Whole-body MR angiography in patients with peripheral arterial disease

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1. GENERAL PART

This thesis is divided into 3 main sections: A general part, a special part, and a conclusion. The general part describes the background for the study, and outlines the study aims. The special part summarises the results of the research, with reference to the original papers. Overall results of the study are discussed in the conclusion.

The thesis is based on 4 original studies:

I. Nielsen YW, Eiberg JP, Løgager VB, Hansen MA, Schroeder TV, Thomsen HS. Whole-body MR angiography with body coil acquisition at 3T in patients with peripheral arterial disease using the contrast agent gadofosveset trisodium. Acad Radiol 2009; 16:654-61.

II. Nielsen YW, Eiberg JP, Løgager VB, Schroeder TV, Just S, Thomsen HS. Whole-body magnetic resonance angiography at 3 Tesla using a hybrid protocol in patients with peripheral arterial disease. Cardiovasc Intervent Radiol 2009; 32:877-86.

III. Nielsen YW, Eiberg JP, Løgager VB, Just S, Schroeder TV, Thomsen HS. Whole-body MRA with additional steady-state acquisition of the infra-genicular arteries in patients with peripheral arterial disease. Cardiovasc Intervent Radiol 2009; Epub Dec 3.

IV. Nielsen YW, Eiberg JP, Løgager VB, Just S, Schroeder TV, Thomsen HS. Patient acceptance of whole-body MRA – a prospective questionnaire study. Acta Radiol 2010; 51:277-83.

1.1 STUDY AIMS

The principal aim of the study was to investigate whole-body magnetic resonance angiography (WB-MRA) as diagnostic tool in patients with peripheral arterial disease (PAD). Focus has been on feasibility of WB-MRA with body coil acquisition, means of improving the technique, and patient acceptance of the method. Both an extracellular and a blood-pool MRI contrast agent have been used in the study. However, it has not been a study aim to perform a large scale comparison of WB-MRA using different contrast agents.

Specific aims of individual studies

Study I
The aim of this study was to investigate the feasibility of performing WB-MRA in a 3 Tesla (T) MRI system with use of body coil acquisition and a blood-pool contrast agent.

Study II
The aim of this study was to determine the impact of a hybrid scan technique on the diagnostic performance of 3T WB-MRA using an extracellular contrast agent.

Study III
The aim of this study was to investigate if addition of infra-genicular steady-state MRA (SS-MRA) to first-pass imaging improves diagnostic performance compared to first-pass imaging alone, in WB-MRA of patients with PAD.

Study IV
This study assessed patient acceptance of WB-MRA compared to conventional x-ray angiography.

1.2 BACKGROUND

1.2.1 Atherosclerosis

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in the Western world [1]. This chapter gives a brief overview of the pathogenesis, risk factors and pharmacological treat-

ment of atherosclerosis. Finally, the systemic nature of atherosclerosis will be discussed.

Atherosclerosis is characterized by plaque formation in the walls of the large and medium size arteries. The first event in plaque formation is migration of monocytes into the arterial intima, where they differentiate into macrophages. These absorb lipids and become foam cells. Arterial fatty streaks consist of intimal collections of foam cells, and are considered the primary atherosclerotic lesion. More advanced stages of atherosclerosis occur when the lipid-loaded foam cells become apoptotic and release lipids to the extracellular space. This accelerates collagen production and a true atherosclerotic plaque consisting of a lipid core surrounded by a fibrous cap is the result [2]. Initially, the plaque does not narrow the arterial lumen by in-growth, instead remodelling occurs and the plaque expands through the outer layers of the arterial wall. However, at some point compensatory enlargement is no longer possible, and the plaque begins to expand inwards leading to progressive reduction of the arterial lumen. Artherosclerotic plaques usually do not cause ischemic symptoms before luminal narrowing exceeds 50%. Hence, a large quantum of asymptomatic atherosclerosis may be present once symptoms occur. The majority of acute cardiovascular events are due to plaque complications that acutely occlude the arterial lumen [3]. Plaque rupture causes platelet aggregation and formation of an occluding thrombus at the site of the plaque (atherothrombosis). Additionally, particulate matter may also be shed from the ruptured plaque leading to embolization. Together, these mechanisms account for most of the acute ischemic manifestations of atherosclerosis (unstable angina, myocardial infarction, and ischemic stroke).

Established risk factors for atherosclerosis include hypertension, diabetes, dyslipidaemia, smoking, obesity, and physical inactivity [4]. Lifestyle modifications such as reductions in the amount of dietary fat, calorie control, exercise, and smoking cessation are important factors in prevention of atherosclerosis. Pharmacological treatment of hypertension, diabetes, and dyslipidaemia is also essential in management of patients with atherosclerosis. Another important mechanism in atherosclerosis treatment is platelet inhibition, since platelets are key components in the atherothrombotic process succeeding plaque rupture.

Presence of atherosclerosis in one vascular bed often implies presence of the disease in other vascular territories. Hence, atherosclerosis is regarded a systemic disease. Predisposed sites for atherosclerosis exist in the vascular tree including the carotids, coronaries, aorta, renal arteries, and lower extremity arteries from the level of the aortic bifurcation. Low shear stress acting on the endothelium in the outer areas of vessel bifurcations is believed to play a role in the development of atherosclerosis in these predisposed areas [5].

Numerous studies have investigated the systemic nature of atherosclerosis. In patients with peripheral arterial disease (PAD) con-comitant carotid stenosis has been found in 25% [6;7], renal artery stenosis in 14% [8], and coronary heart disease (CHD) in 46% [9]. Similary, 14% of patients with primary CHD also suffer PAD [10]. A recent study showed that polyvascular disease (> 1 region) is present in 71% of vascular surgery patients with atherosclerosis [11].

1.2.2 Peripheral arterial disease

In the context of this thesis PAD is defined as chronic atherosclerotic disease of the arteries to the legs. This chapter briefly describes the basic concepts of PAD.

Intermittent claudication, defined as exercise-induced pain in the muscles of the leg, is the earliest and most frequent symptom of PAD. Claudication begins after a reproducible length of walk, and resolves within few minutes after the patient stops walking. With disease progression (critical limb ischemia), PAD patients have rest pain, and clinical findings might include ischemic ulceration and gangrene. The Fontaine classification is the classic scheme used to describe the severity of PAD (Table 1) [12]. Patients in Fontaine class III and IV suffer critical limb ischemia.

PAD is a frequent disease. In a population-based study, PAD (ankle-brachial index <0.9) was present in 19% of subjects > 55 years old [13]. Traditional cardiovascular risks factors (advanced age, male gender, diabetes, smoking, hypertension, hyperlipidaemia) are related to PAD [14]. Due to con-comitant atherosclerotic complications in the coronary and cerebrovascular beds, PAD patients have increased risk of mortality compared to the general population [15].

An accurate medical history and thorough physical examination are important factors in the diagnostic approach to the PAD patient. However, exact determination of the extent of atherosclerosis requires diagnostic imaging, which is the subject of the next chapter.

Treatment options of PAD include preventive measures against atherosclerosis, surgery, and endovascular interventions. Preventive measures with life-style modifications (smoking cessation and exercise) as well as pharmacological interventions (antihypertensives, antiplatelets, blood sugar control, antihyperlipidaemics) are the most important part of PAD treatment [14]. Surgical procedures are endarterectomy, bypass grafting, and amputation, whereas endovascular interventions are PTA (percutaneous transluminal angioplasty) and stent placement.

Table 1. The Fontaine classification

Stage	Symptoms / Findings
I	Asymptomatic
II a	Intermittant claudication Pain-free walking distance > 200 m
II b	Intermittant claudication Pain-free walking distance < 200 m
III	Rest pain
IV	Tissue loss and/or gangrene

1.2.3 Diagnostic imaging of atherosclerosis

Numerous imaging methods are used clinically to depict atherosclerotic lesions. This chapter gives an overview of these methods.

Conventional x-ray angiography

In conventional x-ray angiography a catheter is placed inside the arterial system. Most commonly, the common femoral artery is used to gain arterial access, but other options include brachial and trans-lumbar access. With the catheter tip advanced to the artery of interest, an iodinated contrast agent is injected followed by acquisition of x-ray images to achieve selective arterial visualization. Atherosclerotic lesions will show as luminal filling defects.

Today, conventional x-ray angiography is usually performed using a subtraction technique (DSA – digital subtraction angiography). With this technique two images are acquired; before and after contrast injection. The pre-contrast image is subtracted from the post-contrast image, with the resulting image selectively showing the injected contrast agent. Hence, DSA is an effective means of removing overlying structures, which else could interfere with the diagnostic assessment. DSA is regarded as the gold standard method for imaging of atherosclerosis. The main advantage of DSA is high spatial and temporal resolution. Another advantage is that DSA can be combined with endovascular treatment. Drawbacks of DSA are radiation exposure to the patient and staff, use of nephrotoxic iodinated contrast agents, and risk of procedure-related complications. The rate of major complications (hemmorhage, embolism) following angiography is approximately 2%, while the rate of minor complications (local pain, puncture site haematoma) is approximately 23% [16;17].

Computed tomography angiography

Computed tomography (CT) is an imaging procedure that combines the use of special x-ray equipment and computer processing to generate cross-sectional images of the body. Recently, technological advances with multi-detector CT systems have made it possible to increase temporal and spatial resolution, facilitating use of CT angiography (CTA). CTA is a minimal invasive imaging test, only requiring upper extremity venous puncture and injection of an iodinated contrast agent. Imaging is performed during the arterial first-pass phase. Advantages of CTA are minimal invasiveness, short examination time, and high diagnostic accuracy. The latter has been shown in a recent meta-analysis on diagnostic performance of CTA in patients with PAD [18]. Disadvantages of CTA include use of nephrotoxic contrast agents, decreased diagnostic confidence in calcified vessels (blooming effect), and use of ionizing radiation. In example, a radiation dose of 12 mSv has been measured in CTA [19], this should be compared to an annual background radiation exposure of 3 mSv. Lately, CTA has been established as an accurate method of performing minimal invasive coronary angiography [20]. Whole-body CTA has proven feasible [21] but should not be performed as a general screening examination, as legislation in the European Union prohibits use of ionizing radiation for any other screening purpose than mammography [22].

Duplex Doppler ultrasound

The technical details of ultrasound (US) imaging can be found elsewhere [23]. In brief, US imaging is based on transmission of high frequency sound waves (2-18 MHz) into the body. As the body's reflection of sound waves is tissue-specific, computer processing of the received echoes can be used to produce images of the examined structures.
In vascular imaging, Doppler US is used to provide flow information. This is based on frequency shifts in sound waves reflected from moving objects (i.e. red blood cells). Duplex Doppler US combines conventional structural US imaging (B/ brightness mode) with Doppler flow information. Advantages of duplex Doppler US include non-invasive procedure, relatively inexpensive equipment, wide availability, no harmful effects, and no use of radiation or nephrotoxic contrast agents. Furthermore, real-time images are acquired, which may assist functional assessments. A disadvantage of duplex Doppler US is inability to examine the abdominal vessels in obese patients. Also, overlying abdominal air may obstruct the ultrasound signal.
Three meta-analyses have assessed diagnostic performance of duplex Doppler US in PAD patients [24-26]. Sensitivities and specificities for detection of >50% arterial stenosis, ranged from 0.80-0.88 and 0.84-0.97, respectively. More recent prospective studies report similar sensitivities and specificities as the meta-analyses [27;28]. When performed by experienced staff, the interobserver agreement of duplex Doppler US is comparable to that of DSA [29].

