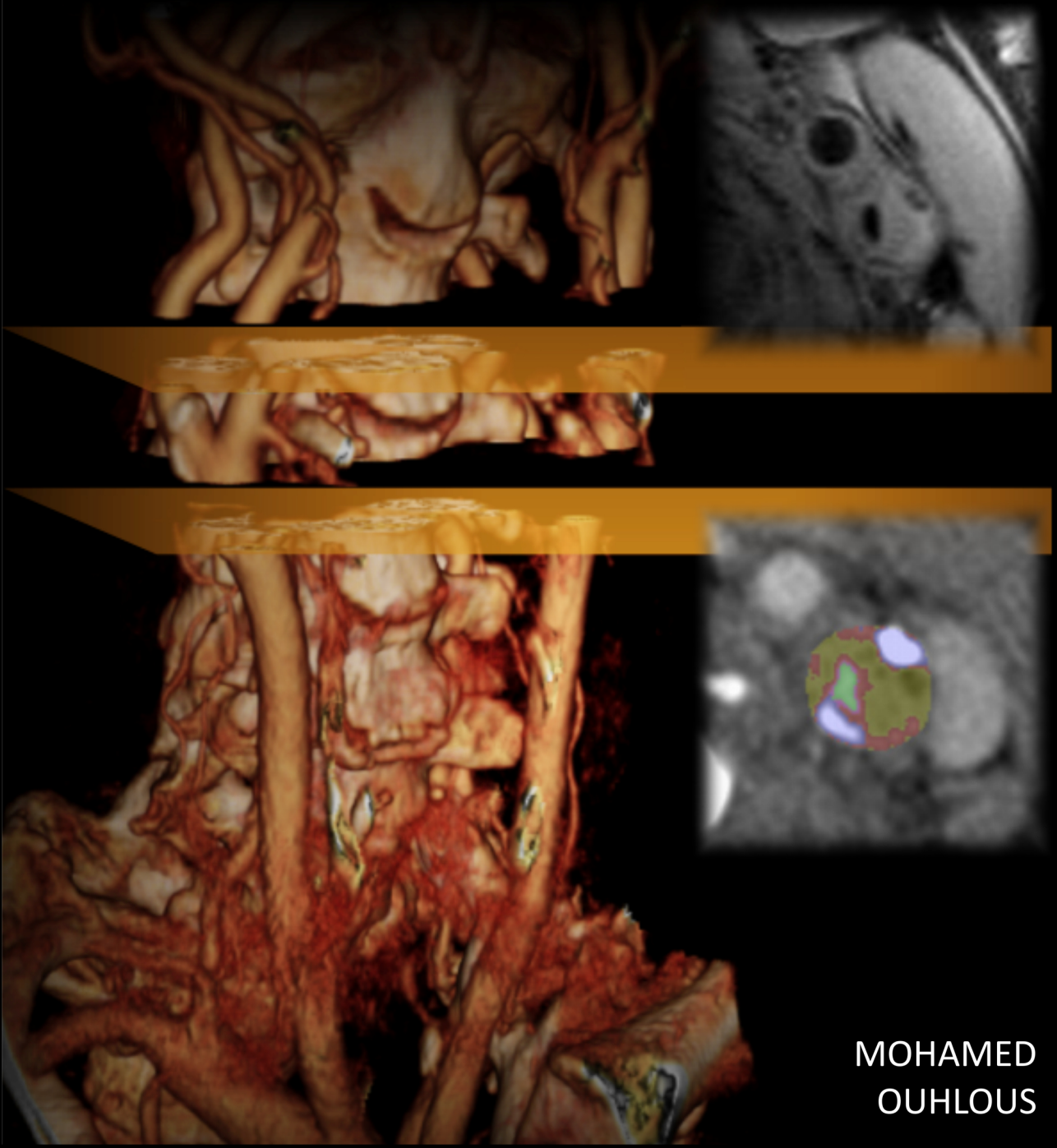
MAGNETIC RESONANCE IMAGING AND MULTI-DETECTOR COMPUTED TOMOGRAPHY ANGIOGRAPHY OF THE ATHEROSCLEROTIC PLAQUE AT THE CAROTID ARTERY

