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## **Automated image segmentation and registration of vessel wall MRI for quantitative assessment of carotid artery vessel wall dimensions and plaque composition**

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## **Chapter 1**

### **General introduction**

## 1.1 Atherosclerosis of the carotid artery

Atherosclerosis is the primary cause of heart disease and stroke. These cardiovascular diseases (CVD) are the leading cause of death in the Western world and accounted for 29% of all deaths in 2010 in The Netherlands. Other major causes of death in The Netherlands are cancer (31%) and chronic lower respiratory disease (10%) [1]. Due to an increased use of evidence-based medical therapies and due to changes in risk factors in the population attributable to lifestyle and environmental changes a decline of 65% in CVD deaths was achieved from 1950 to 2011. Additionally, the duration of hospital admission was almost halved in the period from 1994 to 2010. In 2007, the cost of CVD in the Netherlands was 9,3% of the total healthcare budget [2].

Atherosclerosis is a progressive systemic disease which, at an early stage, is characterized by the accumulation of lipids, inflammatory cells, and scar tissue in the vessel wall of large arteries, and, at a later stage, by the formation of plaque lesions inside the vessel wall [3] (Fig. 1.1). Initially, the vessel accommodates for the expanding lesions inside the vessel wall by an enlargement of the outer wall (outward remodeling) [4]. When the plaque burden exceeds the capacity of the artery to remodel outward, inward remodeling, reduction of the lumen size, occurs causing narrowing of the vessel lumen [5]. In case of severe narrowing, a stenosis, the artery can be occluded blocking the blood stream.

Over time, lesions can progress into larger, complicated plaques. Atherosclerotic plaques are separated into two categories: stable and unstable plaque, the latter also called vulnerable plaque. Stable plaques consist of a thick fibrous cap, which is the layer of extracellular matrix separating the lesion from the arterial lumen, and are rich in extracellular matrix and smooth muscle cells. Vulnerable plaques are rich in macrophages and foam cells and the fibrous cap is usually weak and prone to rupture [6]. In patients with vulnerable plaques, rupture of the thin fibrous cap causes the plaque contents to enter the vessel lumen possibly causing myocardial infarction or stroke.

Individuals who develop atherosclerosis tend to develop it in a number of different

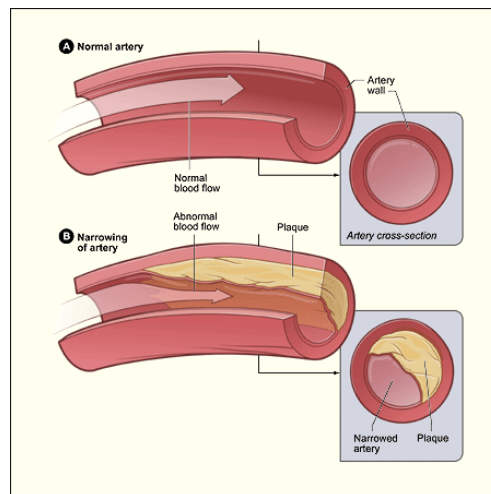


Figure 1.1: a) normal artery, b) buildup of atherosclerotic plaque inside the vessel wall causes narrowing of the lumen. (image from commons.wikimedia.org)

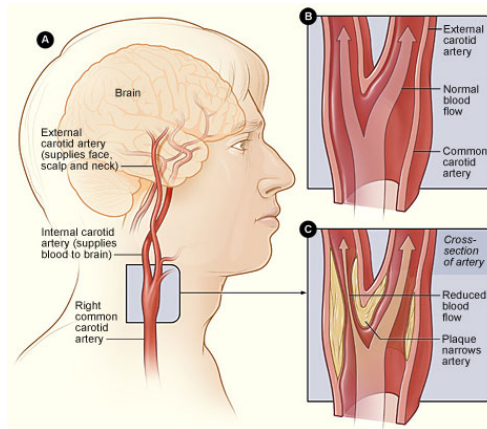


Figure 1.2: a) Overview of the common, internal and external carotid artery in the head and neck, b) cross-section of a normal carotid artery bifurcation, c) carotid bifurcation with plaque buildup and reduced blood flow (image from commons.wikimedia.org).