Magnetic resonance angiography

This section provides an overview of the most important MRA applications, with special focus on use of MRA in PAD patients. Comprehensive reviews of MRA can be found elsewhere [30;31].
Magnetic resonance angiography (MRA) applications include both contrast-enhanced and un-enhanced techniques.
Un-enhanced MRA applications comprise the classic time-of-flight (TOF) and phase-contrast (PC) techniques. Newer techniques like electrocardiographically (ECG)-gated fast spin echo subtraction MRA or steady-state free precession MRA have proven feasible, and the potential for clinical use is under investigation [32]. In recent years, interest in un-enhanced MRA has been growing. Two main factors have contributed to this interest: First, developments in MRI technology leading to reduced acquisition times, have made some methods clinically practical. Secondly, some MRI contrast agents have been associated with development of the potentially fatal disease nephrogenic systemic fibrosis (details in chapter 1.2.4).
TOF-MRA is the most commonly used un-enhanced MRA application. The TOF technique relies on difference in the MRI signal originating from protons in the flowing blood, and stationary protons within the imaging slab. Today the most common clinical application of TOF is MRA of the intracranial circulation [32]. However, TOF-MRA may also be used in the assessment of the peripheral arteries, as shown in various studies [33-37]. Artefacts related to flow direction in the examined vessels can degrade image quality in TOF-MRA. In-plane saturation in vessels transversing the imaging plane may lead to false-positive detection of stenosis or occlusion. Such artefacts can be seen in the iliac arteries and proximal part of the anterior tibial artery. Retrograde reconstitution of arteries distal to occlusions is not seen with TOF-MRA, because the technique is designed to detect uni-directional flow. Also the triphasic flow pattern in the peripheral arteries can degrade image quality, but this can be compensated for by using ECG-gating [38]. TOF-MRA sensitivity and specificity for detecting > 50% arterial stenosis in the peripheral arteries seem to be high. Systematic reviews report median sensitivities and specificities of 0.92-0.93 and 0.88/0.88, respectively [24;39]. An interesting observation has been that peripheral TOF-MRA is capable of demonstrating patency of distal runoff vessels not seen on conventional angiography [33;40;41]. Despite this, TOF-MRA has never gained widespread use as imaging method in PAD patients.
Phase-contrast (PC) MRA is another un-enhanced technique. As shown in one study, PC-MRA holds potential for highly accurate detection of PAD with sensitivity and specificity of 0.95 and 0.90, respectively [42]. However, long acquisition times in PC-MRA have precluded its use in the routine clinical setting.
Contrast-enhanced (CE) MRA was introduced in the early 1990-ies [43;44]. In CE-MRA, a paramagnetic gadolinium-based contrast agent is injected intravenously and images are acquired during the subsequent arterial first-pass. Due to the T1 shortening effect

of the contrast agent arteries appear bright on T1 weighted MRI images. Technically, CE-MRA may be performed using a single- or a multi-station approach. Single-station (single field of view) CE-MRA is suitable for assessment of the carotid and renal arteries, whereas multi-station CE-MRA is appropriate for assessment of the peripheral arteries. The typical peripheral CE-MRA examination acquires data from 3 consecutive stations (i.e. pelvic, thigh and calf stations) [45-47]. An example of peripheral CE-MRA is shown in Figure 1. As the arterial bolus is imaged over multiple stations, the multi-station technique is also known as bolus-chase MRA.
Systematic reviews have assessed the diagnostic performance of peripheral CE-MRA, with reported sensitivities and specificities (median or pooled values) ranging from 0.95-0.98 and 0.96-0.97, respectively [24;26;39]. The diagnostic accuracy of peripheral CE-MRA is superior to that of TOF-MRA [48;49]. Today, CE-MRA is widely used for diagnosing PAD.

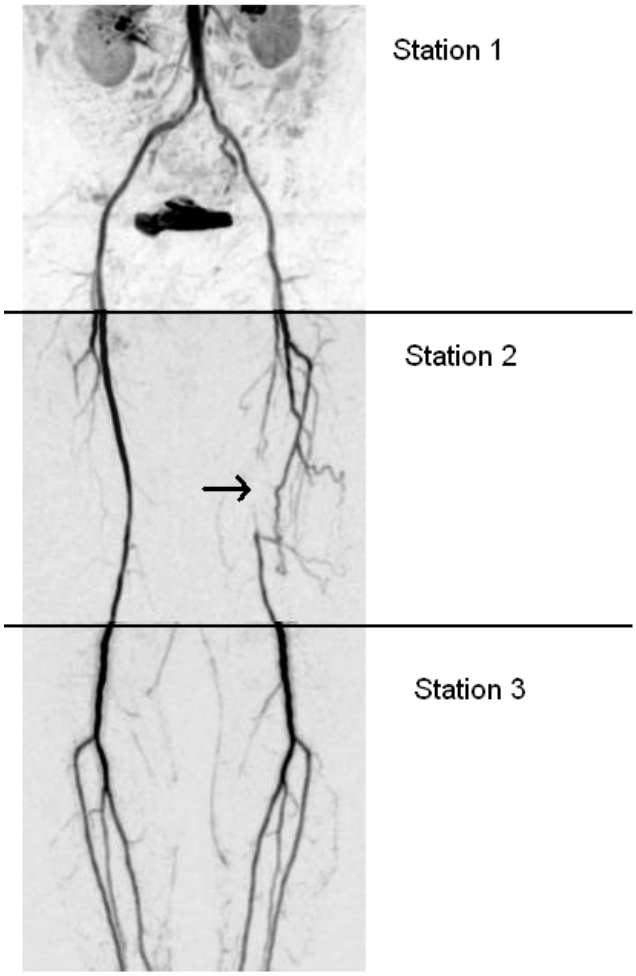

Figure 1. Contrast-enhanced MRA of the peripheral arteries.

Advantages of CE-MRA are that the examination is non-invasive, has high diagnostic accuracy, and is cost-effective [50]. Limitations of CE-MRA are problems related to metal implants, pacemakers, claustrophobic patients, and gadolinium-based contrast agents. A final limitation is that endovascular can not be performed during CE-MRA.
Contrast-enhanced whole-body MRA is described in section 1.2.5.

1.2.4 Magnetic resonance imaging contrast agents

Magnetic resonance imaging contrast agents (MRI-CA) are chemical compounds that affect the properties of the MRI signal from the surrounding tissues. They are used to enhance tissue contrast and characterize lesions, as well as to provide functional information. This chapter reviews the basic concepts of MRI-CA, a more comprehensive review of MRI-CA can be found elsewhere [51;52].

Extracellular gadolinium contrast agents

Gadolinum-based contrast agents (Gd-CA) contain the gadolinium Gd^{3+} ion. Gd^{3+} is paramagnetic and shortens T1, T2 and T2* relaxation times in adjacent tissues, leading to contrast enhancement on T1 weighted images (and signal loss on T2/T2* weighted images). Free Gd^{3+} is highly toxic, causing tissue necrosis and blocking intracellular physiological processes dependent on Ca^{2+}. Thus, all Gd-CA consist of Gd^{3+} chelated to a ligand that should prevent cellular uptake of free gadolinium. Depending on the chemical structure of the ligand, Gd-CA are classified as linear or macrocyclic, as well as ionic or non-ionic (Figure 2) [51;53;54]. Some special Gd-CA used as liver specific contrast agents or blood-pool agents will be discussed below. The remaining part of this section deals with the non-specific extracellular gadolinium-based contrast agents (EC Gd-CA). An overview of the six approved EC Gd-CA is shown in Table 2.
EC Gd-CA are administered intravenously. For most clinical indications a single dose (0.1 mmol/kg body weight) are used, but higher doses up to double or triple dose (0.2 and 0.3 mmol/kg) may be required for CE-MRA or CNS imaging. Most EC Gd-CA has 0.5 mol/L concentration; however gadobutrol is available in 1 mol/L concentration. This higher concentration makes gadobutrol suitable for bolus-chase CE-MRA [55-58].
The pharmacokinetic profile of EC Gd-CA is similar to that of iodinated contrast agents. Distribution is in the extracellular compartment, and elimination is exclusively by passive glomerular filtration in the kidneys. In patients without renal impairment, 98% of EC Gd-CA is excreted within 24 hours of injection [54].

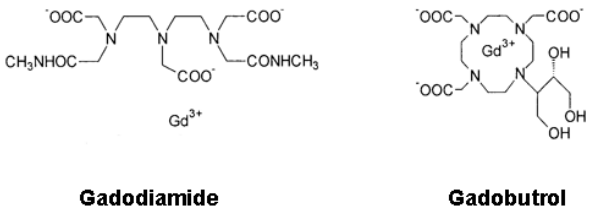

Figure 2. Examples of linear (gadodiamide) and macro-cyclic (gadobutrol) gd-CA.

Hepatobiliary contrast agents

MRI-CA for selective imaging of the hepatobiliary system are included in this group. Three different types of hepatobiliary contrast agents exist: Iron oxides, manganese- , and gadolinium-based contrast agents. As some of these agents also hold potential for MR angiographic applications, they are reviewed here.
First group is the superparamagnetic iron oxide particles (SPIO). These agents are taken up by the reticuloendothelial system. As they have a predominant T2 shortening effect, they are used as negative contrast agents to decrease signal from normal liver

Table 2. Non-specific extracellular gadolinum-based contrast agents

Generic name	Gadopentate dimeglumine	Gadoterate meglumine	Gadoteriol	Gadodiamide	Gadobutrol	Gadoversetamide
Brand name	Magnevist	Dotarem	ProHance	Omniscan	Gadovist	OptiMark
Manufacturer	Bayer Schering Pharma	Guerbet	Bracco	GE Healthcare	Bayer Schering Pharma	Covidien
Concentration	0.5 mol/L	0.5 mol/L	0.5 mol/L	0.5 mol/L	1 mol/L	0.5 mol/L
Structure	Linear	Cyclic	Cyclic	Linear	Cyclic	Linear
Charge	Ionic	Ionic	Non-ionic	Non-ionic	Non-ionic	Non-ionic
Thermodynamic stability constant (log K_{eq})	22.1	25.8	23.8	16.9	21.8	16.6

parenchyma on T2- and T2*-weighted images. SPIOs include ferumoxides (Endorem; Guerbet) and ferucarbotran (Resovist; Bayer Schering Pharma). The latter agent also has strong T1 shortening effect and can theoretically be used for MRA [53].
The second group of MRI-CA for hepato-biliary imaging is manganese-based agents, which includes both agents for intravenous infusion (mangafodipir trisodium, Teslascan; GE Healthcare) and oral intake (CMC-001; CMC Contrast AB). Manganese contrast agents produce positive contrast on T1 weighted images.
Gd-CA for imaging of the liver includes gadobenate dimeglumine (Gd-BOPTA, Multihance; Bracco) and gadoxetic acid (Gd-EOB-DTPA, Primovist; Bayer Schering Pharma) both of which produce positive contrast on T1 weighted images. Gd-BOPTA behaves mainly like a pure extracellular agent, but it is a high relaxivity-contrast agent due to weak protein binding in plasma. In plasma at 37°C and at 1.5T the r1 relaxivity of Gd-BOPTA is 6.3 L $mmol^{-1}$ s^{-1} compared to 4.1 for Gd-DTPA [59]. Because Gd-BOPTA initially acts like an extracellular agent with high relaxivity it is suitable for MRA, as shown in multiple studies [57;60-67]. Gd-BOPTA is occasionally referred to as a blood-pool contrast agent, because of it's protein binding. However, the binding is weak and transistent, so it is not a true blood-pool agent. Delayed phase imaging with Gd-BOPTA is used for liver imaging.

Blood-pool contrast agents

Whereas extracellular gadolinium chelates are characterized by rapid extravasation to the extracellular compartment, the new generation of blood-pool MRI-CA has prolonged intravascular stay. Accordingly, MR angiographic applications using blood-pool MRI-CA encompass both first-pass and steady-state MRA (Figure 3). Due to the long plasma half-life of blood-pool MRI-CA, they are often referred to as intravascular contrast agents.
Blood-pool MRI-CA can be classified into 3 groups: 1) Iron Oxides; 2) Gadolinium-based macromolecules; and 3) Small gadolinium-based molecules with reversible protein binding [68].

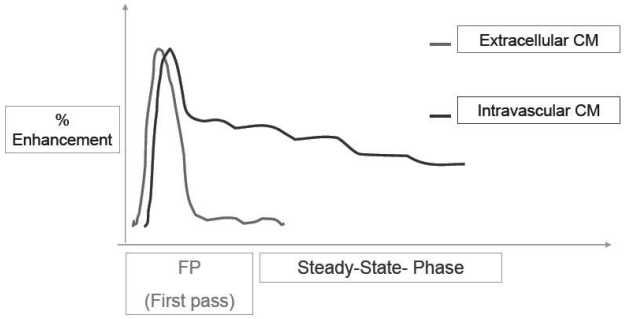

Figure 3. First-pass and steady-state MRA is possible using blood-pool (intravascular) contrast agents. On the contrary, only first-pass MRA is possible using extracellular contrast agents.

Iron oxides

Iron-based blood-pool MRI-CA are ultrasmall super-paramagnetic iron-oxide particles (USPIO). These contrast agents have high r1 and r2 relaxivities. At low doses they decrease the T1 of blood, whereas at higher doses the T2* effect dominates [52]. Because of their large size these contrast agents exhibit slow leakage from the intravascular compartment. Examples of USPIO's are: Ferucarbotran (SHU-555C, Supravist; Bayer Schering Pharma) and ferumoxtran (Sinerem, Guerbet; Combidex, AMAG Pharma). Ferucarbotran has proven feasible for first-pass and steady-state MRA [69], and was recently approved for clinical use. Eventhough ferumoxtran may potentially be used for MRA, it is primarily developed for MRI lymphography [53]. Elimination of USPIOs from the body is through the reticuloendothelial system.

Gadolinium-based macromolecules

This group of blood-pool MRI-CA consists of macromolecules with multiple gadolinium ions bound to the surface. The blood-pool effect of these contrast agents is due to the large size of the macromolecules, ensuring slow or absent leakage into the interstitial space. Gadolinum-based macromolecules are high relaxivity contrast agents because their large size leads to slow rotational dynamics [52]. Examples of contrast agents in this group are (Gd-DTPA)-17 (Gadomer-17; Bayer Schering Pharma) and Gadomelitol

(P-792, Vistarem; Guerbet) [70;71]. Both of these agents are undergoing clinical trials. Elimination of this group of contrast agents is through glomerular filtration in the kidneys, which limits the maximum size of the macromolecules.