OPTIMIZATION, VALIDATION, AND CLINICAL IMPLICATION



MOHAMED OUHLOUS

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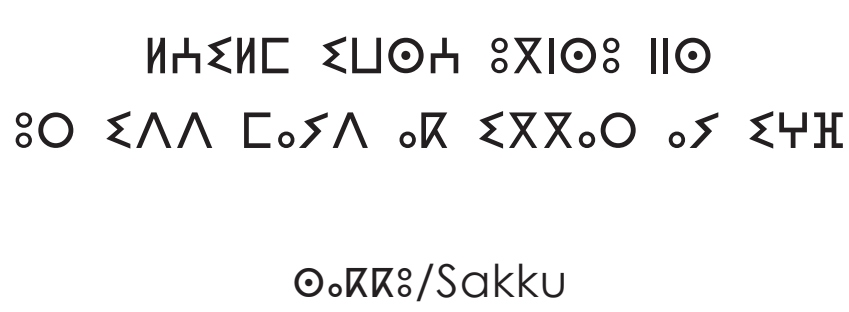

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To Faïrouz, Ili and Tybére
To my wife Siham
To my mother and father

CONTENTS

GENERAL INTRODUCTION

INTRODUCTION

Stroke mortality is the third largest cause of death in the Netherlands and a leading cause of long term disability. The number of stroke patients in the Netherlands will rise continuously until the year 2020 due to an inevitable consequence of aging of the population[1].

Stroke is a clinical syndrome of a sudden neurological deficit that is presumed to be of vascular origin. The underlying pathology can be subdivided into three main categories cerebral ischemia, primary intracerebral hemorrhage and subarachnoid hemorrhage[2].

Characteristic for cerebral ischemia which is present in 80% of the stroke patients is obstructed blood flow to (some part of) the brain. The causes can be grouped under three main pathophysiological mechanisms. Firstly, the most common mechanism is atherosclerosis of the greater vessels that supply the brain with blood like the aortic arch, the carotid arteries, vertebral arteries, and the basilar artery. Cerebral ischemia occurs when an atherosclerotic lesion significantly obstructs the blood flow to the brain (near occlusion). More frequently, an atherosclerotic lesion ruptures with thrombus formation on the irregular plaque surface. Subsequent thrombus and/or plaque material embolisation obstructs a smaller distal vessel in the brain[2]. Secondly, small vessel disease, which is characterized by occlusion of small arteries perforating the brain, leads to lacunar infarcts and leucoariosis. Thirdly, cardiac embolism (≈20%), which can be caused by many conditions. The most common condition being atrial fibrillation with presumed, but seldom proven, thrombus in the left atrium[3].

Other possible conditions are recent myocardial infarction, prosthetic valves, dilated cardiomyopathy, and infectious endocarditis. Finally, cerebral ischemia can originate infrequently (≈5%) from some rare causes like vasculitis and dissection.

Severity of luminal stenosis is a predictor of (recurrent) stroke[4-8] and is used as parameter in the therapeutic decision as to which patients will benefit from carotid intervention[9,10]. Beside the severity of stenosis, plaque morphology is considered an important determinant of symptoms. Unstable atherosclerotic plaques, the so-called vulnerable plaques, are plaques

with a large necrotic lipid core covered by a thin or disrupted fibrous cap prone to rupture [11-13]. Imaging of these plaque features might give insight into the pathophysiology of atherosclerotic disease and improve risk prediction.

Carotid plaque components in vivo have been evaluated extensively with ultrasonography (US)[14-22]. Characterisation of plaque components was based on the echogenicity of the plaque: high echogenicity corresponds to fibrous tissue, while low echogenicity corresponds to lipid core or thrombus [20,23,24]. However, subsequent histologic validation demonstrated no clear relationship with different plaque components and interobserver variability was high. To overcome the later drawback a more quantitative method with a lower interobserver variability, the Gray Scale Median (GSM), was introduced to characterise the plaque[25,26]. This methodology however provides only one compound plaque parameter.

