Clinical advances in cardiovascular magnetic resonace imaging and angiography

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Chapter 9

Summary and conclusions

Samenvatting en conclusies

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The aim of this thesis was to evaluate new magnetic resonance imaging (MRI) techniques in cardiovascular radiology in clinical practice and to explore the prognostic value of new cardiovascular magnetic resonance (CMR) imaging biomarkers in patients with peripheral arterial occlusive disease.

The first part of the thesis focusses on cardiac MRI. **Chapter 1** provides a general background and introduction of the current role of MRI in cardiovascular disease in daily clinical practice.
In **chapter 2** the acquisition planning of the specific cardiac MR imaging planes is described and the normal cardiac anatomy assessed with CMR is addressed. Additionally, aspects and new developments of cardiac imaging on (ultra-) high-field MRI are discussed.
Chapter 3 describes the validation of a new free-breathing 2D delayed-enhancement imaging sequence, based on single-shot inversion-recovery steady-state free precession (SSFP), to be used for assessing myocardial infarction. This new technique was compared with a standardized and validated 3D gradient echo (FFE) technique which was used to image the entire left ventricle during end-expiratory breath-holding. In 33 patients with suspected chronic myocardial infarction, both sequences were performed. In the free-breathing 2D approach, respiratory motion was avoided using triggering from a respiratory belt. The intraclass correlation for infarct quantification between both delayed-enhancement techniques was excellent (ICC = 0.99 [$p<0.01$]). The agreement in assessing the transmural extent of infarction was good to excellent between the 2D free-breathing technique and the 3D breath-hold technique (kappa varied between 0.70 and 0.96 for all of the 16 standardized myocardial segments). Therefore, when used for quantification of left ventricular infarction, respiratory-triggered 2D single-shot inversion-recovery SSFP delayed-enhancement MRI is comparable to breath-hold 3D segmented gradient-echo inversion-recovery delayed-enhancement MRI. In conclusion, free-breathing 2D delayed-enhancement MRI sequence is a fast and reliable tool for detecting myocardial infarction and provides an alternative imaging technique when patients are not capable of performing (long) breath-holding.

The second part of the thesis addresses the application of CMR for the purpose of magnetic resonance angiography (MRA). First, the current state-of-art is described followed by the results of a study comparing MRA of the peripheral arteries on 1.5T and 3T MRI systems. Moreover, the results of a study comparing a conventional contrast-enhanced MRA (CE-MRA) scan protocol with a new and optimized, faster multiposition CE-MRA protocol are described. For the above mentioned studies, patients with suspected peripheral artery disease were included and follow-up studies

were performed. Another study describes which biomarkers may be required for full vascular risk assessment in the clinical workup of patients with peripheral arterial disease. Finally, the prognostic value of outcome of CMR imaging biomarkers in patients with symptomatic peripheral arterial occlusive disease are explored in a six year follow-up study.

In the first part of **chapter 4,** currently available techniques for MRA are described. CE-MRA, and black-blood and bright-blood non-CE-MRA techniques are discussed. Additionally, time-resolved 3D phase contrast (i.e., 4D flow MRI) is addressed. This relatively new technique may be used to visualize complex flow structures with the aid of newly developed visualization tools adding quantitative hemodynamic information as well. In the second part of this chapter, anatomical regions that are imaged by MRA and state-of-the-art applications are discussed. Special focus is on the carotid arteries, thoracic and abdominal aorta, renal arteries, mesenteric artery, and the peripheral arteries.
In **Chapter 5**, a new and optimized single-injection multiposition CE-MRA protocol is compared with a conventional scan protocol. The optimized single-injection multiposition CE-MRA protocol uses sensitivity encoding and random central k-space segmentation in a centric filling order. For this comparison, 15 patients with peripheral arterial occlusive disease were imaged with both protocols on 1.5T MRI. Midstream aortic Conventional digital subtraction angiography (DSA) was used as the standard of reference.
In the sensitivity-encoded CE-MRA protocol, imaging times in the pelvic and upper-leg positions were reduced and isotropic submillimeter voxel volumes were acquired in the lower-leg position. For analysis, the arterial tree in each patient was divided into 29 standardizes segments and in each segment, the most severe stenosis was chosen for classification.
In the trajectory from the aorta to the popliteal arteries, sensitivity-encoded CE-MRA showed a higher sensitivity for detection of stenoses with a severity of 50% and higher: 85% versus 79% for conventional CE-MRA. The specificity of both protocols was almost similar: 99% for sensitivity-encoded CE-MRA versus 97% for conventional CE-MRA. For the detection of stenoses of 75% and higher, the sensitivity of sensitivity-encoded CE-MRA was 100% versus 93% for conventional CE-MRA, while the detection of occlusion showed a sensitivity of 100% for sensitivity-encoded CE-MRA versus 92% for conventional CE-MRA. Specificities were equal (i.e., 100%). In the infragenual arteries, the sensitivity for the detection of a significant (i.e., 50% or higher) stenosis was 87% with both CE-MRA techniques, while the specificity showed a statistically significant increase from 84% with conventional CE-MRA to 93% with sensitivity-encoded CE- MRA. For the detection of diffuse stenoses in arterial segments, the specificity was significantly higher with sensitivity-encoded CE-MRA than that with conventional CE-MRA, 100% and 86% respectively. Sensitivities were similar (92% and