Small gadolinium-based molecules with reversible protein binding

The most important contrast agent in this group is gadofosveset trisodium (MS-325, Vasovist, Ablavar; Bayer Schering Pharma, Lantheus Medical Imaging). It is a monomeric linear and non-ionic gadolinium-based contrast agent (Figure 4) [68]. The blood-pool property of gadofosevset is due to non-covalent binding to protein (albumin) in human plasma. When bound to albumin, the rotational speed of the contrast agent decreases, leading to increased relaxivity [59;72-74]. The r1 relaxivity of gadofosveset increases from 4.1 in water to 19 L $mmol^{-1}$ s^{-1} in plasma at 1.5T at 37℃ [59]. In comparison, the r1 relaxivity of gadopentate (Gd-DTPA) only increases from 3.3 in water, to 5.2 L $mmol^{-1}$ s^{-1} in plasma under similar conditions.
In human plasma 4-20% of gadofosveset remain unbound and follows the same distribution as the non-specific extracellular agents [74].
Elimination of gadofosveset is predominantly renal filtration (91-95%) and to a lesser extent hepato-biliary excretion (5-9%). Half-life for elimination is 18.5 hours [54;75].
Due to the high relaxivity of gadofosveset it is administered at lower doses than the extracellular agents. The standard dose for gadofosveset-enhanced MRA is 0.03 mmol/kg [76;77]. This dose has proven both efficient and safe [78-80]. Following intravenous administration of gadofosveset, first-pass MRA can be performed during the bolus phase. Furthermore, steady-state MRA is possible for up to an hour following contrast injection [81-84]. Gadofosveset has been the first blood-pool MRI-CA to become commercially available. However, gadofosveset is not the only blood-pool agent to exhibit protein binding. Another example is gadocoletic acid (B-22956; Bracco) [85;86]. However, this agent has not yet been approved.

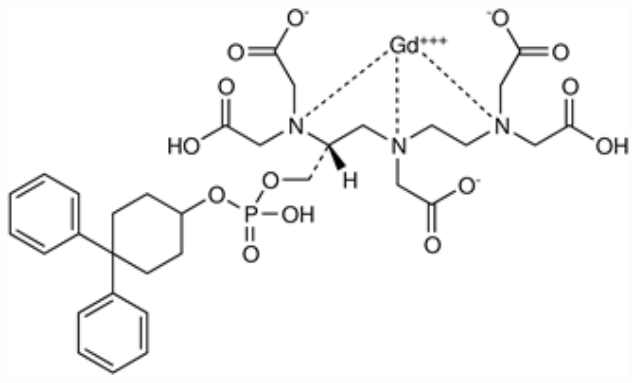

Figure 4. Chemical structure of the blood-pool contrast agent gadofosveset.

Nephrogenic systemic fibrosis

In many years gadolinium-based CA were believed to have an excellent safety profile. However, in the recent years intravenous administration of gadolinium-based CA has been linked to development of neprhogenic systemic fibrosis (NSF), a potentially fatal disease causing fibrosis of the skin and internal organs [87-89]. NSF has solely been reported in patients with renal insufficiency, including patients on dialysis [90]. So far, NSF cases have been seen following administration of linear gadolinium-based CA (gadopentate and gadodiamide) with most cases being caused by gadodiamide. No un-confounded cases of NSF following administration of high relaxivity agents (gadobenate and gadofosveset) have been reported in the peer-reviewed literature [51;91]. One case of NSF following exposure to the macrocyclic agent gadobutrol has been reported [92]. There is evidence that cumulative doses of gadolinium increase the risk of NSF [93]. Accordingly, the agents that leaves the smallest amount of gadolinium in the body should be preferred, in order to reduce the risk of NSF [51]. It is believed that release of free Gd^{3+} from their ligands plays a role in NSF development. However, the exact pathophysiological mechanisms of NSF remain unknown. Currently, no curable treatment to NSF is known.

1.2.5 Whole-body magnetic resonance angiography

Due to the systemic nature of atherosclerosis whole-body assessment of the arterial system seems desirable. Established imaging modalities have limitations curtailing their use in whole-body angiography. Use of conventional x-ray angiography is limited by the invasive procedure as well as use of ionizing radiation. Likewise, a major limitation of CTA is the high radiation doses of this modality. Duplex Doppler ultrasound is time consuming, and technically difficult in adipose patients. Un-enhanced MRA techniques have limited use for whole-body MRA because of long acquisition times and susceptibility to artefacts [94].
As opposed to the modalities mentioned above, contrast-enhanced whole-body MRA (WB-MRA) is both technically and practically feasible. The first section of this chapter outlines the technical aspects of WB-MRA, while the next section presents the previous published literature on WB-MRA.

Technical aspects of WB-MRA

WB-MRA definition

Despite the designation “whole-body” MRA not all arteries of the body are examined. The intracranial, coronary, distal mesenteric and upper limb arteries are generally not included in the WB-MRA examination. However, the intracranial arteries can easily be examined with unenhanced MRA (time-of-flight MRA). MRA of the coronary arteries requires ECG triggering and navigator techniques to compensate for cardiac and respiratory motion, respectively. Currently it is not feasible to include these techniques in the WB-MRA bolus-chase technique. Assessment of the mesenteric arteries with WB-MRA is currently limited to the most proximal parts of the celiac trunk, superior and inferior mesenteric arteries. The distal parts of the mesenteric arteries are typically located too far anteriorly to be included within the slab thickness used in WB-MRA. Exclusion of the upper limb arteries is of minor importance as atherosclerotic lesions in these vessels are rare.
In relation to the above listed limitations, the definition of WB-MRA used in this thesis is: A contrast-enhanced MRA method

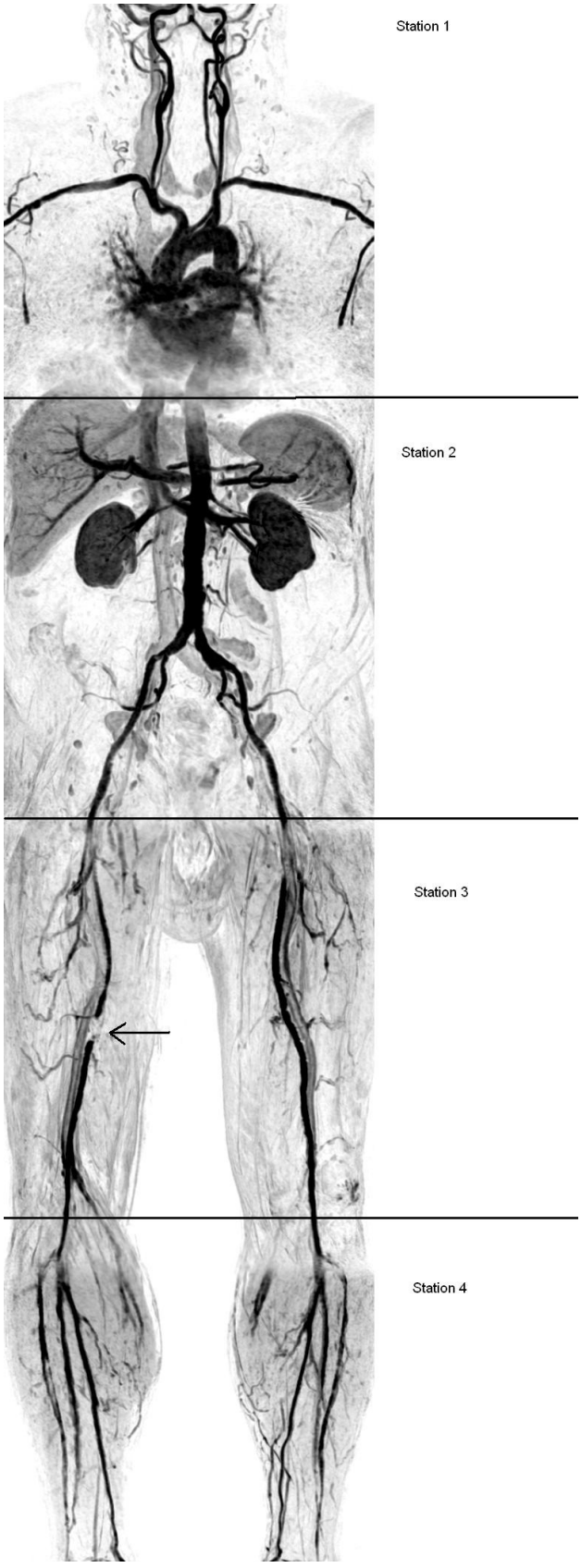

Figure 5. Example of WB-MRA.

encompassing the thoracic aorta with the supra-aortic branches, the abdominal aorta, renal arteries, iliac arteries, and upper and lower leg arteries (Figure 5).

Extending bolus-chase MRA to whole-body coverage

The basis of WB-MRA is the bolus-chase technique, in which image data are acquired in consecutive field of views (FOVs) following intravenous injection of a paramagnetic contrast agent bolus. Initially, bolus-chase MRA was used for peripheral MRA examining the arteries from the abdominal aorta to the ankles [45-47]. In these studies, data acquisition was performed in 3 consecutive FOVs (stations). An essential requirement in contrast-enhanced MRA is to synchronize acquisition of the central lines of k-space to the peak of the arterial contrast bolus. As this is to be respected in all stations of a bolus-chase examination, image acquisition needs to be fast, in order to achieve images suitable for diagnostic use. If the central lines of k-space are acquired too late, i.e. after the peak of the arterial contrast bolus, venous contamination occurs, rendering images of limited or non-diagnostic quality. Expanding the anatomical coverage of MRA from the peripheral arteries to the whole-body level, images must be acquired from additional stations to ensure coverage of the neck, thorax and upper abdomen. The exact number of stations in WB-MRA depends on the size of the magnet bore, and whether or not the feet are to be included in the imaging volume. So far, WB-MRA has been performed using 4 to 6 stations [95-97]. In the following, a 4-station WB-MRA approach will be assumed if nothing else is stated. Hence, WB-MRA requires rapid data acquisition synchronized to the arterial contrast bolus peak in 4 stations compared to 3 in peripheral MRA. Technical developments in MRI hardware with increased gradient strength and fast switching made WB-MRA feasible in 1999 [98]. Such high-performance gradient systems are solely used in high-field MRI systems (magnetic field strength ≥ 1.5 Tesla). Accordingly, WB-MRA requires a high-field MRI system. Typical gradient characteristics in a 1.5T MRI system are: Amplitude 30 mT/m, slew rate 150 mT/m/ms [99], whereas typical gradient characteristics in a 3T system are: Amplitude 45 mT/m, slew rate 200 mT/m/ms [100].

Moving table MRA

Besides fast data acquisition WB-MRA requires a MRI system capable of performing whole-body examinations. Therefore, movement of the patient table should be extensive to ensure that all parts of the patient's body can be focused within the bore of the magnet. In some MRI systems, such extended anatomical coverage, is acomplished by mounting a table-top extender to the existing patient table. To image the different stations in WB-MRA most modern MRI systems use automatic motor-driven and accurate patient table movement. However, manual table translation is also possible [101].

Magnetic field strength and receiver coils

A key factor in WB-MRA is the trade-off between spatial and temporal resolution. It is desirable to acquire images of high spatial resolution (i.e. small voxel size) however this cause the temporal resolution to decrease (i.e. longer acquisition times). Balance must be reached securing high enough spatial resolution to depict the arteries of interest, while temporal resolution is kept high enough to complete imaging in the arterial phase. Important

determinants for achievable spatial and temporal resolution are the MRI system's field strength and the coil configuration used for data acquisition. Increasing the magnetic field strength leads to an increase in the MRI signal. The signal-to-noise ratio (SNR), a measurement of the MRI signal, has a linear relation to the field strength. Thus, an increase from 1.5 to 3T results in a theoretical doubling of the SNR. In relation to spatial resolution SNR is an essential factor, as high SNR means that small voxels can be acquired. Different coil configurations can be used for reception of the MRI signal in WB-MRA. Most simply, images may be acquired with the MRI system's built-in body coil [95;97;99;102]. Alternatively, surface coils can be used, either as a fixed set of coils inside the magnet bore which the patient slides through during the examination [101], or as an extensive coil arrangement of phased array coils stretching from head to feet [103]. The closer the coil is to the imaged anatomy, the stronger is the received MRI signal. Hence, SNR is dependent of the coil used, with surface coils resulting in images of higher SNR than images acquired with the built-in body coil. Consequently, surface coils are used to improve the spatial resolution in WB-MRA.