In the past decade, high resolution Magnetic Resonance Imaging (MRI)[27-31] and Multi Detector Computed Tomography (MDCT)[32,33] have been introduced to evaluate the atherosclerotic plaque at the carotid artery. High field MRI resonance scanners, optimized imaging sequences, and the use of dedicated surface coils made high resolution of the atherosclerotic plaque at the carotid artery in vivo possible[27,31,34].

The first studies on single slice CT scanners did not able the characterisation of the plaque components[35,36]. The introduction of MDCT scanners made the use of thin slices possible with less volume averaging which might improve the accurate characterizing of the atherosclerotic plaque.

The work in this thesis evaluates the role MRI and MDCT in the characterisation of the atherosclerotic plaque at the carotid artery. Firstly the technical issues associated with both imaging techniques are explored to optimize data acquisition. Secondly, both techniques are validated against histology. Finally, a clinical MRI study has been performed.

Part 1: Optimization of image acquisition.

MRI Coils

In vivo high resolution MRI of the atherosclerotic plaque at the carotid artery requires surface coils to provide high-resolution images. We evaluated whether a custom build dual phased array coil performs better than a standard three-inch single loop coil. To this end, a phantom study was performed and we measured signal to noise ratio at the center of the phantom and off-center and at different depths (Chapter 1).

Theoretically, a quadrature coil may give an additional increase in SNR by sampling both the real and imaginary component of the signal, which doubles the signal amplitude while the noise is less increased with the square root of the increase in signal amplitude. As a follow-up to the previous study, we compared the performance of a quadrature coil design with the previously evaluated phased-array coil design. To evaluate both coils we performed Biot- Savart calculations, B1 field measurements and a phantom study (Chapter 2).

MRI sequences

Fast spin echo (FSE) sequences are normally used to assess the atherosclerotic plaque[27,30]. Motions of the vessel wall during systole caused motion artefacts. In addition, high signal intensity of streaming blood some times did not enable to distinguish between vessel lumen and vessel wall. This was mainly the case at the site of the bifurcation where the blood flow shows a turbulent pattern. Evaluation of the atherosclerotic plaque requires good delineation of the lumen and the vessel wall, without disturbance from motion artefacts caused by flow or patient movements. Flow artefacts may be addressed by a black-blood double inversion recovery technique, which effectively removes signal from flowing blood. We tested a black-blood fast spin echo (BB-FSE) pulse in 15 volunteers and 10 patients, and the ability of MRI to provide morphologic and quantitative parameters of atherosclerotic disease in the carotid arteries was assessed (Chapter 1).

MDCT scanning and reconstruction protocol

On CT images of the atherosclerotic plaque high density calcifications create a so-called blooming artifact which results in a larger appearance

of the calcifications. Such a blooming artifact leads to overestimation of the true volume of the calcium, which hampers plaque volume assessment and optimal characterization of the non-calcified part of the plaque. CT image reconstruction algorithms differ in the averaging of image data and the subsequent enhancement of contrast differences. Voltage settings have an influence on the contrast between different structures. These parameters may have an impact on the evaluation of the calcified and non-calcified parts of the atherosclerotic plaque. Therefore, we analyzed in five endarterectomy specimens the effects of different voltage settings (80, 100, 120 and 140 kVp) and different reconstruction algorithms (smooth, medium smooth, medium sharp and sharp) on the depiction of calcifications and image quality, in order to optimize these settings for atherosclerotic plaque analysis (Chapter 4).

Part 2: MRI and MDCT validation studies

Previous MRI studies have demonstrated that lipid core has a shorter T2 than fibrous tissue, both in vitro and in vivo[37]. Lipid core will therefore experience a relative signal drop from PDw to T2w images in comparison to fibrous tissue. Calcifications should be dark on all MRI sequences. We tested in 35 patients with known atherosclerotic disease in the carotid artery who were scheduled for CEA, whether PDw and T2w images accurately assessed the presence of a lipid core and calcifications. In vivo MR images of the atherosclerotic plaque of the carotid artery were compared with histologic sections obtained at carotid endarterectomy (CEA). We measured the signal intensity of different plaque components in PDw and T2w images and calculated the relative signal drop of the plaque components. Based on an optimal cut-off point the accuracy of MRI for identifying lipid core and calcifications was assessed (Chapter 3).

