Chapter

8

Summary and Conclusions

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Since the discovery that the components of atherosclerotic plaque could be characterized by density and signal intensity, high-resolution MR imaging has become a potential alternative to intravascular ultrasound in the assessment of the severity of atherosclerosis disease. MR has proven to be capable of detecting early, subclinical vulnerable plaque. However, when the analysis of atherosclerosis is based on visual interpretation of the images or manually delineated structures, the outcome is often not reliable. The main objective of this thesis was to investigate different methods to automatically quantify markers of the severity of atherosclerosis in a reproducible manner, by automatically outlining the boundaries of the blood vessel wall, lumen and plaque burden. Different algorithms have been developed and applied to different vascular beds (aorta and carotid arteries) proving to be versatile and powerful tools, that provide quantitative reproducible parameters. This assists the physician in making a diagnosis and identifying high-risk patients, who may benefit from treatment. Reproducibility is also crucial in order to monitor the progression or regression of the disease (changes in the vessel wall) over time, and to evaluate the effects of drug therapies.

Chapter 1 presents a general introduction to this thesis, whilst in Chapter 2 the basic principles of the atherosclerotic process are described, as well as an extensive overview of imaging modalities currently in use to image atherosclerotic arteries. In addition, some image processing techniques reported in the literature for segmenting vessel wall structures are described. The novel contributions of this research and the results from the validation studies are described in Chapters 3 to 7.

In Chapter 3 a method is presented to automatically detect the lumen, outer vessel wall boundary and lipid core in *in vivo* contrast-enhanced black blood MR images of the human carotid artery (the operator only needs to provide a seed point). A geometrical model of the vessel (ellipse) was employed to obtain a first rough approximation of the outer vessel wall. The model was then, iteratively, deformed, rotated and translated to match the vessel wall boundary. The cumulative signed gradient along the contour of the ellipse was used as a measure of the goodness of fit. Lumen and lipid core were detected by means of a classification technique, fuzzy clustering. This technique consists of classification of gray values in different tissue types. Fibrous cap thickness was measured as the shortest distance between any point in the lumen contour and the closest point in the lipid contour. This method was validated against a manually defined independent standard in a study based on fifty PDW and T1W MR images that were acquired from 17 patients. This study demonstrated a high correlation between manual and automated measurements for both lumen ($r = 0.92$) and outer wall contours ($r=0.91$), and fibrous cap thickness ($r = 0.71$).

Chapter 4 presents an extension of the method described in Chapter 3. Information from two different contrast-weighted MR images (PDW and T1W) was combined to guide the model to the correct border between vessel wall and surrounding tissue. Also the fuzzy clustering, despite the difficulties occurring in registering the corresponding two images, benefitted from the combination of two sources of information, yielding a better segmentation of the structures of interest. This method was validated against the same fifty patients described in Chapter 3, plus two extra patients, whose data was available at the time of this study. The correlation proved to be higher than that in the previous study: lumen area ($r = 0.94$), outer wall area ($r = 0.92$) and fibrous cap thickness (0.76).

In Chapter 5 a novel application of the method described in Chapter 3 was developed to study a different vascular structure: the aorta. The goal of this chapter was the development of a tool to assist the expert radiologists in the detection of the contours of the aortic vessel wall and measure the average and maximum wall thickness. By using the Hough transform for finding circular structures, the aorta was automatically detected and further geometrical models for both lumen and outer wall were employed to extract the vessel wall boundaries. Measurements were found to be accurate when compared to a manually defined independent standard: correlation for lumen area was $r = 0.99$, and for outer wall area, $r = 0.96$.

In Chapter 6 a novel integrated approach is described, which is based on a combination of two imaging modalities, namely magnetic resonance angiography (MRA) and vessel wall MR. The objective of this combination was to develop a robust algorithm to automatically segment lumen in MRA images, and lumen and outer wall boundary in vessel wall MR images, and to estimate plaque burden and degree of stenosis. Data from twenty-two patients (different from those used in Chapters 3 and 4) were used for validation purposes, showing a high reproducibility and accuracy: lumen ($r = 0.96$) and outer wall ($r=0.96$). Furthermore, the combination of both modalities (MRA and vessel wall MR) integrated global and local features, which made this approach more robust than those relying only on one source of information. As mentioned in Chapter 4, also here the difficulties in registration were a limitation to the algorithm. Better image quality is expected to overcome those problems.