Parallel imaging

Parallel imaging is an important technique related to use of surface coils [104;105]. With parallel imaging, data acquisition times can be decreased by a factor of 2 or more (the acceleration factor) while preserving the spatial resolution. Alternatively, spatial resolution can be increased with unaltered acquisition time. In parallel imaging, data are acquired simultaneously using two or more surface coils with different spatial sensitivities. Not all lines of k-space are filled, but the missing data are calculated from the spatial sensitivities of the surface coils. Parallel imaging has been established as a powerful method to adjust spatial and temporal resolutions in both WB-MRA [100;103;106-111] and MRI in general. However, one should be aware that SNR is reduced with a factor of √2 × acceleration factor when using parallel imaging. This is due to the incomplete k-space filling acquired with parallel imaging.

k-space filling in WB-MRA

Different methods of k-space filling are used in WB-MRA. Commonly, linear k-space filling is employed for the proximal stations, while centric k-space filling is used for the distal stations [100;106;112;113]. The use of linear k-space filling in the proximal stations ensures that peripheral k-space lines are acquired during rise of the arterial bolus, while the contrast-deciding central k-space lines are acquired during peak of the arterial contrast bolus (Figure 6A). In the distal stations of WB-MRA, the contrast bolus is peaking when image acquisition commence. Accordingly, central of k-space must be acquired first (centric k-space filling) and the peripheral lines last (Figure 6B). This ensures images containing good arterial contrast and minimal venous contamination.

WB-MRA scanning protocols

Earliest WB-MRA scan protocols acquired data from stations 1 to 4 in a consecutive manner (Figure 7A). With this approach late data acquisition of the lower leg station increase the risk of venous contamination [95;114]. In order to reduce distal venous contamination, hybrid WB-MRA scan protocols have been developed [100;106;115]. Using these protocols the examination is divided into two parts with separate contrast injections (Figure 7B). After injection of the first contrast bolus, imaging of the thoracic aorta, supra-aortic branches and lower leg is performed (stations 1 and 4). The second contrast bolus is injected 5-10 minutes later, and data are acquired from the remaining stations (2 and 3). The advantage of hybrid scan protocols is the reduction of lower leg venous contamination implied by the early acquisition of data from this region. Increased signal from the stationary tissues resulting from extracellular distribution of contrast agent from the first bolus injection is a potential drawback. However, this can be counteracted by using a slightly higher contrast dose for the second contrast injection compared to the first [100].

Current status of WB-MRA

Since the introduction in 1999 numerous WB-MRA studies have been published. This section gives an overview of the existing WB-MRA literature, dividing the published studies into 3 categories: 1) Feasibility and clinical studies, 2) Screening studies, and 3) WB-MRA utility studies. Details of the individual studies are shown in Table 3.

Feasibility and clinical studies

The feasibility of WB-MRA using body coil acquisition has been shown in 4 studies, all of which were performed at 1.5T [95;97;99;102]. More extensive research has been performed regarding 1.5T WB-MRA using surface coils for data acquisition. The aims of these studies have varied from feasibility studies [101;114;116-120] and contrast agent optimization studies [121;122] to a study on the clinical consequence of WB-MRA [123]. Different extracellular contrast agents have been used in the studies. Some were performed using the high-relaxivity contrast agent gadobenate dimeglumine [101;116;119;121;123]. However, none has been performed using a true blood-pool contrast agent.

Addition of parallel imaging techniques to 1.5T WB-MRA has been comprehensively investigated [96;106;107;109-112;124-129]. Some of the studies focused on feasibility of the method [106;107;109;111;112], whereas others compared WB-MRA using different contrast agents [96;126;128]. In the group of 1.5T WB-MRA studies performed using parallel imaging a wide range of contrast agents has been used, including 3 studies using the blood-pool agent gadofosveset trisodium [124;126;127].

WB-MRA has also been investigated at 3T: Two studies assessed the feasibility of applying highly accelerated parallel imaging to 3T WB-MRA [100;108], whereas another study explored different contrast injection schemes [113].

To date, most WB-MRA studies have been performed using a consecutive scan protocol. However, the number of studies using hybrid scan protocols is increasing (Table 3).

Screening studies

Due to its minimal invasive nature WB-MRA is technically suitable as a screening examination to assess the prevalence of atherosclerosis [130;131]. Accordingly, WB-MRA screening has been performed in healthy volunteers [103;132], as part of corporation-sponsored preventive health care for employees [133], and in a population study [134] (Table 3B). Despite, the technical feasibility of WB-MRA screening, a number of unresolved issues may limit wide acceptance of the method. This includes ethical problems related to false-positive MRI findings, as well as guidelines for handling unexpected serious disease diagnosed with the

Table 3. Whole-body MRA studies

A. Feasibility and clinical studies

Author	Year	B_0	Coil	Scan protocol	Sample size	Contrast agent(s)	Reference method	Sensitivity	Specificity
Ruehm et al. (97)	2001	1.5	Body	Consecutive	11	Gadobenate	DSA	0.91/0.94	0.93/0.90
Brennan et al. (95)	2005	1.5	Body	Consecutive	10	Gadobutrol	N/A	N/A	N/A
Hansen et al. (99)	2006	1.5	Body	Consecutive	33	Gadodiamide/ gadobenate	DSA	N/A	N/A
Ahlstrøm (102)	2004	1.5	Body	Consecutive	34	Gadobenate	N/A	N/A	N/A
Ruehm et al. (118)	2000	1.5	Surface	Consecutive	4	Gadopentate	N/A	N/A	N/A
Goyen et al. (101)	2002	1.5	Surface	Consecutive	13	Gadobenate	DSA	0.95	0.95
Goyen et al. (121)	2002	1.5	Surface	Consecutive	10	Gadobenate	N/A	N/A	N/A
Goyen et al. (116)	2003	1.5	Surface	Consecutive	102	Gadobenate	N/A	N/A	N/A
Goyen et al. (122)	2003	1.5	Surface	Consecutive	13	Gadobutrol	DSA	0.96	0.96
Herborn et al. (117)	2004	1.5	Surface	Consecutive	15	Gadobutrol	DSA	0.91	0.95
Herborn et al. (114)	2004	1.5	Surface	Consecutive	51	Gadobutrol	DSA	0.92/0.93	0.89/0.88
Ruehm et al. (119)	2004	1.5	Surface	Consecutive	180	Gadobenate	N/A	N/A	N/A
Goyen et al. (123)	2006	1.5	Surface	Consecutive	249	Gadobenate	N/A	N/A	N/A
Du et al. (115)	2007	1.5	Surface	Hybrid	10	Gadodiamide	N/A	N/A	N/A
Vogt et al. (120)	2008	1.5	Surface	Consecutive	10	Gadopentate	N/A	N/A	N/A
Quick et al. (111)	2004	1.5	PI	Consecutive	5	Gadobutrol	N/A	N/A	N/A
Tombach (129)	2004	1.5	PI	Consecutive	N/A	Gadobutrol	N/A	N/A	N/A
Fenchel et al. (106)	2005	1.5	PI	Hybrid	18	Gadopentate	DSA	0.98/0.96	0.96/0.95
Fenchel et al. (107)	2006	1.5	PI	Hybrid	34	Gadopentate	DSA	0.96	0.96
Lin et al. (109)	2006	1.5	PI	Consecutive	37	Gadopentate	N/A	N/A	N/A
Klessen et al. (125)	2006	1.5	PI	Hybrid	40	Gadopentate	N/A	N/A	N/A
Klessen et al. (126)	2007	1.5	PI	Consecutive	40	Gadopentate/ Gadofosveset	N/A	N/A	N/A
Nael et al. (112)	2007	1.5	PI	Hybrid	50	Gadodiamide	DSA	0.92/0.93	0.96/0.97
Napoli et al. (127)	2007	1.5	PI	Consecutive	20	Gadofosveset	CTA	0.92-1	0.95-1
Rasmus et al. (96)	2008	1.5	PI	Hybrid	10	Gadobenate/ gadoterate	N/A	N/A	N/A
Seeger et al. (128)	2008	1.5	PI	Hybrid	165	Gadobutrol/ gadopentate	DSA	0.93/0.94	0.95/0.94
Napoli et al. (110)	2009	1.5	PI	Consecutive	40	Gadobenate	DSA	0.84-1	0.88-1
Huppertz et al. (124)	2009	1.5	PI	Consecutive	50	Gadofosveset	DSA	0.68	0.89
Nael et al. (100)	2007	3	PI	Hybrid	14	Gadodiamide	N/A	N/A	N/A
Fenchel et al. (108)	2008	3	PI	Consecutive	23	Gadobutrol	N/A	N/A	N/A
Waugh et al. (113)	2009	3	PI	Hybrid	120	Gadoterate	N/A	N/A	N/A

B_0: magnetic field strength, N/A: no data available, PI: parallel imaging, DSA: digital subtraction angiography, CTA: computed tomography angiography

screening examination [130]. However, one recent study has defined a comprehensive system on how to deal with findings at whole-body MRI screening [132].

WB-MRA utility studies

WB-MRA utility studies (Table 3C) are to be separated from feasibility and screening studies, as it is not the WB-MRA method itself that is studied. Instead these studies use WB-MRA as an investigational tool, as outlined in this section.

Different atherosclerosis scoring systems based on WB-MRA findings have been developed [135;136]. Significant correlation between cardiovascular risk factors (Framingham score) and WB-MRA atherosclerosis score has been shown [135]. Likewise, WB-MRA atherosclerosis score is higher in diabetic patients compared to healthy controls [136]. The relation of systemic atherosclerosis to coronary atherosclerosis has been confirmed by relating the WB-MRA atherosclerosis score to findings at coronary catheterization [137], while other aspects of coronary hearth disease have been the focus of additional WB-MRA studies [138;139]. Correlation studies between biochemical markers, distribution of adipose tissue, arterial compliance, and endothelium-dependent vasodilation to WB-MRA atherosclerosis score have been performed [140-142]. Furthermore, the distribution of arterial stenoses at WB-MRA has been used to evaluate the accuracy of the ankle brachial index < 0.9 to detect PAD [143].

Patient acceptance of WB-MRA

In the process of introducing new imaging procedures most studies investigate feasibility and diagnostic performance. It is beyond doubt important that such studies are performed to ensure a high level of diagnostic confidence with the new procedures. However,

Table 3. (continued)

B. Screening studies

Author	Year	B_0	Coil	Scan protocol	Sample size	Study population	Contrast agent	Other MRI studies performed in same session
Kramer et al. (103)	2005	1.5	PI	Hybrid	50	Healthy volunteers	Gadopentate	Brain, heart, abdomen, lungs
Goehde et al. (133)	2005	1.5	Surface	Consecutive	298	Self-reported healty	Gadobutrol	Brain, heart, colon
Hansen et al. (134)	2007	1.5	Body	Consecutive	307	General population	Gadodiamide	None reported
Hegenscheid et al. (132)	2009	1.5	PI	Consecutive	200	General population	Gadobutrol	Brain, heart, abdomen, lungs, MRCP, spine

C. WB-MRA utility studies

Author	Year	B_0	Coil	Scan protocol	Sample size	Study population	Contrast agent	Aim of study
Ladd et al. (138)	2007	1.5	Surface	Consecutive	160	Patients with positive history of CHD	Gadobenate	Investigate prevalence of cerebrovascular disease and peripheral arterial disease in CHD patients
Ebeling Barbier et al. (139)	2007	1.5	Body	Consecutive	248	General population	Gadodiamide	Investigate the distribution of atherosclerosis in subjects with/without previous myocardial infarction
Hansen et al. (135)	2008	1.5	Body	Consecutive	306	General population	Gadodiamide	Develop WB-MRA atherosclerosis score, and relate this to cardiovascular risk factors
Wikström et al. (143)	2008	1.5	Body	Consecutive	306	General population	Gadodiamide	Validate ankle-brachial index <0.9 as diagnostic test for PAD, using WB-MRA as method of reference
Hansen et al. (140)	2009	1.5	Body	Consecutive	306	General population	Gadodiamide	Correlate body fat distribution and biochemical markers to WB-MRA atherosclerosis score
Lind et al. (141)	2009	1.5	Body	Consecutive	306	General population	Gadodiamide	Study relationship between arterial compliance, endothelium-dependent vasodilation and WB-MRA atherosclerosis score
Weckbach et al. (136)	2009	1.5/3	Surface	Hybrid	265	Diabetic patients and healthy controls	Gadodiamide	Compare prevalence of atherosclerosis in diabetic patients and healthy controls
Mirza et al. (142)	2009	1.5	Surface	Consecutive	306	General population	Gadodiamide	Correlate the hormone FGF-23 to WB-MRA atherosclerosis score
Lehrke et al. (137)	2009	1.5	Body	Hybrid	50	CHD patients	Gadopentate	Examine relation between systemic and coronary atherosclerosis

MRCP: Magnetic resonance cholangiopancretography, CHD: coronary hearth disease, PAD: peripheral arterial disease, FGF: fibroblast growth factor.

equally important patient acceptance of any imaging procedure needs to be examined. An imaging procedure with high diagnostic confidence but low patient acceptance will have limited clinical value, as patients are likely to refuse participating in the procedure. Few studies have investigated patient acceptance of peripheral, carotid and renal CE-MRA [144-147]. So far, no studies have investigated patient acceptance of WB-MRA.

2. SPECIFIC PART

This thesis is based on 4 original studies published in international peer-reviewed radiological journals. Research has been performed on the use of WB-MRA as a diagnostic tool in patients with PAD. Studies I-III focused on technical aspects of WB-MRA, while study IV focused on patient acceptance of WB-MRA.
The studies are described briefly below.

