Magnetic resonance imaging techniques for risk stratification in cardiovascular disease

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Chapter 1

General introduction and outline

Cardiovascular disease remains a major burden in the Western world accounting for nearly 30% of all deaths in The Netherlands (1). The growing epidemic of obesity further increases the prevalence of cardiovascular disease. In the Netherlands, 53% of the men and 41% of the women older than 20 years were overweight (body mass index ≥ 25 kg/m^2) in 2009 (2). This growing prevalence of obesity is associated with an increase in type 2 diabetes and the metabolic syndrome, a clustering of cardiovascular risk factors including abnormalities in glucose and lipid metabolism, hypertension and abdominal obesity (3,4). The metabolic syndrome and type 2 diabetes are both associated with an elevated risk of cardiovascular morbidity and mortality (5,6).

In order to reduce this morbidity and mortality, identification of subjects at risk of cardiovascular disease, and identification of patients with cardiovascular disease who are at risk of complications is highly desirable. Furthermore, optimization of treatment of patients with for instance a previous myocardial infarction (ischemic cardiomyopathy) can reduce hospitalization and may improve prognosis (7).

During the last decades, magnetic resonance imaging (MRI) has emerged as a reliable, accurate, noninvasive imaging modality providing information on anatomy and function of the heart and vessels without the need for ionizing radiation (8). Multiple technical innovations have improved image quality dramatically (8). In the early days of MRI, imaging relied on magnets with field strengths of 0.35 Tesla (T) and 0.5T, while cardiac MRI is currently performed on MRI systems equipped with 1.5T magnets and more recently introduced 3T magnets. MRI systems with higher field strengths enable imaging with increased signal-to-noise ratio, allowing for improved spatial resolution, improved temporal resolution, or reduced scanning times. Furthermore, image blurring due to cardiac contraction has been minimized by synchronization of data acquisition with the cardiac cycle using electrocardiographic gating or triggering (8,9). In addition, the development of respiratory navigator technology enables imaging during free-breathing while reducing the adverse effect of respiratory motion on image quality (10,11).

Accordingly, MRI is now routinely applied and enables evaluation of various manifestations of cardiovascular disease at all anatomical levels, from subclinical atherosclerosis of the aortic vessel wall to overt myocardial infarction. This thesis evaluates MRI techniques for imaging of the aorta, the heart and coronary arteries, that are optimized and can be applied for risk stratification in cardiovascular disease, as is summarized in the following paragraphs.

First, morphology and function of the aortic vessel wall can be accurately assessed using MRI. Atherosclerosis is regarded as a chronic systemic disease of the vessel wall that occurs in the peripheral arteries, the coronary arteries, and the aorta (12). Autopsy studies and in vivo studies report a strong association between thoracic aortic atherosclerosis and coronary artery disease (CAD) (13,14). Consequently, imaging of (subclinical) aortic atherosclerosis (by measuring aortic vessel wall thickness) may provide valuable information on cardiovascular risk (15). Also, aortic stiffness, expressed as pulse wave velocity, is associated with an increased risk of cardiovascular events (16,17). Accordingly, the capability of MRI to measure aortic vessel wall thickness and aortic pulse wave velocity enables cardiovascular risk stratification.

Furthermore, over the past 15 years, substantial progress has been made in noninvasive assessment of the anatomy (coronary stenosis) and function (coronary flow and flow reserve) of the coronary arteries using magnetic resonance angiography (MRA) and velocity encoded MRI (18). These techniques remain challenging due to the small vessel size and cardiac and respiratory motion, and are not yet routinely applicable clinical tools. However, ongoing research and technical innovations in software and hardware may in the future make MRI of the coronary arteries valuable for diagnosis of significant CAD.

Valvular regurgitation is frequently seen in clinical practice and can be due to primary abnormalities of the valvular apparatus or secondary to ischemic or non-ischemic dilated cardiomyopathy (19-23). Volume overload due to valvular regurgitation may cause (or aggravate) ventricular remodeling, which can lead to heart failure and ultimately death (19,24). Surgical repair or replacement of the regurgitant valve may reduce heart failure symptoms and improve survival (24,25). MRI enables accurate quantification of valvular regurgitation and is therefore important for identification of patients with valvular regurgitation, optimization of treatment and timing of surgical intervention (19,25).