types of arteries including the carotid artery. This artery is located in the neck and supplies the head and neck with oxygenated blood. Inside the neck, the common carotid artery (CCA) bifurcates into the internal carotid artery (ICA) and the external carotid artery (ECA) (Fig. 1.2). The ICA runs deeper towards the skull supplying the brain with blood. The ECA runs closer to the skin and splits into numerous branches that supply the neck and face. The bifurcation is a common site for atherosclerosis and the buildup of atherosclerotic plaque can narrow the lumen of the CCA and ICA, decreasing blood flow to the brain, or a plaque can rupture causing its contents and blood clots to travel through the circulation to blood vessels in the brain. As the vessel gets smaller, the particles can get stuck inside the vessel restricting blood flow to parts of the brain. A disruption in blood flow, an ischemia, causing a shortage of oxygen and glucose in areas in the brain, can result in temporary loss of vision, difficulty speaking, and weakness, numbness or tingling, usually on one side of the body. This ischemia can be either temporary, yielding a transient ischemic attack (TIA), or permanent resulting in a stroke. A TIA doesn't generally cause permanent brain damage but is considered as a serious warning sign of stroke.

Symptoms of atherosclerosis in the carotid artery are narrowing of the lumen, a thickened vessel wall and the presence of atherosclerotic plaques. There are often no signs of atherosclerosis in the carotid artery until the occurrence of a TIA or stroke. Diagnostic procedures for carotid artery atherosclerosis are a physical examination and several tests using noninvasive imaging techniques. During physical examination a stethoscope is used to listen to the arteries in the neck. If an abnormal sound is heard over an artery, it may reflect turbulent blood flow which could indicate a stenosis. Non invasive imaging techniques for diagnosis of atherosclerosis include duplex ultrasound imaging, computerized tomography angiography (CTA), magnetic resonance angiography (MRA), and magnetic resonance imaging (MRI) [7]. Duplex ultrasound uses high-frequency sound waves to generate real-time images of the structure of the carotid artery. The static images can show the degree of a stenosis and the presence of plaque lesions, the dynamic images can be used to detect and quantify a stenosis based on the speed of the blood through the blood vessel. CTA uses a CT-scanner and the administration of contrast agent to gen-

erate a 3D image of the arterial structure which can accurately depict stenosis. Similarly, MRA aims to depict blood inside the body and is used for the evaluation of carotid artery stenosis. The application of multiple MRI contrast weightings enables the identification and classification of individual plaque components [8]. A more detailed description of the diagnosis of atherosclerosis of the carotid artery by MRA and MRI is given in the next section. Other, invasive, imaging techniques are conventional angiography, digital subtraction angiography, intravascular ultrasound and optical coherence tomography. These techniques require the administration of a contrast medium or the use of a catheter, are time consuming and include the risk of complications.

Different options are available to treat atherosclerosis. These options include lifestyle changes, medication, and surgery. Life style changes involve following a healthy diet to reduce high blood pressure or high blood cholesterol and to maintain a healthy weight, an increase in physical activity, quit smoking, and managing stress. Medication includes drugs to lower the cholesterol level or blood pressure and medicines to prevent blood clots from forming. In case of severe atherosclerosis, surgical procedures to treat carotid artery disease are carotid endarterectomy (CEA) or carotid artery stenting. In a CEA procedure, an incision is made on the side of the neck, then the carotid artery is opened and atherosclerotic plaque buildup on the inside of the carotid artery wall is surgically removed, restoring normal blood flow to the brain. Carotid artery stenting is a minimally invasive procedure performed through catheter techniques. Using catheters a small balloon is inflated in the narrowed area of the carotid artery opening the artery for improved blood flow. A stent is then inserted into the newly-opened area to help keep the artery from narrowing or closing again.