Although MDCT angiography has the potential to analyze atherosclerotic plaque morphology in more detail than is possible with single-slice CT, validation studies have not been conducted and it was unknown which Hounsfield unit thresholds had to be applied to characterise specific plaque components. The aim of our in vitro study was to assess the ability of MDCT to characterize and quantify plaque components in carotid

endarterectomy specimens, with histology as gold standard. We imaged in vitro 21 endarterectomy specimens, and matched MDCT images with corresponding histologic sections. Identification of pure lipid regions and pure fibrous regions in the histologic sections allowed us to assess the true Hounsfield unit value (HV) of these components. Based on these measurements an optimal HV cutoff point was assessed to differentiate between lipid and fibrous tissue (Chapter 4).

Subsequent to our in vitro study we performed an in vivo study in which we evaluated the ability of MDCTA to characterize and quantify atherosclerotic carotid plaque and plaque component areas, also with histology as gold standard. Fifteen patients were imaged with an optimized protocol, based on the results of our former studies. MDCTA images and corresponding histologic sections were matched, and we assessed the HV's for lipid and fibrous tissue. Based on these measurements an optimal HV cutoff point was assessed to differentiate between lipid and fibrous tissue. Finally, we investigated the interpretation of hypodense regions, assumed to be lipid, on MDCTA images (Chapter 5).

Besides the detection of specific plaque components, quantification of the absolute and relative contribution of specific plaque components to the total plaque volume is important. Freely available software with custom-made plug-ins allowed semi-automatic assessment of plaque and plaque component areas in the MDCT images. The custom-made plug-ins were developed because no tools exist, that we were aware of, that allows such area measurements. The plaque and plaque component areas were, after an observer had drawn the outer and inner vessel wall contour in the MDCT image, semi automatically calculated. Area calculations of the plaque components were based on the, in this study, determined plaque component specific HV ranges. We compared the measurements of plaque and plaque component areas in MDCT images of carotid endarterectomy specimens with histologic area measurements (Chapter 4). Subsequently this study was repeated in the MDCTA data from the in-vivo study (Chapter 5).

MRI and MDCTA have not been compared head to head. We analysed seven patients in who both imaging techniques were employed before CEA. The aim of this study was to compare MRI and MDCTA in the characterization and quantification of the atherosclerotic carotid plaque components with histology as gold standard (Chapter 6).

Part 3: Clinical implication

Ischemic cerebral infarcts are related to the presence of atherosclerotic disease in the carotid artery[9,10,38]. Plaque morphology is considered an important determinant of symptoms. The concept of unstable or vulnerable plaque which may rupture and lead to release of thrombo-embolic material has been postulated for the coronary arteries[38-41] and may also be applicable to the carotid arteries. This vulnerable plaque contains a large necrotic lipid core covered by a thin or disrupted fibrous cap.[11-13]. To prove the concept of vulnerable plaque leading to an increased risk for cerebrovascular events, we studied in 41 patients the relation between the morphology of the atherosclerotic plaque at the carotid artery assessed with MRI and ipsilateral ischemic cerebral lesions (Chapter 7).

Chapter 8 gives a review of the CT and MDCT validation studies on evaluation of plaque surface, quantification of calcifications, and characterization and quantification of the non-calcified portion of coronary and carotid atherosclerotic plaque. The influence of scanning and reconstruction parameters on plaque imaging is described. The clinical applications and future direction of CT based plaque imaging is discussed.

Chapter 9 contains general discussion, potential clinical applications and the direction of further research.

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PART 1

OPTIMIZATION OF IMAGE ACQUISITION

PART 1

CHAPTER 1

EVALUATION OF A DEDICATED DUAL PHASED-ARRAY SURFACE COIL USING A BLACK-BLOOD FSE SEQUENCE FOR HIGH RESOLUTION MRI OF THE CAROTID VESSEL WALL