Magnetic resonance imaging techniques for risk stratification in cardiovascular disease

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Chapter 14

Summary and conclusions

Samenvatting en conclusies

List of publications

Dankwoord

Curriculum vitae

Summary and conclusions

The aim of this thesis was to evaluate and optimize MRI techniques that can be applied for risk stratification in cardiovascular disease.

Chapter 1 provides general background information about cardiovascular disease and briefly describes the rapid progress made in MRI during the last decades and its potential for cardiovascular risk stratification.

Chapter 2 evaluates a free-breathing three-dimensional (3D) dual inversion recovery (DIR) segmented k-space gradient echo imaging sequence at 3T for the quantification of aortic vessel wall dimensions. The effect of respiratory motion suppression on image quality was tested in 7 healthy volunteers. Furthermore, the reproducibility of the aortic vessel wall measurements was investigated in 10 healthy volunteers. Signal-to-noise (SNR), contrast-to-noise ratio (CNR), and vessel wall sharpness were superior in scans performed with respiratory navigator compared to scans performed without. The intraclass correlations concerning intraobserver, interobserver, and interscan reproducibility of measurements of vessel wall volume were excellent (0.99, 0.94, and 0.95 respectively). In conclusion, respiratory motion suppression substantially improves image quality of 3D DIR segmented k-space gradient echo imaging of the aortic vessel wall at 3T. Furthermore, this optimized technique enables assessment of aortic vessel wall dimensions with high reproducibility.

Chapter 3 describes the effect of a real-time adaptive trigger delay on image quality to correct for heart rate variability in 3D whole-heart coronary magnetic resonance angiography (MRA). Twelve healthy adults underwent 3D whole-heart coronary MRA with and without the use of an adaptive trigger delay. Throughout the scan performed without adaptive trigger delay, trigger delay was kept constant, whereas during the scan performed with adaptive trigger delay, trigger delay was continuously updated after each RR-interval using physiological modelling. With the use of the adaptive trigger delay, vessel sharpness improved significantly for the middle segment of the right coronary artery (RCA) and subjective image quality was significantly better in the middle segments of RCA and left anterior descending artery (LAD). Accordingly, the use of an adaptive trigger delay to correct for heart rate variability improves image quality mainly in the middle segments of RCA and LAD.

Chapter 4 evaluates accuracy and reproducibility of flow velocity and volume measurements in a phantom and in human right coronary arteries using breath-hold velocity-encoded (VE) MRI with spiral k-space sampling at 3T. In vitro, MRI-measured flow rates correlated strongly with volumetric collection ($r = 0.99$, $p < 0.01$). Due to

limited sample resolution, VE MRI overestimated the flow rate by 47% on average when non-constricted region-of-interest segmentation was used. Using constricted region-of-interest segmentation with lumen size equal to ground-truth luminal size, less than 13% error in flow rate was found. In vivo RCA flow velocity assessment was successful in 82% of the applied studies. High interscan, intraobserver and interobserver agreement was found for almost all indices describing coronary flow velocity. In conclusion, 3T breath-hold VE MRI with spiral k-space sampling enables accurate and reproducible assessment of RCA flow velocity.

Chapter 5 validates flow assessment performed with 3D three-directional VE MRI with retrospective valve tracking and compares this modality with conventional two-dimensional (2D) one-directional VE MRI in healthy subjects and in patients with regurgitation. First, the 3D three-directional VE MRI sequence was validated in vitro and compared with 2D one-directional VE MRI, showing less than 5% error for both techniques. Mitral valve (MV) and tricuspid valve (TV) flow was assessed in 10 volunteers without valve insufficiency and in 20 patients with valve insufficiency, with aortic systolic stroke volume (ASSV) as the reference standard. In volunteers, 3D three-directional VE MRI showed no bias for MV or TV flow when compared with ASSV, whereas 2D one-directional VE MRI showed considerable bias for MV flow (15% overestimation, $p < 0.01$) and TV flow (25%, p = ns). Correlation between ASSV and MV flow and TV flow was strong for 3D three-directional VE MRI ($r = 0.96$, $p < 0.01$ for MV flow, $r = 0.88$, $p < 0.01$ for TV flow), and between MV flow and TV flow ($r = 0.91$, $p < 0.01$). However, weaker correlations were observed for 2D one-directional VE MRI ($r = 0.80$, $p < 0.01$ for MV flow, $r = 0.22$, $p = 0.55$ for TV flow, and $r = 0.34$, $p = 0.34$ between MV flow and TV flow). In patients with valve regurgitation, correlation between MV flow and TV flow for 3D three-directional VE MRI was strong ($r = 0.97$, $p < 0.01$). Accordingly, 3D three-directional VE MRI enables accurate MV flow and TV flow quantification in healthy volunteers and in patients with valve regurgitation.