Stroke, often caused by carotid atherosclerosis, results in considerable morbidity, and mortality, and costs. Prevention is essential. Patient symptomatology and degree of luminal stenosis are currently the main grounds to perform CEA. However, many patients undergo CEA with its attendant risks without taking advantage, whereas in other patients, with a low to moderate degree of stenosis, CEA is probably incorrectly withheld [7]. Therefore, the focus has changed from stenosis evaluation towards the assessment of vulnerable plaque as morphological features of the plaque itself other than the degree of luminal narrowing may be important to identify patients at high risk of stroke. Advances in carotid MRI have enabled the noninvasive assessment of a wide-range of parameters associated with atherosclerotic disease [9]. Moreover, these parameters are possible candidate biomarkers which can be used to evaluate new treatment methods or outcome of clinical trials.

## 1.2 Magnetic resonance imaging

The key advantage of MRI over US and CTA is that MRI has the ability to characterize morphological, structural, and compositional features of atherosclerotic plaque in vivo [9, 10]. Additionally, MRA provides 3D images of the vessel lumen, allowing detection and quantification of a luminal stenosis. Furthermore, MRI is noninvasive, does not involve ionizing radiation, and can be repeated serially to track progression or regression [11]. Drawbacks of MRI are long scanning times and the high cost of the MRI system.

Imaging and plaque characterization of carotid arteries is relatively simple compared to other major arteries such as the coronary or the femoral arteries. The carotid arteries are superficial and not subject to significant motion of moving organs [12]. Most imaging

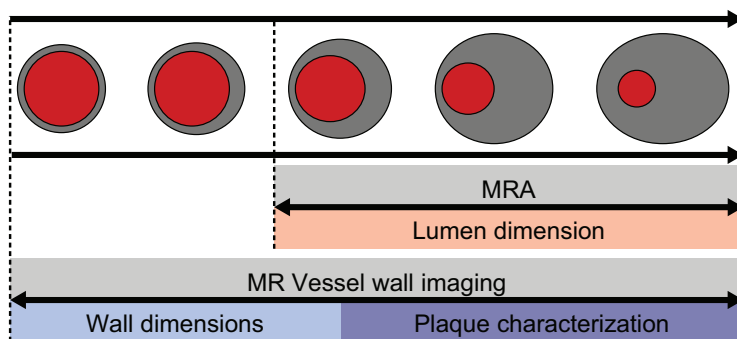


Figure 1.3: Schematic representation of atherosclerotic disease progress in relation to magnetic resonance imaging techniques and extractable metrics.

of the vessel wall by MRI has been performed on 1.5T scanners using a carotid coil resulting in a voxel size in the order of  $0.4 \times 0.4 \times 3$  mm. More recent studies are performed using a 3.0T scanner enabling increased image quality and resolution (e.g.  $0.3 \times 0.3 \times 2$  mm). Because the carotid arteries are superficial structures, the use of an MR phased array surface coil has shown to be extremely effective. Coil usage provides higher resolution and higher signal to noise ratio reducing scanning time [13].

A typical MRI protocol to study the status of atherosclerosis in the carotid artery consists of the application of multiple MR sequences. First a survey scan, generally a fast sequence, is used to get an anatomical overview of the area of interest. Based on this scan, the carotid artery of interest is identified and further sequences are planned in which the imaging volume is centered on the area of interest (e.g. the bifurcation, the atherosclerotic plaque, or the stenosed area). Optionally a TOF or MRA is acquired to enable stenosis assessment. Subsequently, several additional vessel wall acquisitions are planned and acquired to obtain information about the vessel wall morphology and plaque composition. These vessel wall images are usually scanned perpendicular to the carotid artery and typically have a high resolution in-plane ( $0.2$ - $0.4$  mm) and a much lower through-plane resolution ( $2$ - $3$  mm). As illustrated in Figure 1.3, the analysis of both the MRA and vessel wall images allows the assessment of lumen and vessel wall dimensions as well as characterization of the plaque components. The duration of a multi-sequence MRI protocol, depending on the number of sequences, can be between 20 and 60 minutes.