The inclusion and exclusion criteria were identical in studies I-IV. Patient eligible for inclusion were patients referred to DSA of the peripheral arteries due to PAD. Exclusion criteria were inability to participate in the imaging procedure (overweight exceeding the MRI system's limitations, inability to lie still due to rest pain), allergy to gadolinium-based contrast media, chronic renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, dialysis, claustrophobia, inability to obtain informed consent, and contraindications for MRI (pacemaker etc.)..

Study I

Whole-body MR angiography with body coil acquisition at 3T in patients with peripheral arterial disease using the contrast agent gadofosveset trisodium

Study aim

To investigate the feasibility of 3T WB-MRA using body coil acquisition and the blood-pool contrast agent gadofosveset trisodium in patients with PAD.

Design

Prospective and blinded validation study.

Material and methods

Eleven consecutive patients with PAD (9 severe claudication, 2 critical limb ischemia) scheduled for DSA of the peripheral arteries underwent WB-MRA 1-8 days before DSA. WB-MRA was performed in a 3T MRI system with body coil acquisition. A first-pass 4-station approach (station 1: neck/thorax, station 2: abdomen/pelvis, station 3: thigh, and station 4: calf) with total FOV 161 cm was used to examine the arteries from the neck to the ankles. Acquisition voxels were 1.23 x 1.60 x 1.70 mm (3.4 mm^3) in stations 1-3, and 1.27 x 1.57 x 1.50 mm (3 mm^3) in the calf. Zero interpolation to 0.73 mm isotropic resolution was applied to all stations. Gadofosveset trisodium was used at a dose of 0.03 mmol/kg body weight. Injection rate was 0.7 ml/s, followed by a 30 ml saline chaser injected similarly.

Two observers evaluated all WB-MRA examinations independently and blinded to results from DSA. Likewise, DSA was interpreted blinded to WB-MRA results. In the evaluation of WB-MRA, the arterial system was divided into 42 segments, each of which was graded as being of diagnostic or non-diagnostic quality. Furthermore, each segment was classified as insignificantly diseased (0-49% stenosis) or significantly diseased (≥ 50% stenosis or occlusion).Using DSA as reference method, sensitivities and specificities for detecting significant arterial stenoses with WB-MRA were calculated. Kappa statistics was used to assess interobserver agreement for the two observers interpreting WB-MRA, as well as intermodality agreement between WB-MRA and DSA.

Results

All examinations were successfully performed (an example is shown in Figure 5). No acute non-renal adverse reactions were observed or reported by any patients. The number of non-diagnostic arterial segments in WB-MRA were 17 (4%) and 28 (6%) for observers 1 and 2, respectively.

Overall sensitivities for detecting significant arterial stenoses with WB-MRA were 0.66 (95% Confidence interval: 0.49-0.79) and 0.68 (0.52-0.81) for the two observers. Specificities were 0.82 (0.74-0.88) and 0.93 (0.87-0.96), respectively. Sensitivities ranged from 0.77-0.91 in the iliac and femoral-popliteal tract, whereas lower sensitivities ranging from 0.20-0.50 were present below the knee. A similar trend was seen in intermodality agreement between WB-MRA and DSA, with κ-values ranging from 0.65-0.84 in the iliac and femoral-popliteal tract, and lower κ-values ranging from 0.09-0.22 below the knee.

Overall interobserver agreement in WB-MRA was good with κ = 0.60 (0.50-0.71). The range of κ-values were 0.57-0.84; best in the thoracic region (κ = 0.84), and worst in the distal part of the calf (κ = 0.57).

In the assessment of WB-MRA, observers 1 and 2 reported significant arterial pathologies outside the peripheral arteries in 5 (46%) and 4 patients (36%), respectively. The absolute numbers of detected pathologies were 14 and 10 for observers 1 and 2, respectively. Sites of arterial pathologies included the carotid, subclavian, and renal arteries, as well as the abdominal aorta (Figure 8).

Conclusion

WB-MRA at 3T with body coil acquisition and a blood-pool contrast agent proved feasible in a population of patients with PAD. The reproducibility in terms of interobserver agreement was good. Optimization of the WB-MRA method, especially below the knee, is needed to improve agreement with DSA.

Study II

Whole-body magnetic resonance angiography at 3T using a hybrid protocol in patients with peripheral arterial disease

Study aim

To determine the diagnostic performance of 3T WB-MRA using a hybrid protocol in comparison to a standard protocol in patients with PAD.

Design

Prospective and blinded comparative study.

Material and methods

Twenty-six consecutive patients referred to DSA due to PAD underwent WB-MRA. Of the patients 19 had claudication and 7 had critical limb ischemia. WB-MRA was performed in a 3T MRI system with body coil acquisition. The total FOV and distribution of the 4 WB-MRA stations were identical to what is described in study I. Acquisition voxels were 1.38 x 1.38 x 3.4 mm (6.5 mm^3) (stations 1-3) and 1.1 x 1.2 x 3 mm (4 mm^3) in the calf. Voxels were zero interpolated to 0.66 x 0.66 x 1.7 (stations 1-3) and 0.66 x 0.66 x 1.5 in the calf station.

Gadoterate meglumine, a non-specific extracellular contrast agent, was used at a dose of 0.3 mmol/kg body weight. Injection rate was 1 ml/s, followed by a saline chaser injected similarly. The first 13 patients were examined using a standard sequential WB-MRA protocol in which data from the thoracic/neck station was acquired first, followed by the abdominal/pelvic, thigh, and calf stations. A single contrast bolus was used in these examinations. The last 13 patients were examined with a hybrid WB-MRA protocol, which divides the examination in two parts with separate contrast injections. Following injection of the first contrast bolus (40% of total dose) data were acquired from the thoracic/neck station followed by the calf station. After waiting 5 minutes for the contrast agent to be distributed into the extracellular compartment, the second bolus (60% of total dose) was injected and data from the abdominal/pelvic and thigh stations were acquired. Figure 7 shows an outline of the two WB-MRA protocols.

Evaluation of WB-MRA and DSA images was done mutual independent and blinded. Two observers assessed WB-MRA images independent of each other. In the evaluation of WB-MRA, the arterial system was divided into 42 segments, each of which was graded as being of diagnostic or non-diagnostic quality. Furthermore, each segment was classified as insignificantly diseased (0-

49% stenosis) or significantly diseased (≥ 50% stenosis or occlusion).Using DSA as reference method, sensitivities and specificities for detecting significant arterial stenoses with WB-MRA were calculated. To assess the qualitative performance of the two WB-MRA protocols, image quality scores (4 - excellent, 3 - good, 2 - fair, and 1 - poor) and venous contamination scores (1 – none, 2 – some, 3 – pronounced) were obtained from each station in all WB-MRA examinations. The Mann-Whitney U-test was used to analyze the impact of the two WB-MRA protocols on the image quality and venous contamination scores. Kappa statistics was used to assess interobserver agreement in WB-MRA interpretation, and to assess intermodality agreement between WB-MRA and DSA.

Results

WB-MRA was successfully performed in 24/26 (92%) of patients (Figure 9). Two examinations (one standard protocol, one hybrid protocol) were technically flawed by mistiming between data acquisition and contrast arrival (Figure 10). No acute non-renal adverse reactions were observed or reported by any patients.The number of non-diagnostic arterial segments in WB-MRA were 103 (9.4%) and 108 (9.9%) for observers 1 and 2, respectively. Approximately two thirds (66-68%) of these were in examinations performed using the standard WB-MRA protocol.

Overall sensitivities for detecting significant arterial stenoses with standard protocol WB-MRA were 0.63 (95%CI: 0.51-0.73) and 0.66 (0.58-0.78) for observers 1 and 2, respectively. Correspondingly, sensitivities were 0.75 (0.64-0.84) and 0.70 (0.58-0.8) using the hybrid WB-MRA protocol. Specificities were high using both protocols, with values ranging from 0.93-0.96.

Intermodality agreement between WB-MRA and DSA was good for both the standard (κ-values 0.61-0.65) and the hybrid protocol (κ-values 0.69-0.70). Likewise, interobserver agreement was good: Standard protocol κ = 0.62 (0.44-0.67), and hybrid protocol κ = 0.70 (0.59-0.79).

In the quantitative assessment, image quality scores were similar in the three proximal WB-MRA stations, whereas the calf station had better image quality scores using the hybrid protocol compared to the standard WB-MRA protocol ($p<0.03$). Venous contamination scores were lower in the two distal WB-MRA stations when using the hybrid protocol (p-values <0.03).

Outside the peripheral arteries, WB-MRA showed significant arterial stenoses in 6 (23%) and 5 (19%) patients (according to observers 1 and 2). Sites of involvement included the carotid, subclavian, and renal arteries. Also, a stenosis was detected in the thoracic aorta of one patient.

Conclusion

3T WB-MRA shows better performance with a hybrid scan protocol compared to a standard sequential protocol in patients with PAD.

Study III

Whole-body magnetic resonance angiography with additional steady-state acquisition of the infra-genicular arteries in patients with peripheral arterial disease

Purpose

To investigate if addition of infra-genicular steady-state MRA (SS-MRA) to first-pass imaging improves diagnostic performance compared with first-pass imaging alone in WB-MRA of patients with PAD.

Design

Prospective and blinded comparative study.

Material and methods

Twenty consecutive patients with PAD (14 claudication, 6 critical limb ischemia) referred to DSA were included in the study. MRA was performed in a 3T system and consisted of first-pass (FP) WB-MRA with subsequent SS-MRA of the calf station. The total FOV and distribution of the 4 WB-MRA stations were identical to what is described in study I. The blood-pool contrast agent gadofosveset trisodium was used at a dose 0.03 mmol/kg body weight. Injection rates for the contrast agent and a 30 ml saline chaser were 0.7 ml/s.

FP WB-MRA was performed using body coil acquisition. Acquisition voxel sizes were 1.38 x 1.38 x 3.40 mm (station 1-3) (6.5 mm^3) and 1.1 x 1.2 x 3 mm (4 mm^3) (station 4). Voxels were zero interpolated to 0.66 x 0.66 x 1.7 (stations 1-3) and 0.66 x 0.66 x 1.5 in the calf station. SS-MRA of the calf station was performed 10 minutes after contrast injection. A phased array surface coil and parallel imaging with an acceleration factor of 3 was used to acquire 0.7 mm isotropic voxels (zero interpolated to 0.47 mm). Evaluation of MRA and DSA images was done mutual independent and blinded. Three separate reading sessions were performed for 1) FP WB-MRA, 2) SS-MRA of the calf, and 3) combined assessment of first-pass and SS-MRA of the calf. In the evaluation of FP WB-MRA, the arterial system was divided into 34 segments, each of which were graded as being of diagnostic or non-diagnostic quality. Furthermore, each segment was classified as insignificantly diseased (0-49% stenosis) or significantly diseased (≥ 50% stenosis or occlusion). Similarly, in the assessment of SS-MRA (session 2) and combined first-pass and steady-state MRA (reading session 3) the infra-genicular arterial segments were graded as diagnostic or non-diagnostic, as well as significantly or insignificantly diseased. Using DSA as reference method, sensitivities and specificities for detecting significant arterial stenoses with MRA were calculated. Kappa statistics was used to assess intermodality agreement between MRA and DSA.

Results

In FP WB-MRA 57 arterial segments (8%) were graded as non-diagnostic. Of these segments, 33 (58%) were due to venous contamination in the calf. With steady-state MRA 28 arterial segments (14% of infra-genicular segments) were non-diagnostic, nearly all due to signal-loss in the peripheral part of the FOV (Figure 11). Artery-vein separation was possible in all arterial segments assessed with SS-MRA.

Overall sensitivity and specificity for detecting significant arterial stenosis with FP WB-MRA were 0.70 (95%CI: 0.61-0.78) and 0.97 (0.94-0.99), respectively. Highest sensitivity was in the thigh (0.84), whereas lowest sensitivity was in the calf (0.42). Overall intermodality agreement between FP WB-MRA and DSA was good with κ = 0.72 (0.64-0.80). However, agreement was only moderate in the calf with κ = 0.49 (0.28-0.69).

In SS-MRA of the infra-genicular arteries sensitivity and specificity for detecting significant arterial stenosis were 0.47 (0.27-0.69) and 0.86 (0.78-0.91), respectively. The intermodality agreement between SS-MRA and DSA was fair with κ = 0.31 (0.12-0.51). Combined assessment of first-pass and SS-MRA raised infra-genicular sensitivity for significant arterial stenosis to 0.81 (0.60-0.93). Specificity was 0.94 (0.88-0.97). Intermodality agreement between combined first-pass/SS-MRA and DSA was good with κ = 0.71 (0.57-0.86).

Outside the peripheral arteries, WB-MRA showed significant arterial stenoses in 7 patients (35%). Sites of involvement were the carotid and subclavian arteries.

Conclusion

Addition of infra-genicular SS-MRA to FP WB-MRA improves the diagnostic performance in patients with PAD.