90% respectively). Furthermore, sensitivity-encoded CE-MRA significantly depicted more open infragenual arterial segments than midstream aortic DSA (p=0.001) and conventional CE-MRA (p<0.001). In conclusion, the application of a single-injection multiposition CE-MRA protocol at 1.5T MRI with sensitivity-encoding and random central k-space segmentation in a centric filling order with submillimeter isotropic voxel acquisition in the lower legs improves the diagnostic accuracy and depicts more open infragenual arterial segments compared with both midstream aortic DSA and conventional CE- MRA.

In **Chapter 6**, the diagnostic accuracy of CE-MRA at 3T is compared versus 1.5T. The diagnostic performance of a single-injection, three-station, moving-table protocol with high spatial resolution is evaluated in a prospective study performed at both field strengths in patients with peripheral arterial occlusive disease. Similar acquisition protocols and identical contrast agent dose were used on both 3T as well as 1.5T. DSA served as the standard of reference. In 19 patients suspected of peripheral arterial occlusive disease, who were referred for further work-up, peripheral CE-MRA at both field strengths as well as DSA was performed. Similar excellent agreement with DSA regarding stenosis classification was found for both 3T and 1.5T CE-MRA (kappa = 0.96 and 0.93, respectively). For classification of stenosis larger than 50%, the sensitivity of 3T CE-MRA was 99% and of 1.5T CE-MRA 92%. Specificity of 3T CE-MRA was 99.5%, and of 1.5T CE-MRA 99.6%. For classification of stenosis larger than 75%, sensitivity of 3T CE-MRA was 95% and of 1.5T CE-MRA 92%, while specificity was 100% for both techniques. At 3T CE-MRA a, on average, more than 3 times higher contrast-to-noise ratio (p<0.001) was achieved in the external iliac artery, superficial femoral artery and popliteal artery of the left and the right leg when compared to 1.5T CE-MRA, using the same contrast agent dose. Therefore, 3T and 1.5T single-injection CE-MRA with a three-station moving-table technique showed similar excellent agreement with DSA regarding agreement, sensitivity, and specificity of peripheral arterial occlusive disease stenosis severity classification. We concluded that both 1.5T and 3T CE-MRA with similar acquisition protocols and identical contrast agent dose can be used interchangeably in daily practice of peripheral arterial occlusive disease, because diagnostic performance proved to be similar.

Chapter 7 prospectively evaluates the association between aortic wall stiffness, expressed by pulse wave velocity (PWV), sampled in the distal aorta and the severity of peripheral arterial occlusive disease. This is compared to atherosclerotic markers sampled in remote vascular territories such as the PWV in the proximal aorta and vessel wall thickness of the left common carotid artery. Forty-two patients underwent CMR in the work-up for peripheral arterial occlusive disease using a 3T MRI system. PWV was assessed regionally in the aorta, between the ascending and descending thoracic aorta (i.e., the proximal aorta) and between the thoracic descending and distal abdominal aorta (i.e., the distal aorta). In all patients, whole-body CE-MRA and carotid vessel wall imaging were performed. Stenosis severity correlated well with