Imaging pulse sequences for vascular MRI can be divided into bright blood and dark blood sequences. In bright blood, flow signal enhancement techniques are used to visualize flowing blood while in black blood imaging the signal of the flowing blood is eliminated. Bright blood techniques are used in Phase Contrast MRA and 3D time-of-flight (TOF) to visualize the lumen and stenosis evaluation in the carotid artery. Quantification of lumen size is difficult due to limitations of MRA imaging such as slow blood flow near the vessel wall and irregular blood flow patterns in the bifurcation. Both effects can result in unwanted signal loss. The TOF imaging technique can show specific contrast features which, in conjunction with black blood imaging, can be helpful in identifying certain plaque components [13]. Alternatively, contrast-enhanced MRA can be used in which an MRI contrast agent is injected and images are acquired during the first pass of the agent through the arteries. The use of contrast-enhanced MRA is more complex, but does result in images of higher quality than regular MRA or TOF imaging.

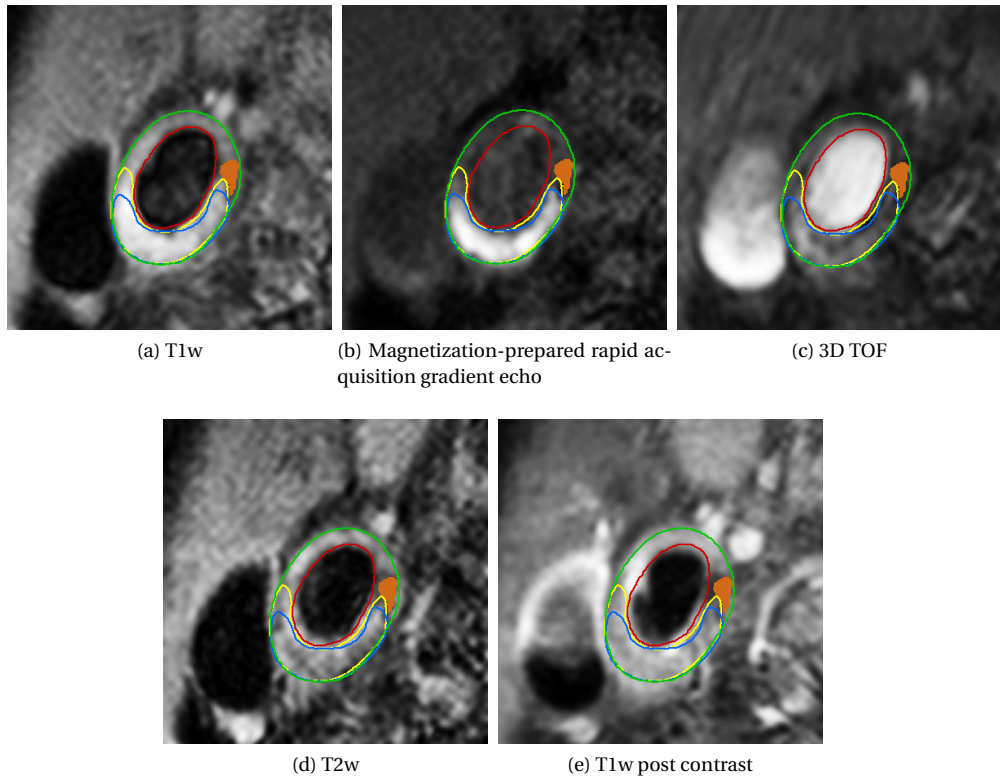


Figure 1.4: Images from a 3.0T multi-sequence MRI protocol including manual segmentations (orange = calcification, yellow = lipid-rich necrotic core, blue = presence of intraplaque hemorrhage).

