Carotid imaging in cardiovascular risk assessment

Ray, A.

CHAPTER 9

Summary

Carotid artery imaging has played a crucial and lasting role in cardiovascular research in the last decades. By proving to be a reliable and valid intermediate cardiovascular end-point it has facilitated clinical trials with shorter follow-up time and limited sample sizes, thereby aiding in the evaluation and development of pharmacological therapies. In this thesis the main focus has been on two other uses for carotid imaging technology, namely as a new parameter in 1) cardiovascular risk assessment in individual patients and 2) pathophysiological studies on atherosclerosis. Two imaging modalities were utilized for measuring carotid vessel wall geometry: high resolution ultrasound plaque detection and quantification of intima-media thickness and magnetic resonance imaging of total vessel wall thickness and area. Ultrasound-based measurements are at a stage of development that may allow its transition from research parameter to clinical tool. This thesis addresses several critical issues surrounding such a transition to clinical practice. Magnetic resonance imaging is a relatively new method for carotid artery assessment. Its potential role in clinical practice and in pathophysiological studies on vascular pathology is not yet clearly defined. This thesis has provided an initial recommendation on the use of magnetic resonance imaging in a clinical setting. Furthermore, a novel parameter is put forth, derived from a combination of ultrasound and magnetic resonance imaging for future studies on the role of the lamina adventitia in the atherosclerotic process.

In chapter 1 a general outline is provided on the current uses of carotid artery imaging and a several key technical issues are addressed.

In chapter 2 the results of a study on the practical feasibility of carotid ultrasound measurement by clinicians are discussed. The study included 112 patients recruited from the vascular outpatient department. Two trained physicians performed ultrasound scans during their normal clinical outpatient routine. The results were compared to the findings of an experienced vascular sonographer in a specialized vascular laboratory, as the gold standard for carotid ultrasound. The results of the study demonstrate that physicians, after a short training program are able to incorporate ultrasound scans into their regular clinical routine, with an average scan time of 7.3 minutes. A high level of accuracy was achieved by the physicians regarding carotid plaque detection but not for measurement of intima-media thickness. Based on these findings it can be suggested that physicians

could carry out office-based carotid plaque detection in their vascular patients without the aid of radiologists of laboratory technicians. Quantification of intima-media thickness should be done in a vascular laboratory or using specialized equipment. Current guidelines recommend some form of testing for subclinical atherosclerosis in the work-up for cardiovascular risk assessment, be it ankle-brachial index, CT-based coronary calcification scores, pulse wave analysis or carotid ultrasound. Increasingly physicians are utilizing (hand-held) ultrasound in clinical practice for point of care testing. Based on our study results and the recommendations in the guidelines we would advise physicians to screen for carotid plaque in office, especially in patients at intermediate cardiovascular risk. If abnormalities are found, intensifying risk management strategies can be considered. It should be noted that there is as of now no evidence that imaging-based management of cardiovascular risk improves outcome. Informing patients carefully about this fact, but also of the fact that they may be at slightly elevated risk will hopefully lead to a more shared and balanced decision.

In chapter 3 the effect of incorporating carotid ultrasound parameters in clinical decision making is explored further. Carotid ultrasound may not be readily available in a primary care setting. In the Netherlands initial cardiovascular risk management is done by general practitioners. It can therefore be assumed that patients referred to a specialized vascular care unit will already be at an elevated risk because the initial management was deemed to be insufficient by the general practitioner. In a high risk population performing carotid ultrasound testing is unnecessary because their risk profile already warrants intensive management. We therefore looked at the distribution of carotid abnormalities in relation to calculated risk in specifically this referred population.
The carotid parameters measured in the 112 patients from the vascular outpatient department were related to traditional cardiovascular risk factors and calculated risk scores. Intima-media thickness and carotid plaque presence were related to, but only partly explained by traditional cardiovascular risk factors. A high prevalence of subclinical carotid atherosclerosis was demonstrated in patients not treated with statins and with low calculated cardiovascular risk scores. Adding the carotid plaque presence to the clinical decision process would result in a 22% increase in patients classified as higher risk. When including both plaque presence and increased intima-media thickness to the decision process 36% of subjects

would be reclassified. These results suggest that including carotid ultrasound parameters in clinical practice may aide in identifying high-risk patients at an early stage. Seen in combination with the results discussed in chapter 2 it can be argued that especially carotid plaque detection may be an essential tool in cardiovascular risk assessment and should be broadly implemented in clinical practice. Reclassifying patients with carotid plaque to a higher risk category is now also recommended by several guidelines. Implementing standard carotid scanning in vascular outpatients treated in a primary prevention setting will, according to our findings, lead to identifying a large number of subjects with low calculated risk who nonetheless have subclinical atherosclerosis. For these patients it will be a shared decision with their physician whether to step up risk reduction efforts.