Chapter 6 evaluates 3D three-directional velocity-encoded MRI with retrospective valve tracking, introduced and validated in chapter 5, for flow assessment through all four heart valves simultaneously, in 22 healthy volunteers and 29 patients with valve regurgitation. Furthermore, the off-line analysis was repeated for each valve in 10 healthy volunteers and in 10 regurgitant valves to assess intraobserver and interobserver agreement for assessment of net flow volumes and regurgitation fraction. In healthy volunteers, strong correlations between net flow volumes through the four heart valves were observed (intraclass correlation coefficient (ICC) 0.93 to 0.95) and the coefficient of variance (CV) was small (6-9%), with excellent intraobserver and interobserver agreement (ICC 0.93 to 0.99 and CV 3-7%). Strong correlations between the net flow volumes through the four heart valves were also observed in the patients with valve regurgitation (ICC 0.85-

0.95 and CV 7-18%). Furthermore, the intraobserver and interobserver agreement for assessment of regurgitation fraction was good (ICC 0.86 and 0.85, CV 12% and 13%). Thus, flow assessment using 3D three-directional VE MR with retrospective valve tracking during off-line analysis enables accurate quantification of net flow volumes through four heart valves within a single acquisition in healthy volunteers and in patients with valve regurgitation.

Chapter 7 studies the influence of lipid and glucose metabolism in the metabolic syndrome on aortic pulse wave velocity (PWV) and left ventricular (LV) diastolic function using MRI. Aortic PWV and LV diastolic function were assessed in 16 subjects with the metabolic syndrome and 16 subjects without the metabolic syndrome matched for age, waist circumference, and blood pressure. Aortic PWV was increased and LV diastolic function was decreased in subjects with the metabolic syndrome compared to those without the metabolic syndrome. HDL cholesterol was independently associated with aortic PWV ($r = -0.470$, $p < 0.01$) and LV diastolic function ($r = -0.421$, $p = 0.02$). Accordingly, increased aortic PWV and decreased LV diastolic function is observed in subjects with the metabolic syndrome, regardless of blood pressure. Moreover, HDL cholesterol is independently associated with aortic PWV and LV diastolic function.

Chapter 8 evaluates the effect of lifestyle intervention in conjunction with rosiglitazone or placebo therapy on LV mass, using MRI in subjects with the metabolic syndrome. Twenty subjects with the metabolic syndrome underwent intensive lifestyle intervention including a diet and physical exercise during 52 weeks. During this year, 10 subjects were treated with rosiglitazone therapy and 10 patients were treated with placebo therapy (double blind randomization). At baseline and follow-up (52 weeks), clinical and laboratory measurements were assessed and an MRI examination was performed to evaluate LV mass indexed for body surface area (LV mass-I). Subsequently, the effect of therapy (rosiglitazone versus placebo) and clinical and laboratory variables on LV mass-I was evaluated. In both groups, body mass index, waist circumference, systolic and diastolic blood pressure significantly decreased during follow-up. Interestingly, LV mass-I significantly decreased in the placebo group (48.9 ± 5.3 g/m^2 vs. 44.3 ± 5.6 g/m^2, $p < 0.001$) indicating reverse remodeling, whereas LV mass-I remained unchanged in the rosiglitazone group (54.7 ± 9.9 g/m^2 vs. 53.7 ± 9.2 g/m^2, $p = 0.3$). After correction for systolic and diastolic blood pressure and triglyceride, the kind of therapy (rosiglitazone vs. placebo) remained the only significant predictor of LV mass reduction. Accordingly, lifestyle intervention resulted in a reduction of LV mass-I in the metabolic syndrome, indicating reverse remodeling. However, rosiglitazone therapy inhibited this positive reverse remodeling.

Chapter 9 compares contrast-enhanced MRI and nuclear imaging with ^{99m}Technetium-tetrofosmin and ^{18}F- fluorodeoxyglucose (^{18}F-FDG) single photon emission computed tomography (SPECT) for assessment of myocardial viability in 60 patients with severe ischemic LV dysfunction. The results showed high agreement (91%) for viability assessment between contrast-enhanced MRI and nuclear imaging in segments without scar tissue on contrast-enhanced MRI as well as in segment with transmural scar tissue (83%). However, evident disagreement was observed in segments with subendocardial scar tissue on contrast-enhanced MRI, illustrating that the non-enhanced epicardial rim can contain either normal or ischemically jeopardized myocardium.

Chapter 10 compares longitudinal strain assessed by 2D speckle tracking using echocardiography with scar tissue on contrast-enhanced MRI in 90 patients with chronic ischemic LV dysfunction. Also, the aim was to define a cut-off value for regional strain to discriminate between viable myocardium and transmural scar tissue (non-viable myocardium). A good correlation existed between global LV strain and global extent of scar tissue on contrast-enhanced MRI ($r = 0.62$, $p < 0.001$). Mean segmental strain in segments without scar tissue was -10.4 ± 5.2%, as compared to 0.6 ± 4.9% in segments with transmural scar tissue ($p < 0.001$). A strain value of -4.5% discriminated between segments with viable myocardium and segments with transmural scar tissue on contrast-enhanced MRI with a sensitivity of 81.2% and a specificity of 81.6%. In conclusion, global and regional longitudinal strain measured with 2D speckle tracking is associated with global and regional (transmural) extent of scar tissue on contrast-enhanced MRI. A cut-off value of -4.5% for regional strain discriminated between segments with viable myocardium and those with transmural scar tissue on contrast-enhanced MRI with good sensitivity (81.2%) and specificity (81.6%).