Black blood imaging techniques are used to create multiple contrast weightings with the common goal to visualize the vessel wall. Based on these contrast weightings, individual components inside the plaque can be identified. Common black blood sequences are T1-, T2-, and proton density (PD) weighted image contrasts, where T1w and PDw images are especially helpful for evaluation of vessel wall morphology and show good contrast for fibrous matrix and lipid core [13]. Often a second T1w sequence is acquired after administration of gadolinium-based contrast agent which improves the reproducibility and quantification of the lipid-rich necrotic core [9]. Another approach is to develop sequences which are tailored to identify a specific plaque component. Examples are magnetic resonance direct thrombus imaging [14], magnetization-prepared rapid acquisition gradient echo [15], and diffusion-weighted magnetic resonance imaging for the detection of lipid-rich necrotic core [16]. A multi-contrast approach with bright and dark blood sequences enables comprehensive characterization of individual plaque components. An example is shown in Figure 1.4.



### 1.3 Image derived measures of atherosclerosis

Application of an extensive multi-contrast MRI protocol allows the assessment of morphological, structural and plaque composition features. MRA techniques provide information about the vessel lumen enabling stenosis detection and quantification. MRI vessel wall imaging provides detailed information of the vessel wall and can be used to quantify morphological features such as average, minimum and maximum vessel wall thickness, vessel wall area, vessel wall volume and derived metrics such as eccentricity or plaque index. Plaque index, also referred to normalized wall index, is the ratio between vessel wall volume against the volume of the whole vessel (lumen and vessel wall volume). Structural features of the plaque are the status of the fibrous cap and the presence of an ulceration. Individual plaque components, such as calcification, lipid, intraplaque hemorrhage (IPH), and loose matrix can be identified and quantified using multi-contrast vessel wall images. Volumes of different tissue components inside the plaque can be measured and also the type of plaque according to the AHA classification [17], which is a derived measure based on the plaque composition, can be obtained.

Measurement of vessel wall dimensions can be used to detect early onset of atherosclerosis and follow-up measurements of vessel wall dimensions can be used as an endpoint in clinical trials assessing the effect of pharmacological treatment of systemic atherosclerosis [18]. The fibrous cap status and cap thickness may identify patients at risk for stroke, which may lead to better patient selection for surgical intervention [19]. The vulnerability of an atherosclerotic plaque, the risk to rupture, can be assessed by evaluating the size of the plaque and its composition [20].

### 1.4 Manual image analysis

The current practice in clinical research to derive atherosclerotic features from the multi-contrast vessel wall imaging data is manual processing of the images. Several processing steps, such as lumen boundary detection, outer wall boundary detection, multi-contrast image registration, and plaque segmentation, are needed for a complete analysis of all image data. A common workflow to analyze the image data is as follows:

1. One of the contrast-weightings is defined as reference. Usually this is an image with clear depiction of the vessel wall, in most studies a T1w image is used.
2. In case the other contrast weightings were acquired at a different resolution or geometry, these contrast weightings are processed to match the resolution and geometry of the reference image using multiplanar reconstruction.
3. The lumen boundary and outer wall boundary are manually delineated in the reference image and copied to the other sequences.
4. To correct for possible patient movement while scanning, the other MR sequences are manually aligned to the reference image by applying a combination of through-plane translation of the complete image stack and in-plane translations for the individual image slices. The expert takes into account the appearance of the images and uses the lumen and outer wall contours as a reference.