Study IV

Patient acceptance of whole-body MRA versus digital subtraction angiography

Purpose
To investigate patient acceptance of WB-MRA compared to DSA in patients with PAD.
Design
Prospective questionnaire study.
Material and methods
Seventy-nine consecutive patients suffering PAD (55 claudication, 24 critical limb ischemia) scheduled for lower extremity DSA were recruited to undergo WB-MRA. A 3T closed-bore MRI system with body coil acquisition was used. Dimensions of MR bore were length 157 cm and diameter 60 cm. Similar to studies I-III, a 4-station WB-MRA approach was used to examine the arteries from the neck to the ankles. Breath-holding was used during acquisition of stations 1 and 2, each breath hold lasted 23 seconds. Two different contrast agents were used for WB-MRA: Either 0.03 mmol/kg gadofosveset trisodium, or 0.3 mmol/kg gadoterate meglumine. DSA of the peripheral arteries was performed by experienced interventional radiologists. On average, 135 ml of 400 mg I/ml iomeprol was used as contrast agent. Puncture site compression lasted 10 minutes. If PTA or stent-placement had been performed compression lasted 20 minutes.
One week following completion of both WB-MRA and DSA an anonymized questionnaire was sent to the patients. Questions were asked about the overall discomfort of WB-MRA and DSA, as well as specific factors related to each imaging modality. In WB-MRA these factors were: confined feeling in MRI system, acoustic noise during examination, injection of gadolinium-based contrast agent, and breath-holding. In DSA the factors were: arterial puncture, injection of iodinated contrast agent, and post-procedural compression. A 5 point rank scale (1-no discomfort, 5-severe discomfort) was used to grade the discomfort. Furthermore, patients were asked about their willingness to have WB-MRA and DSA repeated if they needed another vascular examination in the future. Finally, patients were asked which of the two imaging procedure, if any, they preferred if the diagnostic accuracy of them were identical and the patient had to be examined again. Statistical analysis was performed with the Wilcoxon-Mann-Whitney U-test for variables in rank scales. Correlations were calculated using Spearman rank correlation. Fischer exact test was used for proportions and exact binomial test was used to assess patient preference of either WB-MRA or DSA. Following Bonferroni correction for multiple statistical tests $p<0.0028$ (0.05/18 tests) was established as level of significance.
Results
In 74 patients (94%), both WB-MRA and DSA were completed. Five patients did not undergo, or failed to complete, either WB-MRA or DSA. One patient was rescheduled for CTA instead of DSA, as WB-MRA revealed an abdominal aortic aneurysm (Figure 12). Two patients did not complete DSA because of discomfort, and two patients failed to complete WB-MRA because of claustrophobia. In the 77 completed WB-MRA examinations no acute non-renal adverse events occurred. In the 76 completed DSA procedures (33 with PTA/stent placement), one serious complication (hemorrhage) occurred.
The response rate to the questionnaire was 88% (69/78). WB-MRA was the preferred examination in 60% of patients, DSA was preferred by 17%, whereas 23% did not have any preference. Patient preferral of WB-MRA over DSA was statistically significant. Overall discomfort scores were lower in WB-MRA with mean score 1.7 (1.5-2) compared to a mean score of 2.1 (1.8-2.4) in DSA. This difference was not significant ($p = 0.06$).
In WB-MRA the overall discomfort scores were significantly correlated to feeling confined in the MRI scanner (correlation coefficient, $R=0.77$) and acoustic noise level during the scan ($R=0.43$). In DSA overall discomfort scores were significantly correlated to arterial puncture ($R=0.66$), injection of iodinated contrast agent ($R=0.65$) and post-procedural compression ($R=0.46$). Discomfort scores for injection of iodinated contrast agent at DSA (mean 2.1 [1.8-2.4]) were significantly higher than for injection of gadolinium-based contrast agents at WB-MRA (mean 1.5 [1.3-1.7]).
No significant difference was found in the number of patients willing to repeat WB-MRA and DSA (90% would repeat WB-MRA, 93% DSA). Overall discomfort scores were higher in the proportion of patients not willing to repeat WB-MRA and DSA, compared to patients willing to have the examination repeated. For WB-MRA the difference was significant ($p<0.001$).
No significant differences were present in WB-MRA discomfort scores reported by patients with and without prior MRI examination.
Conclusion
Patient acceptance of WB-MRA is superior to that of DSA in patients with PAD, with the majority of patients preferring WB-MRA.

3. DISCUSSION AND CONCLUSION

This Ph.D. study has investigated the use of WB-MRA as a diagnostic tool in patients with PAD. Technical feasibility and diagnostic accuracy of WB-MRA was already established in 2007 when this study was planned. Nevertheless, some specific aspects of WB-MRA were unexplored, which led to design of 4 studies (I-IV), each investigating new aspects of WB-MRA. Studies I-III were technically oriented, with study I focusing on feasibility of performing blood-pool agent enhanced 3T WB-MRA with body coil acquisition. Studies II and III investigated optimization of 3T WB-MRA with a hybrid scan technique and additional infra-genicular steady-state MRA, respectively. The last study (IV) focused on patient acceptance of WB-MRA.
First, study results are discussed. This is followed by a discussion of which precautionary measures were used in relation to reduce the risk of NSF development when using gadolinium-based contrast agents. Finally, study limitations and future perspectives for WB-MRA are addressed.

3.1 Discussion of study results

Overall diagnostic performance of WB-MRA

Overall sensitivities and specificities for detection of significant arterial stenoses with WB-MRA ranged from 0.63-0.75 and 0.82-0.97, respectively (study I-III).
These results must be compared to findings in previous studies. So far, 10 studies have reported overall WB-MRA sensitivities and specificities for detecting arterial stenoses (Table 3A) [97;101;106;107;112;114;117;122;124;128]. In these studies, overall sensitivities and specificities range from 0.68-0.98 and

0.89-0.97, respectively. The majority of the studies report sensitivities > 0.90.

Several factors, including method of acquisition, magnetic field strength, number of assessed arterial segments, and the used contrast agents may have contributed to the inferior sensitivity of the studies of this thesis compared with the previous published studies. First of all, the built-in body coil was used for data acquisition in the studies of this Ph.D. thesis. Body coil acquisition restrains the achievable SNR which is likely to have a negative effect on the diagnostic performance of WB-MRA. Previously, only a single study has reported sensitivity (0.91-0.94) for body coil acquisition WB-MRA [97]. However, an important limitation of that study was a low sample size of 6 patients. In the diagnostic oriented studies of this thesis (I-III) 57 PAD patients were investigated. It is possible that this larger sample size yields a more realistic picture of the diagnostic performance of body coil acquisition WB-MRA.

The use of surface coils improve SNR in MRI, and the majority of WB-MRA studies (9/10) reporting overall sensitivities have used this method of data acquisition [101;106;107;112;114;117;122;124;128]. In these 9 studies (n = 388 patients), sensitivities range from 0.68-0.98. Only one of the 9 studies reports sensitivity < 0.91 [124]. Thus, in general surface coil acquisition WB-MRA has excellent sensitivities for stenosis detection, exceeding the sensitivities reported in the body coil acquisition-based studies (I-III) of this thesis. Smaller voxels may be acquired when using surface coil acquisition compared to body coil acquisition because of the higher SNR with the former. In relation to detection of arterial stenosis voxel size plays an important role. Using an experimental setup it has been shown that reliable detection of arterial stenosis, requires at least 3 pixels to be present in-plane across the arterial lumen [148]. In the above mentioned WB-MRA study using body coil acquisition [97] voxel sizes were 10.9 mm^3, whereas voxel sizes ranged from 1.1 to 7.9 mm^3 in the studies performed with surface coil acquisition. In the studies of this thesis voxels sizes were 3-3.4 mm^3 (I) and 4-6.5 mm^3 (II, III) even though body coil acquisition was used. The small voxel sizes were chosen based on the theoretical consideration that the studies were performed at 3T, in contrast to the previous studies which were performed at 1.5T. When increasing the magnetic field strength from 1.5 to 3T, SNR increases with the same factor. Thus, it was expected that 3T body coil acquisition-based WB-MRA with voxel sizes similar to what have been used for 1.5T surface coil acquisition-based WB-MRA, could be performed, while maintaining high diagnostic accuracy. The overall sensitivities of 0.63-0.75 in studies I-III showed that this was not the case. Other factors besides voxel size need to be taken into consideration to explain the low sensitivities.

Factors associated with the high magnetic field strength at 3T (magnetic field inhomogeneity and susceptibility artefacts) may also have contributed to the low sensitivities. However, only in few arterial segments were these artefacts severe enough to render the segment of non-diagnostic quality. In study I susceptibility artefacts were the cause of 10/45 (22%) non-diagnostic arterial segments; in study II 22/210 (10%); and 3/57 (5%) in study III. Use of short echo times (1.3-1.4 ms) probably limited the occurrence and importance of these artefacts. Similar observations have been made by another group investigating 3T WB-MRA [100].

Another potential cause of low sensitivities is that assessment of the internal iliac and deep femoral arteries was included, whereas this has only been the case in 2 of the 10 previous studies reporting overall WB-MRA sensitivities. Of these 2 studies, one included the internal iliac artery [112], while the other included both the internal iliac and deep femoral artery in the diagnostic assessment [124].

Presumably, the used contrast agents may also have contributed to low sensitivities. The blood-pool contrast agent gadofosveset trisodium was used for first-pass WB-MRA in studies I and III. Overall sensitivities for stenosis detection in the studies were 0.66-0.70. Thus far, only two studies have reported sensitivities for gadofosveset-enhanced WB-MRA [124;127]. Similar to the results of this thesis, one of these studies reports sensitivity of 0.68 for gadofosveset-enhanced first-pass WB-MRA [124]. The agreement is not caused by similarities in method of acquisition or magnetic field strength, as data were acquired with surface coils and a 1.5T MRI system was used. The other study previously investigating gadofosveset-enhanced WB-MRA found sensitivities ranging from 0.92-1 in various regions of the body [127]. Nevertheless this study has an important methodological difference from above mentioned, as the reference method was CTA and not DSA. Accordingly, gadofosveset-enhanced WB-MRA seems to have low sensitivity for stenosis detection, when using the established gold standard (i.e. DSA) as reference method.

Gadofosveset has a relaxivity profile that favours use in 1.5T MRI systems [59]. Therefore it may be argued that using gadofosveset in a 3T MRI system is a non-optimal approach. However, it has been performed by another group without any problems relating to vessel enhancement [149]. Also speaking in favour of the used approach is that the WB-MRA sensitivities for arterial stenosis were similar in the 3T studies of this thesis (0.66-0.70) and in the previous 1.5T study (0.68) [124].

A triple dose of gadoterate (0.3 mmol/kg) was used in study II, yielding overall sensitivities ranging from 0.63-0.75. It is possible that this high dose may have resulted in some signal loss due to the T2*-effect related to high local concentrations of paramagnetic contrast agent. However, as mentioned above susceptibility artefacts were only a minor problem in the studies of this thesis, so the importance of this artefact is presumably little. The unusual high dose was chosen in order to maximize the intravascular signal as the body coil was used for data acquisition. No previous studies have reported sensitivities for gadoterate-enhanced WB-MRA. As gadoterate is a non-specific extracellular contrast agent, comparison can be made to studies that have performed WB-MRA using other non-specific extracellular agents (gadopentate, gadodiamide, gadobutrol) [106;107;112;114;117;122]. These studies reports sensitivities ranging from 0.91-0.98. All studies were performed using surface coils and in 1.5T MRI systems. Contrast doses ranged from 0.15-0.25 mmol/kg. Most likely, the lower sensitivity for gadoterate-enhanced 3T WB-MRA (II) in this thesis was caused by the use of body coil acquisition.

The excellent specificities (>0.82 in studies I-III) for detecting significant arterial stenoses demonstrate that few false-positive stenoses were detected. These specificities are comparable to what has previously been reported in WB-MRA studies (Table 3A).

Another way of assessing the diagnostic performance of WB-MRA was to calculate intermodality agreement between WB-MRA and DSA. Good to moderate agreement was found in studies I-III (overall κ-values 0.44-0.72). Up till now, intermodality agreement between WB-MRA and DSA has only been reported in a single study [128], in which agreement was excellent (κ = 0.83). Excellent intermodality agreement to DSA was not achieved in this thesis, most likely caused by the same factors as mentioned above in the discussion of low sensitivity for arterial stenosis detection.

