The cardiac sympathetic nervous system may serve as an important determinant for risk stratification in heart failure as it is directly involved in preservation of cardiovascular homeostasis by regulation of heart frequency, electrical conduction and cardiac contractility. A chronic dysfunctional cardiac sympathetic nervous system exerts pleiotropic detrimental effects on the structural and functional integrity of the myocardium, including stimulation of cardiomyocyte hypertrophy, fibroblast and smooth muscle cell proliferation, which altogether contribute to a worse cardiovascular outcome. As a consequence, the cardiac sympathetic nervous system can be used for risk stratification of patients with cardiovascular disease, most commonly in the setting of chronic heart failure.

Although plasma norepinephrine levels and the rate of norepinephrine spillover can be used as determinants for identification of patients at risk for adverse cardiovascular outcome, a direct assessment of cardiac sympathetic innervation by nuclear imaging may represent a more sensitive marker for risk stratification of patients with heart failure.
Among nuclear imaging techniques, SPECT can be used for mapping the cardiac sympathetic nervous system as it provides enough sensitivity to assess distinct aspects of the cardiac neurotransmission itself, including norepinephrine uptake at the presynaptic site (sympathetic innervation) as well as binding of norepinephrine at the post-synaptic site.\textsuperscript{46-48} Moreover, the rate in which radionuclide SPECT tracers are washed out of the myocardium provides information on the degree of sympathetic activity within the heart.

The norepinephrine analogue metaiodobenzylguanidine labeled to iodine-123 (123-I MIBG) has been used most commonly as a SPECT radionuclide tracer for assessment of cardiac sympathetic innervation (Figure 3).\textsuperscript{44, 45} Thus far, a large number of studies have demonstrated the predictive value of cardiac 123-I MIBG imaging in patients with heart failure.\textsuperscript{44, 45, 49} Agostini et al.\textsuperscript{50} evaluated whether 123-I MIBG scintigraphy allowed risk stratification of 290 heart failure patients. Patients with adverse events (n=67) showed significantly lower cardiac 123-I MIBG uptake on late planar imaging (as expressed as the heart-to-mediastinum (H/M) ratio) when compared to patient without adverse events (n=223) (p<0.001). Moreover, both H/M ratio (on late planar 123-I MIBG scintigraphy) and LVEF were significant predictors for adverse cardiac events. More recently, the prospective multicenter AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study has evaluated the predictive value of cardiac neuronal status as derived from cardiac 123-I MIBG scintigraphy in 961 patients with NYHA functional class II or III. Heart failure patients with a late H/M ratio of <1.60 experienced significantly more adverse events than heart failure patients with a late H/M ratio of \textgeq1.60 (p<0.001).\textsuperscript{45}

**Figure 3.** 123-iodine metaiodobenzylguanidine (123-I MIBG) for assessment of cardiac sympathetic innervation using planar imaging (panel A) and single photon emission computed tomography (SPECT) (panel B). Planar imaging is used for assessment of global sympathetic innervation patterns by calculation of the heart-to-mediastinum (H/M) ratio, in which the mean counts per pixel within the heart (H) is divided by the mean counts per pixel within the upper mediastinum (M). Regional defects in sympathetic innervation of the myocardium can be assessed using SPECT, as depicted in panel B.
Beyond prediction of cardiac death or worsening heart failure, some studies have also postulated the use of cardiac 123-I MIBG scintigraphy for identification of patients at risk for adverse arrhythmogenic events, including lethal ventricular arrhythmias and sudden cardiac death.\textsuperscript{44, 45} It has been shown that parasympathetic stimulation of the ventricles exerts anti-fibrillatory effects on the myocardium, while ventricular sympathetic activation emerged to have a pro-arrhythmogenic effect on the myocardium.\textsuperscript{51} Moreover, activation of the cardiac sympathetic nervous system contributes to cardiac arrhythmogenesis as regions with abnormalities in cardiac sympathetic innervation may show a denervation supersensitivity response to circulating catecholamines with an enhanced automaticity of cardiomyocytes and a reduction of ventricular effective refraction period.\textsuperscript{51-53} Finally, co-existence of sympathetic denervated regions alongside regions with preserved sympathetic innervation may lead to inhomogeneous neuronal release of neurotransmitter norepinephrine, which subsequently, can cause considerable changes in action potential duration and configuration with associated electrophysiologic heterogeneity of the myocardium.\textsuperscript{51-53}

Accordingly, cardiac 123-I MIBG scintigraphy may provide important information to risk stratify patients with cardiovascular disease by assessment of cardiac sympathetic innervation and activation.

More specifically, cardiac 123-I MIBG scintigraphy may serve as a potent imaging technique for identification of patients at risk for future ventricular arrhythmia or sudden cardiac death, which potentially, could help to improve the current selection of patients indicated for implantable cardioverter-defibrillator (ICD) treatment (Part III).

**Objective and Outline of the Thesis**

Although cardiac imaging has already contributed significantly in the evaluation of patients with cardiovascular disease, novel insights into cardiac imaging techniques may further improve diagnostic and therapeutic algorithms as well as prognostification of patients with cardiovascular disease. More specifically, the current thesis describes the role of novel insights into cardiac imaging for diagnosis (Part I), treatment (Part II) and risk stratification (Part III) of patients with cardiovascular disease.

In **part I**, the value of automated quantitative CT for evaluation of coronary atherosclerosis is described. Chapter 2 provides an overview of the currently available approaches for quantification of coronary atherosclerosis. Additionally, chapter 2 describes the potential role of quantitative CT to guide percutaneous coronary intervention procedures. In chapter 3, the validation of a dedicated CT algorithm for automated quantification of coronary stenosis severity is discussed. Chapter 4 shows the feasibility of automated coronary plaque quantification using dedicated CT software in comparison with IVUS. At last, the feasibility of cardiac CT to assess diastolic function is described in chapter 5.
In part II, the potentials of nuclear imaging with GMPS in heart failure patients referred for CRT are described. Chapter 6 reviews the role of phase analysis on GMPS for assessment of LV systolic dyssynchrony, myocardial infarction and viability. Chapter 7 describes the validation of a dedicated algorithm for phase analysis on GMPS in a direct comparison with echocardiography using TDI for assessment of LV systolic dyssynchrony. Chapter 8 evaluates the relation between the site of latest mechanical activation as derived from GMPS, LV lead position and response to CRT. In chapter 9, the feasibility of GMPS with phase analysis to assess LV diastolic dyssynchrony in a direct comparison with TDI is evaluated. Finally, chapter 10 evaluates the prediction of response to CRT by LV diastolic dyssynchrony as assessed from GMPS with phase analysis.

In part III, the role of cardiac sympathetic nerve imaging with 123-I MIBG for risk stratification of patients with cardiovascular disease is described. Chapter 11 describes the value of cardiac 123-I MIBG scintigraphy for prognostication of patients with heart failure. The potentials of cardiac 123-I MIBG imaging for identification of patients at risk for ventricular arrhythmias are described in chapter 12. In chapter 13, the relation between contrast-enhanced magnetic resonance imaging (MRI) and 123-I MIBG/perfusion scintigraphy for assessment of infarct size and infarct border zone, referred to as myocardium at risk for ventricular arrhythmias, is evaluated.
Reference List


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