Chapter 7 presents a method which performs a 3D segmentation and registration to automatically identify the boundaries of the vessel wall in a segment of the carotid artery in MR images. With this method we tried to investigate different factors that influence the accuracy and reproducibility of the measurements. Accurate and precise assessment of the arterial structure and the possible changes in plaque burden over time, are important to monitor the evolution of atherosclerosis, either naturally or under the effect of drug therapy.
Ten healthy adults were imaged twice using high resolution *in vivo* MRI, generating 2 serial scans (8 T1-weighted MR images/ patient). Those images were automatically segmented using our method, based on a 3D geometrical model and dynamic programming. A 3D registration, based on gradient and intensity profile, was carried out to register the two scans of the same patient and evaluate changes in the vessel wall over time. The accuracy of the segmentation was assessed by comparison with two independent standards (expert radiologists), yielding high correlation coefficients: $r = 0.98$ for lumen, $r = 0.97$ for outer wall, and $r = 0.90$ for vessel wall area. The algorithm was also validated on simulated long-term follow-up atherosclerotic data, to assess its capabilities to detect changes in the vessel wall. The kappa statistic $K = 0.71$ showed substantial agreement between our method and the radiologists. Nevertheless, validation on a larger cohort of patients presenting more severe

atherosclerosis and long-term follow up data (1 to 5 years) would be very interesting and should be studied in the future.

In conclusion, the accurate visualization and quantification of atherosclerosis in a non-invasive manner by means of MR is, nowadays, of high importance, not only regarding morphology but also composition of the atherosclerotic plaques. This development belongs to the so-called Vascular Medicine and Molecular Imaging theme. In this thesis, novel image processing techniques have been developed based on a-priori knowledge and combination of different imaging modalities, to outline the boundaries of the inner and outer wall of the arterial vessel wall, as well as the lipid core. Thereby, yielding quantitative parameters, such as vessel wall thickness and volume, plaque index, degree of stenosis or fibrous cap thickness. These new techniques have been validated in limited populations, proving to be accurate and reproducible. They are, therefore, suitable to be further adapted and to be employed in the clinical vascular research. Hereby, it can be said that the goals stated in Chapter 1 have been realized.

8.1 Future work

With the results achieved in this thesis, a next step towards 3D-segmentation of the vessel wall in the carotid flow-divider (bifurcation) should be taken, since the flow-divider is the region of the carotid artery where atherosclerosis starts to build up, which would allow evaluation of the disease at a very early stage. The key is to make good use of a priori information and find out the right features to achieve the desired segmentation. This is where statistical shape models, markov random fields, or energy-driven B-splines could play an important role; the latest has already been reported in the literature[1] for the automated detection of the lumen contour.

In addition, there is a tendency towards the automated characterization of all different plaque components in different vascular beds. Nevertheless, there are limitations related to the reduced spatial resolution of the data, heterogeneous composition of the diseased intima of the vessel wall, fuzzy boundaries and image artifacts. The ongoing investigation of new contrast agents that target specific plaque components, such as lipid or hemorrhage, opens a whole new range of possibilities for the post-processing. Information from the resulting contrast-weighted images should be extracted in a wise-manner and combined with other sources of information (e.g. computed tomography) in order to accurately characterize atherosclerotic plaque composition.

Coronary arteries are especially challenging too, due to their small size and significant motion during the cardiac cycle. Therefore, other imaging approaches are being investigated, such as molecular imaging which is a rapidly evolving discipline that aims to develop imaging agents and technologies to visualize specific molecular processes *in vivo*. Molecular imaging studies can now elucidate biological aspects of atherosclerosis, and the field is moving rapidly toward the clinical detection of high-risk atheroma[2,3]. Although likely to require substantial effort and cost, molecular imaging of atherosclerosis, in concert with anatomical imaging techniques, will prove instrumental in guiding the detection, risk stratification, systemic

therapy (e.g., optimal medications and doses), and local treatment (e.g, intracoronary stenting) of this disease.

References

1. Makowski P, de Koning PJH, Angelie E, Westenberg JJM, van der Geest RJ, Reiber JHC. 3D cylindrical B-spline segmentation of carotid arteries from MRI images. Proceedings of ISBMS 2006; 4072; 188-96.

2. Jaffer FA, Weissleder R. Molecular imaging in the clinical arena. *JAMA*. 2005: 293:855-62.

3. Jaffer FA, Libby P, Weissleder R. Molecular and cellular imaging of atherosclerosis. *JACC*. 2006; 47(7):1328-38.