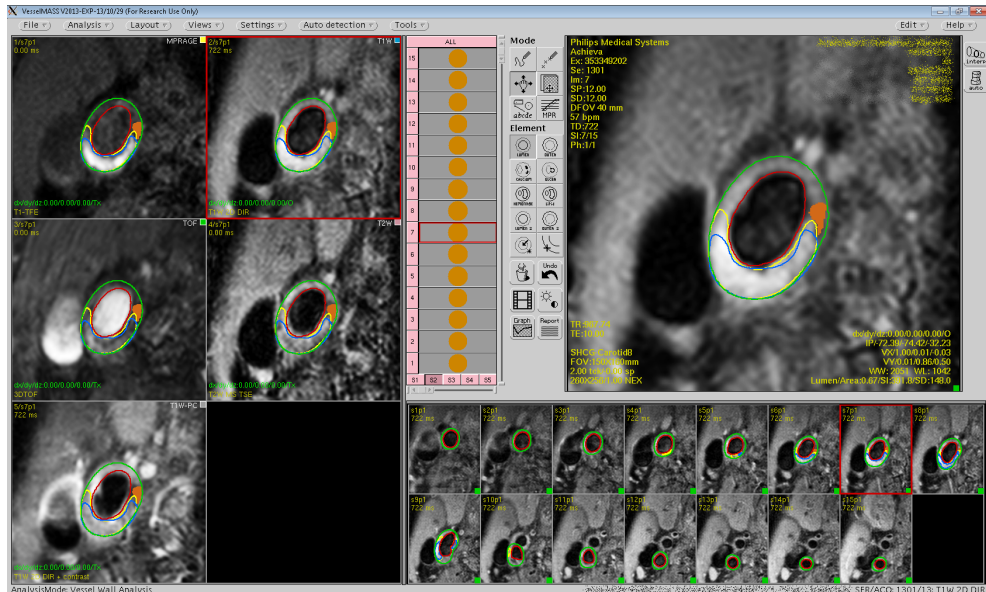


Figure 1.5: Screenshot of the software program VesselMass which can be used for manual segmentation of the multi-sequence MRI images.

5. Once all images are aligned, regions of plaque can be identified and characterized by evaluating the relative signal intensities in the available imaging sequences. Various schemes for plaque classification have been reported for different imaging protocols, which can be used to identify regions of calcification, lipid core, IPH, ulceration, loose matrix and fibrous tissue [19, 21–24]. Alternatively, histological information can be used to aid to segmentation of the different plaque components.

The manual image analysis results in an aligned set of vessel wall images including manual segmentation of the vessel wall and plaque components (e.g. Fig. 1.4). All measures described in the previous section can be extracted from the manual segmentation. To perform the manual image analysis a software program is used which contains functionally to view, align and segment the images. An example of such a software program is VesselMass [25], see Fig. 1.5.

Finally, serial MRI is used to assess progression or regression of atherosclerosis by comparing vessel wall volume, presence and volume of atherosclerotic plaque components over time. Serial MRI is used to study the natural progression of atherosclerosis [26], effectiveness of drug therapy [27, 28], and the immediate and long-term effects of IPH on plaque progression in the carotid artery [29].

## 1.5 Automated image analysis

Manual image analysis is, due to the large amount of image data, a time-consuming procedure and is subject to inter- and intra-observer variation. Consequently, computerized segmentation, registration and classification techniques are being investigated to overcome these limitations. The application of computerized methods is a difficult task due

to the nature and quality of the vessel wall images, the difficulty of obtaining a gold standard and variation in scan protocols between scanners and medical centers. Imaging of the carotid vessel wall requires sub-millimeter resolution which is achieved at the expense of signal-to-noise ratio and is subject to image artifacts due to blood flow and physiologic motion and intensity inhomogeneity caused by the use of surface coils [30]. A gold standard is often not available as the acquisition of a gold standard, such as histology, requires the patient to undergo surgery. In practice, manual segmentation, which suffers from inter- and intra-observer variation, is used as a surrogate gold standard. Another challenge is introduced by the variation in scan protocols between different scanners and hospitals. A method developed on a set of MR images from one scanner, might perform poorly on other images because of differences in contrast between the images. Especially methods for the classification of plaque components, which heavily rely on image contrast, are hindered by variation in scan protocols. Therefore, robust computerized methods are needed which can cope with these challenges and are applicable to a wide range of MR images.

In the past, different steps of the manual segmentation process have been automated. Automated segmentation methods for lumen and outer wall boundary segmentation have been investigated. Reported methods range from interactively guiding a segmentation algorithm [31,32] to approaches requiring one user interaction per image slice [25] or one interaction to start the complete segmentation process [33,34]. Often an MRA or TOF image is used to perform a rough segmentation of the lumen contours which are then copied to a vessel wall sequence in which the lumen contours are refined. Subsequently the outer wall boundary contour is detected with the aid of the information of the lumen contour. More recent methods focus on detecting the lumen and outer wall boundary contours simultaneously [35,36].