The abovementioned considerations are based on many years of experience with and sound population-based research on the predictive potential of carotid ultrasound. Much less is known about other carotid imaging modalities like MRI. The technique provides circumferential images of the artery and is therefore possibly more suited for imaging an asymmetrical process like atherosclerosis than ultrasound is. Digital reconstructions of the vessel geometry make it possible to not only measure wall thickness, but also the volume. It is also a highly reproducible imaging modality. However, MRI scans do not measure the same part of the arterial wall as ultrasound because MRI quantifies the total wall thickness including the lamina adventitia. Conclusions drawn from ultrasound-based IMT studies should not be extrapolated to MRI thickness. In chapter 4 this is illustrated. Ultrasound and MRI scans of the same carotid segment are compared. Although the correlation between MRI and US is very good we observed that MRI measurements were systematically higher. This observation could be explained if indeed the difference between IMT and total vessel thickness represents adventitial thickness. The exact role that this vascular layer and the vasa vasorum therein plays in the atherosclerotic process is subject to ardent research, but is seems clear that the density of the vasa vasorum increases with progressive atherosclerosis. Whether this is a contributing pathological process or a compensatory physiological response is not fully elucidated. The difference between IMT and total wall thickness was more pronounced in the thicker vessels in our study. This would be in line with the hypothesis of concurrent

intimal, medial as well as adventitial thickening. In chapter 5 we explored the possibility of quantifying adventitial thickness by combining ultrasound and MRI measurements in the same vessel. Although our findings are preliminary this may be a step towards facilitating pathophysiological studies on the role of vasa vasorum angiogenesis in vivo. There are data suggesting that it is also possible to visualize and reliably quantify adventitial thickness using ultrasound alone. As of now there is no consensus on the optimal imaging modality for adventitia measurements. Our findings suggest that the combined ultrasound-MRI approach is worth exploring and developing further.

The data reported in chapter 6 address the issue of reference values for IMT in different ethnic groups. Much of the population-based data on the association between IMT and cardiovascular risk is generated in Western Europe and the United States. Pooled data from these studies have shown that IMT increases with age and risk factors and that an IMT value of >0.9mm is associated with higher risk of future cardiovascular events. Guidelines recommend physicians to consider treatment of intensification in patients above this threshold. However, the vast majority of subjects in these large studies was of Caucasian ethnicity. Subjects of Asian Indian descent are susceptible to cardiovascular disease, partly because they develop metabolic syndrome at an earlier age. We studied a cross-section of Asian Indian diabetic patients assumed to be a high cardiovascular risk. When comparing them to age and gender matched Caucasians the risk profile of the Asian Indians was indeed unfavorable, with worse glucose regulation, longer duration of diabetes, more microvascular complications and more pronounced dyslipidemia. IMT values however were found to be significantly lower in the Asian Indians. Although this is a very preliminary finding it suggests that the clinically relevant cut-off values for IMT in Asian Indians may be lower than in Caucasians.

In conclusion, the data reported in this thesis supports the use of carotid plaque detection in routine clinical practice by showing that clinicians themselves can perform the ultrasounds examinations reliably. The data further demonstrate that subclinical atherosclerosis is highly prevalent in a vascular referral center in the Netherlands, also in subjects with low cardiovascular risk scores. Estimating cIMT in office-based ultrasounds is not advised, this requires a specialized

vascular laboratory. Interpreting carotid ultrasound parameters should be done very carefully, taking other factors including ethnicity into account. Carotid MRI is a promising emerging imaging modality. Based on the data in this thesis it is not recommended to extrapolate cIMT data on cardiovascular risk to MRI findings as the two techniques measure different structures. Herein also lies the strength of MRI. Combining MRI-based and ultrasound-based measurements may allow for in vivo studies on the role of the adventitial tissue in the atherosclerotic process.