Optimization of the WB-MRA technique

A standard sequential WB-MRA protocol was used in studies I-III. Study I showed the basic feasibility of the method, while studies II and III used the standard sequential protocol as reference for assessment of two different optimization strategies. For gadofosveset-enhanced WB-MRA optimization of the technique was investigated using infra-genicular SS-MRA (III). Optimization of gadoterate-enhanced WB-MRA was investigated by means of a hybrid examination protocol (II).
The following section discuss the optimization strategy used for gadofosveset-enhanced WB-MRA.
Regional analysis of WB-MRA sensitivities in the feasibility study (I) showed low sensitivities (0.20-0.50) and intermodality agreement (□-values 0.09-0.22) below the knee. Thus optimization was warranted for the distal WB-MRA station (Figure 5). As the contrast agent of interest was a blood-pool agent the obvious strategy was to add infra-genicular SS-MRA to the first-pass WB-MRA protocol (III). This proved to be a robust way of improving stenosis detection in the lower leg region. Combined assessment of first-pass imaging and SS-MRA improved sensitivity to 0.81 and intermodality agreement to DSA (□ = 0.71). There was no benefit in performing isolated assessment of SS-MRA images, as the results obtained were similar to the results from first-pass imaging. This observation is consistant with the recommended diagnostic approach when assessing gadofosveset-enhanced images, i.e. combined assessment of first-pass and steady-state images [77]. Previous studies have investigated combined first-pass/steady-state MRA using gadofosveset for both WB-MRA [124] and various other MRA applications [81-84;150-152]. The conclusion of the studies is similar to the conclusion of this thesis, i.e. it is beneficial to perform combined first-pass/steady-state imaging.
The following section discuss the optimization strategy used for gadoterate-enhanced WB-MRA (II). It was expected that a standard sequential approach would result in low sensitivity, as was seen in gadofosveset-enhanced WB-MRA (I). Thus, a comparative study between standard sequential protocol and hybrid protocol gadoterate-enhanced WB-MRA was performed, to investigate if the hybrid examination technique led to improved diagnostic performance of WB-MRA (II). The hybrid scan protocol was chosen as optimization method based on previous studies demonstrating the capability of this method in improving both peripheral CE-MRA [153-156] and WB-MRA [100;106;107;112]. Nevertheless, none of the previous WB-MRA studies had been performed at 3T with use of body coil acquisition. Looking at the results of study II, it is clear that the hybrid protocol failed to markedly improve diagnostic performance of WB-MRA (overall sensitivities 0.63/0.66 with the standard protocol vs. 0.70/0.75 with the hybrid protocol). Likewise, intermodality agreement to DSA was similar in WB-MRA performed with the two protocols (□-values 0.61/0.65 and 0.69/0.70 for standard and hybrid protocol WB-MRA, respectively). The lack of improvement is probably related to use of body coil acquisition in both study arms. Despite unaltered diagnostic, performance the hybrid approach led to statistical significant improvements of distal image quality and venous contamination scores. This suggests that the hybrid technique did alter the bolus dynamics in WB-MRA.
The hybrid examination technique is not a possible solution to improve examination quality in gadofosveset-enhanced WB-MRA. The blood-pool properties of this contrast agent make it unsuitable for a split bolus injection, because residual contrast in the circulation coming from the first injection would interfere negatively with first-pass imaging of the second bolus.
Although both an extracellular and a blood-pool contrast agent were used for WB-MRA in this thesis, it was not a study aim to perform a direct comparison of these contrast agents. However, if the comparison is made between WB-MRA studies performed in similar manner (i.e. standard consecutive scan protocol) with either the blood-pool agent gadofosveset (I and III) or the extracellular agent gadoterate (II), it is evident that the diagnostic performance of the studies was similar. Overall sensitivitieis in gadofosveset stuides ranged from 0.66-0.70 (I and III), whereas the values of 0.63-0.66 were present in the gadoterate-based study (II). Likewise, overall intermodality agreement to DSA ranged from κ = 0.44 to 0.72 in the gadofosveset studies, and overlapping values of κ = 0.61 to 0.65 were present in the gadoterate study. A study presenting a direct comparison between gadofosveset- and gadoterate-enhanced WB-MRA is still to be performed. One previous study has performed a comparative analysis of WB-MRA performed with gadofosveset and another extracellular contrast agent (gadopentate) [126]. The conclusion of the study was that gadofosveset- and gadopentate-enhanced WB-MRA had similar performance.
Based on the results of this thesis and the above mentioned study, it seems that gadofosveset-enhanced WB-MRA yield similar results to WB-MRA performed using non-specific extracellular contrast agents.

Interobserver agreement

Analysis of interobserver agreement is an important aspect in evaluation of new diagnostic tests [157]. If interobserver agreement is poor, it is likely to cause inconsistency in clinical practise. Thus, it is important to assess interobserver agreement of new diagnostic tests, as a supplement to the evaluation of the diagnostic accuracy in comparison to a reference method.
In this thesis, interobserver agreement for characterization of stenoses with WB-MRA was calculated in two studies (I and II). Although good results (overall κ-range 0.60-0.70) were achieved, the majority of WB-MRA-studies report excellent agreement with κ-values ranging from 0.82-0.94 [97;100;103;106;108;112;114;132;134]. However, one WB-MRA study has reported interobserver agreement similar to the results of this thesis (κ = 0.63) [127]. The cause of low interobserver agreement is probably multi-factorial. Beyond doubt, the experience of observers in interpreting MRA is an important factor. One observer had 3 years of experience in MRA, while the other observer had 10 years of experience (I and II). Compared to other WB-MRA studies providing information of the observer's experience [100;103;108;112;132] 3 years is a rather low level of experience, which might have had negative influence on the interobserver agreement in this thesis. Most of the previous studies investigating interobserver agreement in WB-MRA have been performed in MRI systems using surface coil acquisition, not body coil acquisition. Examinations performed with surface coils yield better image quality and presumably make interpretation easier. However, different acquisition method does not explain all the observed difference, as body coil acquisition WB-MRA may be associated with excellent interobserver agreement as shown in one study (κ = 0.83) [134]. Although most MR-angiographic studies report excellent interobserver agreement it is not a general rule, as two recent studies of lower extremity CE-MRA reported κ-values of 0.66 and 0.64, even with experienced observers and state-of-the-art MRI equipment [65;158].

Regional analysis of interobserver agreement was performed (I). As an indication of image quality being of importance for the interobserver agreement, lowest agreement was present in the lower leg region (κ-range 0.57-0.58) where poor image quality is most likely to occur in WB-MRA because of the small vessel size and difficult bolus-timing. On the contrary, in the thorax and neck regions, where bolus-timing is optimal in WB-MRA and the arteries are of greater size, interobserver agreement was better (κ range 0.79-0.84). A difference was observed between the proximal (κ = 0.59) and distal femoral regions (κ = 0.81), most likely caused by difficult assessment of the deep femoral artery in the proximal region.
Optimization of WB-MRA with a hybrid scan protocol was investigated (II). Image quality in the lower leg region was statistically significant improved when using the hybrid scan protocol as compared to a standard sequential protocol. At the same time, overall κ increased from 0.62 with the standard protocol to 0.70 with the hybrid scan protocol. This result supports, that image quality is a determinant for interobserver agreement.

Detection of systemic disease

The systemic nature of atherosclerosis has been the driving force behind development of WB-MRA as a diagnostic method in patients with PAD. WB-MRA revealed unexpected concomitant arterial stenoses in 28-32% (observer dependent) of the examined PAD patients (I-III). The results are similar to previous studies that found unexpected arterial stenoses in 19-36% of PAD patients investigated with WB-MRA [109;114;116;123]. Confirmatory imaging of unexpected arterial stenoses outside the peripheral arteries was not performed in the studies of this thesis. In previous studies, confirmatory imaging (duplex Doppler US, single-station CE-MRA, DSA, or CTA) have been performed for all [114] or a part [109;116;123] of the unexpected findings. When performed, good agreement between WB-MRA findings and confirmatory imaging was shown.
In both the studies of thesis, as well as in previous studies, the most frequent locations of unexpected arterial stenoses in PAD patients were the internal carotid and renal arteries. One unexpected abdominal aortic aneurysm was detected with WB-MRA (IV) (Figure 12). During data-analysis distribution of concomitant stenoses was not determined in study IV, as focus in this study was on assessment of patient acceptance of WB-MRA. However, as unexpected aneurysms or tumours would lead to further diagnostic assessment, all examinations were evaluated with focus on these entities.
It was not surprising to find a patient with an aortic aneurysm in the studied group of PAD patients. Co-morbidity between PAD and aortic aneurysms has been shown in previous WB-MRA studies where 2-4% of PAD patients also had an aneurysm [109;114;116;123].

Patient acceptance of WB-MRA

Patient acceptance of WB-MRA in comparison to DSA was assessed in PAD patients (IV).
The main finding of this study was a statistically significant proportion of patients preferring WB-MRA to DSA as diagnostic test if they were to be examined again (60 vs. 17%). This result is similar to a study investigating patient acceptance of carotid CE-MRA in comparison to DSA [144].
Most likely this difference is caused by the inherent difference of the two imaging modalities, DSA being more invasive than WB-MRA. In the light of the greater arterial coverage with WB-MRA compared to DSA, the result of patients preferring WB-MRA further points in the direction of WB-MRA be an advantageous imaging procedure in PAD patients.
Another important finding was that the overall discomfort experienced in WB-MRA was lower than in DSA, although the difference was not statistically significant. Speaking in favour of the validity of the result is that a similar result was reported in a comparative study of CE-MRA and DSA of the aorto-iliac arteries [147]. Thus it is important to realize that WB-MRA, although being a minimal invasive procedure, is not without discomfort for the patient.
Factors causing discomfort in WB-MRA were shown to be confined feeling in the scanner as well as acoustic noise during the scan. Not surprisingly, factors causing discomfort in DSA were arterial puncture, injection of iodinated contrast agent, and post-procedural compression.
Logically, it can be expected that patients not willing to repeat WB-MRA or DSA are likely to be the ones who report highest levels of procedure-related discomfort. This assumption was confirmed in the study.
Relating to the different contrast agents used for WB-MRA and DSA, significantly higher levels of discomfort were related to administration of iodinated agents in DSA, as compared to gadolinium-based agents in WB-MRA. Different contrast agent chemistry, as well as different ways of administration might explain this result. Previous studies investigating the same contrast agents as in this thesis, have found similar results [78;159;160].

3.2 Precautionary measures related to use of gadolinium-based contrast agents

The gadolinium-based contrast agents gadofosveset and gadoterate were used to perform WB-MRA in this Ph.D. study. In relation to risk of developing NSF, gadofosveset is considered to be a medium-risk contrast agent, whereas gadoterate is a low-risk agent [161]. According to the current guidelines issued by the European Society of Urogenital Radiology (ESUR) it is not mandatory to estimate GFR before using gadofosveset or gadoterate [162]. However, as MRA was performed in an experimental setting we did not want to expose any patients with severe renal impairment to gadolinium-based contrast media. Thus, eGFR was determined in all patients prior to MRI, and patients with eGFR < 30 ml/min/1.73 m^2 based on the MDRD equation (modification of diet in renal disease) [163] were excluded from the study. Furthermore, the ESUR guidelines state that patients on dialysis are at high risk of developing NSF. Accordingly, dialysis was an exclusion criterion in this study. Total doses of gadolinium-based contrast agents were kept within the maximum limit of 0.3 mmol/kg body weight defined by ESUR [162].
Systematic follow-up in relation to late adverse reactions was not performed. However, when including patients into the study, contact information to the study group was provided, securing that patients could report any late adverse reactions or other unforeseen events. So far, no patients have reported late, or very late, adverse events.

3.3 Study limitations

There are several limitations to the studies in this Ph.D. thesis. First, limitations related to the study design will be addressed. Thereafter technical limitations will be discussed.