PWV in the distal aorta (r≥0.64) but to a lesser extent with PWV in the proximal aorta (r≤0.48). Carotid normalized wall index (NWI) was not associated with peripheral stenosis severity nor with PWV in the proximal or distal aorta. Correlation between stenosis severity and distal aortic PWV remained
statistically significant after correction for age and gender. In conclusion, in patients with PAOD, peripheral arterial stenosis severity is well correlated with aortic PWV sampled in the distal aorta but correlation with markers sampled in remote vascular territories, such as PWV in the proximal aorta or carotid arterial wall thickness, is only moderate at best. Only the correlation between stenosis severity and distal aortic PWV remains statistically significant after correction for age and gender. The association between aortic wall stiffening and stenosis severity in a vascular territory directly linked to this aortic segment suggests that site-specific evaluation of vascular disease may be required for full vascular risk assessment in the clinical workup of peripheral arterial occlusive disease.

Chapter 8 prospectively explores the prognostic value of outcome of CMR imaging biomarkers in patients with symptomatic peripheral arterial occlusive disease in comparison with traditional risk factors [i.e., age, gender, body mass index (BMI), hypertension, diabetes mellitus, levels of triglyceride (TG) and high-density lipoprotein (HDL) in blood plasma samples, ankle-brachial index (ABI) and Fontaine class]. In this study, 42 consecutive patients with symptomatic PAOD were included. At base-line, all patients underwent a comprehensive CMR examination consisting of CE-MRA of the run-off vessels and additionally, carotid vessel wall imaging, cardiac cine imaging for assessing left ventricular volume, mass and function, and assessment of the aortic PWV from velocity encoded MRI as a surrogate marker of aortic stiffness. Follow-up evaluation of the patient population over a 6 year period was performed to examine which CMR imaging biomarker or traditional risk factor is an independent predictor for all-cause mortality, cardiac or cerebral morbidity.

For all-cause mortality, age, diabetes mellitus, MRA stenosis severity and descending aorta PWV were significant predictors. However, only MRA stenosis severity was independently significant (beta 3.0 ± standard error 1.3, p=0.02). Descending aorta PWV, age and diabetes mellitus were interrelated with stenosis severity but none of these were significant independent predictors. For cardiac morbidity, left ventricular ejection fraction (LVEF) and MRA stenosis severity were associated, but only LVEF was a significant independent predictor (beta −0.14 ± 0.05, p=0.005). For cerebral morbidity, only diagnosis of diabetes mellitus (beta 2.8 ± 1.3, p=0.03), but none of the other described CMR imaging biomarkers was a significant independent predictor in this patient population. In conclusion, the CMR imaging biomarkers representing stenosis severity, aortic stiffness (i.e., descending aorta PWV) and left ventricular function (i.e., LVEF) play a role in prognosis of outcome in patients with symptomatic peripheral arterial occlusive disease.

Conclusions

Cardiovascular magnetic resonance imaging is an important noninvasive imaging modality for the diagnosis, clinical work-up and treatment planning in patients suspected for a wide range of cardiovascular pathology. CMR imaging is accurate and reliable, and provides invaluable information to evaluate the cardiovascular system without the need of ionizing radiation.

The studies described in this thesis evaluate new CMR imaging techniques in clinical practice and explore the prognostic value of new CMR imaging biomarkers in patients with symptomatic peripheral arterial occlusive disease.

New advances and innovations in MR imaging technology improve and further expand the clinical applications of cardiovascular imaging in daily clinical practice. In this thesis, a new, fast free-breathing 2D delayed-enhancement MRI sequence is validated and demonstrated to be a reliable tool for detecting myocardial infarction. Furthermore, new technical developments allow single-injection, three-station, moving-table MRA protocol at 3Tesla with similar diagnostic performance when compared to 1.5Tesla. Additionally, submillimeter isotropic voxel acquisition in the lower legs at 1.5Tesla improves the diagnostic accuracy and depicts more open infragenual arterial segments.

Additionally, it is demonstrated that new MRI biomarkers as distal aortic pulse wave velocity statistically significantly correlate with stenosis severity in symptomatic patients with peripheral arterial occlusive disease. Finally, we showed that CMR derived biomarkers relating to stenosis severity, aortic stiffness and left ventricular function play a role in prognosis of outcome in patients with symptomatic PAOD.

In the future, incorporation of the described new MRI biomarkers in the clinical workup of peripheral arterial occlusive disease may play an important role for full vascular risk assessment and ultimately, patients may benefit in clinical practice.