Automated image registration methods have been developed to align the multi-contrast vessel wall images, the fourth step in the manual analysis process. Image registration was mainly performed in 2D ignoring any patient movement in the through-plane direction [37–40]. More recent studies applied image registration in 3D allowing for translation and rotation in all three directions [41,42]. In most studies, a region of interest around the carotid artery, based on the lumen and outer wall boundaries, was used and image similarity metrics based on correlation, mutual information, or gradients in the image were used.

The final step in the analysis is the identification and classification of plaque components. Several methods for automated classification of plaque components in the carotid artery have been described in literature, the majority employing statistical pattern recognition techniques [25,37,38,43]. Commonly a supervised classifier, which is trained on features and classes extracted from example data, is employed to classify unseen image data into different plaque components. Characteristic features are signal intensities and edge information from the multi-contrast MR images, and morphological features such as local vessel wall thickness and distance to the lumen or outer boundary of the vessel wall. Before the extraction of signal intensity features, the MR images are normalized to enabling inter-subject comparison. Preferable the classifier is trained on a training set and tested on a independent test set. In case the size of the dataset is too small, cross validation techniques, e.g. leave-one-patient-out, are used.

Currently, no computerized methods have been proposed to aid the comparison of baseline and follow-up scans of serial MRI studies.

## 1.6 Thesis overview

The main goal of this thesis is to develop methods for automated segmentation, registration and classification of the carotid artery vessel wall and plaque components using multi-sequence MR vessel wall images. Automated analysis seeks to overcome the drawbacks of manual segmentation in terms of accuracy, objectivity, reproducibility and time. The new methods will be clinically validated on patient data and compared to existing methods where possible.

The structure of the remaining part of this thesis is as follows. First, automated segmentation of the lumen and outer boundary is discussed. Then, automated image registration is applied to align multi-sequence images and scans of multiple time points. The third part focuses on several challenges related to the automated classification of plaque components. Finally, we conclude the thesis by providing the summary, the conclusion and a future outlook. A detailed overview of the next chapters:

In **chapter 2** a new method for automated segmentation of the lumen and outer wall boundaries in MR vessel wall studies of the common carotid artery was developed and validated. This new segmentation method was developed using a 3D deformable vessel model requiring only one single user interaction by combining 3D MR angiography and 2D vessel wall images.

**Chapter 3** presents a method for carotid vessel wall volume quantification from MRI which combines lumen and outer wall segmentation based on deformable model fitting, described in **chapter 2**, with a learning-based segmentation correction step to correct for systematic differences between the automated segmentation method and manual annotations by the expert.

In **chapter 4**, we introduced automated image registration techniques to correct for possible patient movement within one scanning session. Furthermore, in **chapter 5**, image registration was used to align scans from serial MRI studies to enable visual assessment of local changes in vessel wall thickness and progression or regression of different plaque components over time.

In **chapter 6**, pattern recognition techniques were introduced to automatically detect and quantify atherosclerotic plaque components based on in vivo MR imaging data of the carotid artery in a multicenter study. A supervised classifier was trained using image features from four MR sequences and morphological features from a training group of 20 patients. The classifier was applied to a testing group of 40 patients and results were compared with the manual segmentation.

In **chapter 7**, we investigated the effect of new morphological features, image normalization methods and the composition of the training data for automated plaque classification and evaluated the reproducibility of automated classification versus manual segmentation.

**Chapters 8 and 9** focus on the evaluation of MR-sequences and the trade-off between scan duration and automated image segmentation performance. In **chapter 8** the image contrast between different plaque components in several high field MR sequences are evaluated using the Mahalanobis distance measure. In **chapter 9** an objective method to optimize the MR sequence set for plaque classification in carotid vessel wall images using automated image segmentation is presented.

**Chapter 10** provides discussions for each of the previous chapters. In each chapter a new method was developed and the improvements over existing methods are discussed

as well as directions for further research. Finally, a general conclusion is drawn and suggestions for future work are given.