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 (ICD) therapy (as surrogate of sudden cardiac death). Ninety-one patients with previous myocardial infarction, who were scheduled for ICD implantation, were included. LV function and volumes were assessed using cine MRI and contrast-enhanced MRI was performed for characterization of scar tissue (infarct gray zone as measure of infarct tissue heterogeneity, infarct core and total infarct size). Appropriate ICD therapy was documented in 18 patients (20%) during a median follow-up of 8.5 months (interquartile range 2.1-20.3). Multivariable Cox proportional hazards analysis revealed that infarct heterogeneity (infarct gray zone) was the strongest predictor of the occurrence of spontaneous ventricular arrhythmia with subsequent ICD therapy (hazard ratio 1.49/10g, 95% confidence interval 1.01-2.20, chi-square 4.0, $p = 0.04$) among other clinical and MRI variables, that is, total infarct size, LV function and volumes.

Chapter 12 evaluates the predictive value of infarct size assessed with contrast-enhanced MRI relative to LV ejection fraction and LV volumes for long-term survival in 231 patients with healed myocardial infarction. Nineteen patients (8.2%) died during a median follow-up of 1.7 years (interquartile range 1.1–2.9 years). Cox proportional hazards analysis revealed that infarct size defined as spatial extent (hazard ratio 1.3, 95% confidence interval 1.1–1.6, chi-square 6.7, $p = 0.010$), transmurality (hazard ratio 1.5, 95% confidence interval 1.1–1.9, chi-square 8.9, $p = 0.003$) and total scar score (hazard ratio 6.2, 95% confidence interval 1.7–23, chi-square 7.4, $p = 0.006$), were stronger predictors of all-cause mortality than LVEF and LV volumes. In conclusion, infarct size on contrast-enhanced MRI may be superior over LVEF and LV volumes for predicting long-term mortality in patients with healed myocardial infarction.

Chapter 13 assesses the predictive value of myocardial infarct size on contrast-enhanced MRI in 177 medically treated patients with chronic myocardial infarction relative to contractile reserve (hibernation) on low-dose dobutamine magnetic resonance (DSMR) for long-term event-free survival. Eleven patients (6.2%) suffered an event during follow-up (20.3 months). Cox proportional hazard analysis revealed that the spatial extent of scar tissue was a stronger predictor of events than LV ejection fraction and LV volumes at rest and during low-dose dobutamine stimulation. The spatial extent of scar tissue on contrast-enhanced MRI was used to separate patients at high risk from those at low risk of events. In the subgroup of 98 patients with ≥ 6 segments with scar tissue, transmurality of infarct was not a predictor of events. However, the presence of contractile reserve was associated with a significantly higher number of events (12.7%) compared to no contractile reserve (6.7%, $p = 0.008$). Accordingly, myocardial infarct size on contrast-enhanced MRI is a stronger predictor of clinical outcome than contractile reserve in medically treated patients with chronic myocardial infarction. In patients with large myocardial scar however, the presence of contractile reserve (hibernation) is more important for the prediction of clinical outcome than infarct size (on contrast-enhanced MRI).

Conclusions

Cardiovascular disease is an important health problem in the western world responsible for high morbidity and mortality rates. Identification of individuals at risk of cardiovascular disease and identification of patients with cardiovascular disease who are at risk of complications is important in order to reduce this morbidity and mortality. The studies described in this thesis show the potential of MRI for risk stratification in cardiovascular disease. MRI enables assessment of morphology and function of the aortic vessel wall, which is important since the thickness and stiffness of the aortic vessel wall are related with coronary artery disease and the occurrence of cardiovascular events. Furthermore, the potential of MRI for visualization of the coronary arteries and assessment of coronary artery flow is explored. This technique is still in a developmental phase, and is not yet routinely used in clinical practice. However, ongoing research and technical innovations may in the future make MRI a valuable technique for detection of coronary artery disease. Valve regurgitation is a common problem in patients with cardiovascular disease, which can result in heart failure or even death. In this thesis is demonstrated that MRI is an excellent technique for detection of valve regurgitation and for quantification of its severity. Furthermore, it is described how MRI can be used for detection of altered cardiac and aortic function in individuals with the metabolic syndrome who are at higher risk of developing cardiovascular disease. In addition, MRI allows for accurate assessment of scar tissue and contractile reserve in patients with ischemic cardiomyopathy enabling assessment of viability, which is important for optimization of treatment and determination of prognosis. Finally, it is demonstrated that infarct size and infarct tissue heterogeneity measured with MRI are important predictors for long-term survival in patients with ischemic cardiomyopathy.