Limitations related to study design

It is a limitation that con-comitant arterial stenoses detected with WB-MRA in areas not investigated with DSA were not confirmed using other imaging modalities (single-station CE MRA, CTA, duplex Doppler US). Systematic follow-up of such findings was not performed, because in Denmark asymptomatic stenoses of the carotid and subclavian artery are not treated surgically or endovascularly, nor are renal artery stenoses without renal impairment or hypertension. However, it was decided that findings of aortic aneurysm or unexpected tumours with WB-MRA should lead to further investigation with other imaging modalities. In practise, 1 patient (study IV) was shown to have an aortic aneurysm at WB-MRA, this was confirmed by CTA. No tumours were detected in any patients. In an optimal design all findings at WB-MRA, both positive and negative, should be confirmed with other imaging modalities. In this thesis WB-MRA specificities were high, whereas sensitivities were low. This translates into few false-positive stenoses and many false-negative stenoses in the WB-MRA examinations. In this point of view, confirmatory imaging of apparently normal arterial segments seems warranted.
It was not investigated whether or not appropriate treatment plans could be made based on the WB-MR-angiograms. This need to be examined before WB-MRA is used to guide treatment of PAD patients.
DSA was performed as part of the management of patients suffering symptomatic PAD, and served as reference method in the studies of this thesis. However, DSA is not a method without limitations. Some run-off vessels may be patent even though they fail to show at DSA [33;40;41]. Like other imaging modalities DSA is also subject to inter- and intraobserver variation [29]. As DSA depicts contrast in the arterial lumen (luminography) it fails to show early stages of atherosclerosis, as these lesions are contained inside the arterial wall due to expansive remodelling [164]. CE-MRA (including WB-MRA) is also a luminographic examination. Hence, neither DSA nor CE-MRA will be capable of depicting all atherosclerotic lesions.
Low sample sizes were used in studies I-III based on two factors: 1) sample sizes in previous WB-MRA studies, and 2) practical considerations on how many patients it would be possible to include into the study. Many of the initial technically oriented WB-MRA studies [95;97;101;106;111;117;118;121;122;127] had sample sizes similar to the ones used in this thesis. The statistical power of the performed studies would undoubtfully have been greater if larger sample sizes had been used. The sample size of study IV was set to be the number of patients examined during the defined study period.
The design of study II must be commented. A better study design to investigate different diagnostic performance of standard vs. hybrid protocol WB-MRA would be a cross-over design. However, as it was a priority to keep the total dose of gadolinium-based contrast agent < 0.3 mmol/kg it was only possible to examine each patient once. This led to the study being performed as a comparison between two identical sized groups of patients. Randomization between the two WB-MRA protocols might have increased the scientific quality of the study, but was not performed due to practical reasons making it preferable to examine the first group of patients using one WB-MRA protocol, and the next group with the other protocol.
It may be considered a limitation that a quantitative questionnaire-based study design was used to assess patient acceptance of WB-MRA (IV). Alternatively, a qualitative interview-based study could have been performed. This was not chosen because it would be difficult to analyze data from such a study, also it would be demanding to perform standardized interviews of 79 patients. To compensate for the quantitative study design, patients could write comments at the end of the questionnaire if they felt the need for it.
Another limitation of study IV relates to use of anonymized questionnaires. This made it impossible to investigate differences between WB-MRA performed with gadoterate and gadofosveset. Also, differences between DSA with and without endovascular treatment (PTA/stent placement) could not be investigated. Despite these limitations, the anonymized study design was chosen, as this has proven an effective means of increasing response rates in postal questionnaire-based studies [165;166].

Technical limitations

An important technical limitation of the first-pass WB-MRA technique is that the coronary arteries are not depicted. Due to the well-known co-morbidity between atherosclerosis in the peripheral and coronary arteries [10] it is highly relevant to image these arteries in PAD patients. Currently, it is not technically feasible to include coronary MRA in the first-pass WB-MRA examination. However, cardiac MRI (cine and delayed enhancement) may be performed as a supplementary examination to first-pass WB-MRA, as have been already been done [103;107;120;133;136;138]. Coronary MRA has not yet been performed as a supplement to WB-MRA, probably because the method still needs some optimization to inprove sensitivity and specificity [167].
Sub-systolic venous compression of the thigh was not used, even though it has proven to be an effective means of reducing peripheral venous contamination in WB-MRA [117]. It was not applied as the department did not dispose over the equipment required for the technique when the study began.
Another limitation is that the total FOV in WB-MRA was 161 cm. This did not allow examination of the pedal arteries in tall patients. A solution to this problem would be to add an extra station to the examination. However, this would increase scan time, making timing between arterial bolus and data acquisition even more difficult in the distal stations.
The lack of parallel imaging in the studies of this thesis (excluding SS-MRA of the infra-genicular arteries in study III) might be considered a limitation. Nevertheless this is not the case, as focus was on WB-MRA performed with body coil acquisition. Technically, this precludes parallel imaging because this technique relies on data acquisition being performed with surface coils.
Despite using the blood-pool agent gadofosveset for first-pass WB-MRA (I,III) steady-state acquisitions were only performed in one study and in one anatomical region (i.e. infra-genicular SS-MRA in study III). SS-MRA was not performed in study I as focus was on feasibility of first-pass WB-MRA using gadofosveset at 3T with body coil acquisition. In study III, SS-MRA was solely performed in one anatomical region, as extended coverage with SS-MRA would lead to an unacceptable increase in examination time. With the technique used in this study, completion of SS-MRA of one station took approximately 10 minutes, caused by need to reposition the phased array surface coil, acquire new

scout images, and long acquisition time (approximately 4 minutes) of the steady-state images. Also, respiratory motion curtails use of long acquisition for assessment of arteries in the thorax and upper abdomen. However, one recent study has successfully performed WB-MRA with steady-state acquisition in all 4 stations [124]. This was accomplished by means of a VIBE (volumetric interpolated breath-hold examination) sequence.
The potential draw-backs of using the contrast agent gadofosveset in a 3T MRI system, as well as a triple dose of gadoterate have already been discussed (Section 3.1).
Finally, it should be noted that no patients with previous arterial reconstructions were examined in the studies of this thesis. With the increasing application of metal stents in management of arterial disease, susceptibility artefacts may become an important problem in future MRA. Also, some stents prompt a contraindication for future MRI.

3.4 Conclusions

The main conclusions of this Ph.D. study are:

- 3T WB-MRA is feasible using body coil acquisition and the blood-pool contrast agent gadofosveset trisodium in a population of patients with PAD.
- Hybrid scan technique improves performance of 3T WB-MRA by means of superior image quality and reduced venous contamination compared to a standard sequential protocol.
- Addition of infra-genicular steady-state MRA to first-pass WB-MRA improves the diagnostic performance in patients with PAD.
- Patient acceptance of WB-MRA is superior to that of DSA, in patients with PAD.

3. 5 Future directions in WB-MRA

The results of this thesis provide valuable information that is useful for further development of the WB-MRA method.
From a clinical point of view, WB-MRA sensitivities for arterial stenosis detection were unacceptably low in the studies of this thesis, most likely caused by limitations related to use of body coil acquisition. In the light of excellent sensitivities for arterial stenosis detection in WB-MRA studies using surface coil acquisition and related advantages of parallel imaging, it seems that future WB-MRA should be performed using surface coils, whenever available.
In this thesis, best diagnostic results were obtained using combined first-pass and steady-state gadofosveset-enhanced MRA. Encouraging results of another gadofosveset-enhanced WB-MRA study [124] points towards this contrast agent being used in future WB-MRA studies. However in Europe, gadofosveset has been withdrawn from clinical use in 2009 (presumably due to non-profitable business results, as there have not been safety problems with gadofosveset). At the same time the contrast agent has been approved in the United States and is now in clinical use. If new blood-pool agents at some point in time become available in Europe, the positive results of SS-MRA in this thesis will support their clinical use.
In this thesis, use of a hybrid examination protocol proved effective in reducing peripheral venous contamination in WB-MRA performed with an extracellular contrast agent. Consistent with other studies investigating hybrid protocol WB-MRA [96;100;103;106;107;112;113;115;128;136;137] this points in direction of wide use of the technique for WB-MRA in the future. Recent WB-MRA studies show tendency towards imaging at 3T [100;108;113;136;168] as was done in this thesis. An advantage of imaging at 3T is that lower amounts of extracellular contrast agent can be used compared to imaging at 1.5T, due to longer T1-values at the higher field strength. A study has shown improved examination quality with reduced dose of gadoterate in surface coil acquisition-based 3T WB-MRA [113]. In extension of this thesis, the influence of gadoterate dose on examination quality in body coil acquisition-based 3T WB-MRA will be investigated. Due to the association between administration of some gadolinium-based contrast agents and development of NSF there is a general interest in reducing dose of gadolinium-based contrast agents. Likewise, interest in non-contrast MRA is growing, and the first investigation of non-contrast WB-MRA was published in early 2010 [94]. It is very likely that further non-contrast WB-MRA studies will follow.
As the investigation of patient acceptance of WB-MRA in this thesis showed that the examination is not without discomfort, this factor is to be remembered when performing WB-MRA. An important factor causing discomfort was the confined feeling inside the MRI system. If future studies are performed using surface coils, it is possible that patient discomfort due to confinement will increase.

Indications for WB-MRA

The strength of WB-MRA is the ability to detect the systemic distribution of atherosclerotic lesions. Hence, potential indications for WB-MRA are:

- PAD
- Ischemic heart disease
- Renovascular hypertension
- Carotid artery stenosis

However, implementation of WB-MRA as a routine diagnostic tool requires prior definition of how to handle all WB-MRA findings, both expected and unexpected. This is a complicated subject and a servere limitation hindering routine clinical use of WB-MRA. Most likely, future use of WB-MRA will mainly be as part of research, either investigating the MRA method itself, or utilising the potential of WB-MRA as a tool to grade the atherosclerotic burden of the examined subjects. In case of suspected vasculitis clinical use of WB-MRA may be advantageous.

SUMMARY

Whole-body magnetic resonance angiography in patients with peripheral arterial disease

Introduction: Ph.D. project performed at Copenhagen University Hospital Herlev in the period 2007-2010.
Purpose: To investigate whole-body magnetic resonance angiography (WB-MRA) as diagnostic method in patients with peripheral arterial disease (PAD).
Background: Due to the systemic nature of atherosclerosis patients with PAD often have con-comitant arterial stenoses outside the peripheral arteries. In this respect, it seems desirable to perform whole-body angiography. Currently, WB-MRA is the only imaging modality allowing assessment of the total arterial system

(excluding the coronary arteries) in one examination without limiting factors like invasiveness or ionizing radiation.

Materials and Methods: Four studies were performed (I-IV). Study I investigated the feasibility of performing WB-MRA in a 3T MRI system using body coil acquisition and a blood-pool contrast agent. Study II investigated the impact of a hybrid scan technique on the performance of 3T WB-MRA using body coil acquisition and an extracellular contrast agent. The aim of study III was to investigate if addition of infra-genicular steady-state MRA (SS-MRA) to first-pass imaging alone improves diagnostic performance in 3T WB-MRA. The last study (IV) was a questionnaire-based investigation of patient acceptance of WB-MRA compared to digital subtraction angiography (DSA). In all studies the inclusion criterium was referral to DSA due to PAD. Exclusion criteria were overweight exceeding the MRI system's limitations, inability to lie still due to rest pain, allergy to gadolinium-based contrast media, chronic renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, dialysis, inability to obtain informed consent, and contraindications for MRI (pacemaker, claustrophobia etc.). In total, 57 patients were investigated in the technical oriented studies (I: n = 11, II: n = 26, and III: n = 20). Seventy-nine patients were included in study IV. DSA served as method of reference for calculation of WB-MRA sensitivity and specificity for detection of significant (>50% luminal narrowing or occlusion) arterial stenoses.

Results: The feasibility of body coil acquisition 3T WB-MRA using the blood-pool contrast agent gadofosveset trisodium was shown in study I. Overall sensitivity and specificity for detection of significant arterial stenoses with WB-MRA were 0.66/0.68 (observer 1/2) and 0.82/0.93, respectively. The low sensitivity was caused by poor sensitivity in the lower leg region.

Study II showed that a hybrid scan protocol improves the performance of body coil acquisition 3T WB-MRA performed with the extracellular contrast agent gadoterate. Compared to a standard sequential WB-MRA protocol, the hybrid protocol resulted in statistically significant higher image quality scores, as well as lower venous contamination scores in the lower leg region. Overall sensitivities for detection of significant stenoses were 0.63/0.66 using the standard sequential WB-MRA protocol, and 0.75/0.70 using the hybrid WB-MRA protocol.

Study III showed that addition of infra-genicular SS-MRA to first-pass imaging is an effective means of improving gadofosveset-enhanced WB-MRA. Combined analysis of steady-state and first-pass images showed infra-genicular sensitivitiy of 0.81, compared to 0.42 for first-pass imaging alone.

In general, specificities for characterization of arterial stenoses with WB-MRA were high, with overall values ranging from 0.82 to 0.97 in studies I-III.

Study IV showed that patient acceptance of WB-MRA was superior to that of DSA in patients with PAD, with the majority of patients (60%) preferring WB-MRA.

Con-comitant arterial stenoses outside the peripheral arteries were found in 28-32% of the investigated PAD patients.

Conclusion: Body coil acquisition 3T WB-MRA is technically feasible using both a blood-pool and a standard non-specific extracellular contrast agent. However, the method is limited by low sensitivities for arterial stenoses. Hybrid examination technique and use of steady-state MRA are methods of improving WB-MRA.

Patient acceptance of WB-MRA is superior to that of DSA.

The rationale of using WB-MRA as diagnostic method in PAD patients is shown by the high prevalence of con-comitant arterial stenosis outside the peripheral arteries.

ABBREVIATIONS

CE-MRA	contrast-enhanced MRA
CHD	coronary hearth disease
CTA	computed tomography a giography
CVD	cardiovascular disease
DSA	digital subtraction angiography
EC	extracellular
eGFR	estimated glomerular filtration rate
ECG	electrocardiography
ESUR	European Society of Urogental Radiology
FOV	field of view
FP-MRA	first-pass MRA
Gd-CA	gadolinium-based contrast agents
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRI-CA	magnetic resonance imaging contrast agents
PAD	peripheral arterial disease
PC-MRA	Phase-contrast MRA
PTA	percutaneous transluminal angioplasty
SNR	signal-to-noise ratio
SPIO	superparamagnetic iron oxide particles
SS-MRA	steady-state MRA
T	tesla
TOF-MRA	time-of-flight MRA
US	ultrasound
USPIO	ultrasmall superparamagnetic iron oxide particles
VIBE	volumetric interpolated breath-hold examination

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