Contrast-enhanced MRI permits accurate delineation of scar tissue in patients with previous myocardial infarction enabling distinction between non-transmural and transmural scar tissue and can therefore be used for viability assessment (26-28). Low-dose dobutamine MRI also allows for detection of viable myocardial tissue by evaluation of contractile reserve (29,30). Assessment of viability is essential for optimization of treatment in patients with ischemic left ventricular (LV) dysfunction, since dysfunctional but viable myocardium is likely to improve after revascularization, whereas dysfunctional but nonviable myocardium will not benefit (31). Furthermore, patients with viable myocardium have improved survival after revascularization compared to medical treatment (7).

Currently, LV ejection fraction and LV volumes are the established predictors of mortality in patients with ischemic cardiomyopathy. However, several studies have now been published stressing the prognostic value of the extent of scar tissue assessed with contrast-enhanced MRI in patients with ischemic cardiomyopathy (32,33). In addition, recent studies showed that infarct tissue heterogeneity (i.e., spatially complex structures containing a mixture of viable and necrotic tissue) is a predictor of ventricular arrhythmias, which is an important complication in patients with ischemic cardiomyopathy (34,35). Accordingly, contrast-enhanced MRI is a valuable tool for identification of patients who are at risk of complications after myocardial infarction, for optimization of treatment and for assessment of prognosis.

This thesis describes and evaluates various MRI techniques that can be applied for risk stratification in cardiovascular disease.

Chapter 2 describes an optimized free-breathing three-dimensional dual inversion recovery segmented k-space gradient echo imaging sequence at 3T for the quantification of aortic vessel wall dimensions and its reproducibility is evaluated. In **chapter 3**, the effect of a real-time adaptive trigger delay on image quality to correct for heart rate variability in three-dimensional whole-heart coronary MRA is tested. **Chapter 4** studies the accuracy and reproducibility of flow velocity and volume measurements in a phantom and in human coronary arteries using breath-hold velocity-encoded MRI with spiral k-space sampling at 3T. **Chapter 5** validates flow assessment at the mitral valve and tricuspid valve using three-dimensional three-directional velocity-encoded MRI with retrospective valve tracking, which is compared to conventional two-dimensional one-directional velocity encoded MRI in healthy subjects and in patients with regurgitation. **Chapter 6** describes the application of three-dimensional three-directional velocity-encoded MRI with retrospective valve tracking as introduced in chapter 5, in order to measure forward and regurgitant flow through all four heart valves simultaneously. In **chapter 7**, the influence of lipid and glucose metabolism in the metabolic syndrome on aortic pulse wave velocity and left ventricular diastolic function is evaluated. **Chapter 8** studies the effect of lifestyle intervention in conjunction with rosiglitazone versus placebo therapy on LV mass in subjects with the metabolic syndrome. **Chapter 9** compares contrast-enhanced MRI and nuclear imaging with ^{99m}Tc-tetrofosmin and ^{18}F- fluorodeoxyglucose single photon emission computed tomography (SPECT) for assessment of myocardial viability. **Chapter 10** compares longitudinal strain assessed by two-dimensional speckle tracking assessed with echocardiography with scar tissue on contrast-enhanced MRI in patients with ischemic cardiomyopathy. **Chapter 11** studies the predictive value of infarct tissue heterogeneity assessed with contrast-enhanced MRI on the occurrence of spontaneous ventricular arrhythmia with subsequent implantable cardioverter-defibrillator therapy (as surrogate of sudden cardiac death) in patients with previous myocardial infarction. **Chapter 12** evaluates the prognostic value of infarct size assessed with contrast-enhanced MRI relative to LV ejection fraction and LV volumes for long-term survival in patients with healed myocardial infarction. **Chapter 13** assesses the predictive value of myocardial infarct size assessed with contrast-enhanced MRI in medically treated patients with chronic myocardial infarction relative to contractile reserve (hibernation) on low-dose dobutamine MRI for long-term event-free survival.

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