In vivo ultrasound assessment of carotid artery walls and plaques

Valorisation

Valorisation

Relevance

In Europe, around 1.1 million people die annually of stroke, which is the second most common cause of death (Nichols 2012) The estimated total cost for the EU economy due to stroke is over 38 billion Euros a year (Nichols 2012). In the Netherlands, around 6,000 people die annually of ischemic stroke and around 33,000 people are hospitalized annually, excluding day care (Koopman et al. 2014). The high costs of stroke are not only due to healthcare costs but also include substantial productivity losses and informal care of stroke patients.

The most common type of stroke is ischemic stroke, caused by an occluded artery due to thrombosis or embolism. Ischemic strokes (15-20%) predominantly originate from rupture of a vulnerable atherosclerotic plaque in the carotid bifurcation or internal carotid artery (ICA) (Chaturvedi et al. 2005), resulting in the release of thrombogenic material and subsequent thrombus formation. The possibility to assess the risk of rupture of a plaque will have tremendous impact in clinical decision making. Although many studies focus on the assessment of plaques at risk, diagnosing impending plaque rupture is still a problem today.

To prevent the patient from suffering symptoms caused by a vulnerable plaque, the plaque can be removed by a surgeon during carotid endarterectomy (CEA). Despite the overt role of plaque morphology nowadays, clinical guidelines only take the luminal narrowing by a plaque into account to select patients eligible for surgery. Previous studies concluded that it is beneficial to operate patients who (1) have experienced a stroke or transient ischemic attack (TIA), (2) have plaques in the carotid bifurcation, and (3) have a severe stenosis (luminal narrowing >70%). Patients with a mild-to-moderate plaque (30-70%) only have a marginal to moderate benefit from CEA. Therefore, these patients usually are medically treated. Nowadays, the risk of recurrent stroke is lower due to better medical treatment (Park and Ovbiagele 2015), which challenges the effectiveness of CEA demanding the best possible selection of patients for surgery. To reduce health costs and provide a better health care (Buisman et al. 2015), indicators to predict individually the risk of plaque rupture are necessary.

Previous studies have shown a good correlation between non-invasive imaging and histology and/or clinical characteristics. However, these studies employed only one or two imaging techniques in relatively small cohorts and did not deliver the necessary evidence to change the current clinical guidelines (Nederlandse Vereniging voor Neurologie 2008). The PARISK (Plaque At RISK) research program is a longitudinal study (baseline and follow-up after 2 years) aimed to evaluate plaques at risk with multiple non-invasive imaging techniques such as ultrasound, MRI, CT and PET. The main advantage of the PARISK study is the use of multiple non-invasive imaging techniques, thereby enabling comparison. Since patients with mild-to-moderate stenosis only marginally or moderately benefit from CEA, PARISK concentrates on this patient group. The present thesis primarily focuses on ultrasound imaging to detect a vulnerable plaque. The main advantage of ultrasound is that it is affordable and can be used readily after anamnestic assessment of symptoms. Ultrasound provides information about the mechanical and morphological characteristics of a blood vessel or plaque. Furthermore, ultrasound can also provide information about plaque composition due to the grey values of the plaque. Therefore, it would be beneficial for healthcare and healthcare costs to predict the risk of plaque rupture with ultrasound.

The results of this thesis are of interest for many professionals. The mechanism of plaque development is still unclear, especially shortly after stroke. Ultrasound provides a good platform for repeated examinations within a short time window to observe changes in morphological and functional characteristics of plaques immediately after stroke. Thereby, repeated ultrasound measurements may enhance the understanding of the mechanisms leading to plaque progression and regression. Since this thesis only pertains to the baseline results of the PARISK study, other scientists will have to complete the follow-up study to firmly establish the relationship between plaque progression and clinical endpoints.

Important outcomes

Currently, local distension, i.e., the diameter change over the cycle, is determined with radiofrequency phase tracking applied to recordings obtained at a high frame rate (>300 fps) (Meinders et al. 2001). Because an expensive and dedicate ultrasound machine is necessary for high frame rate recordings, its application is restricted to a limited number of specialized hospitals. We have shown in **Chapter 3** that the local artery distension can be extracted with semi-automatic edge tracking techniques applied to standard B-mode echo recordings (40 fps) as precise and accurate as with radiofrequency phase tracking. We validated our method in an older patient population. Despite curved arteries and motion artifacts, which are common for this population, validation was successful, corroborating that our edge tracking technique will also work adequately in younger patients or those without atherosclerotic disease. Therefore, the edge tracking technique enables the wider use of local distension technique with the standard ultrasound systems available in any hospital.

Commonly, distance and distension measurements are performed along the ultrasound beam. However, in case of plaques or curved vessels, measurements along the ultrasound beam lose their relevance, because of the discrepancy between the light of sight and the true artery orientation. Therefore, in **Chapter 7** we introduced orthogonal distance measurements, i.e., along the radius of the artery. It was shown that orthogonal distance measurements have a direct impact on the morphological evaluation of an artery segment, specifically the lumen and adventitia-adventitia diameter distribution across a stenosis, providing, e.g., the degree of a stenosis.

Previous studies often focused on either mechanical or morphological characteristics of a plaque. An innovative development in this thesis is the integrated assessment of both characteristics to reveal their associations (**Chapter 6 and 7**). For example, in **Chapter 7** we showed associations between the risetime inhomogeneity of distension distribution obtained for the common carotid artery, and the composition of a distal plaque as determined by magnetic resonance imaging. Therefore, the suggested ultrasound technique might simplify assessment of plaque vulnerability.

Future perspectives towards clinical implementation

This thesis focuses on the baseline results of the PARISK study, because the 2-year follow-up study could not be completed within the available time frame. All non-invasive imaging techniques are reapplied in 150 patients 2 years after inclusion. From these follow-up data plaque progression, i.e. change in plaque size, can be extracted and related to the risk factors obtained with the non-invasive imaging techniques (US, MRI and CT). The main endpoint, i.e. which patients endured a recurrent TIA or stroke, will be available at the end of 2016. Since only a few patients will suffer from a recurrent TIA or stroke, the follow-up is extended for another three years.

It would be very interesting to determine the factors, present at baseline, that predict a TIA or stroke. Moreover, the results might establish the relative relevance of the respective imaging techniques including the sequence of application. Preference should be given to techniques that are widely available and can be imminently applied to act as a first screening tool for patient selection. A large randomized trial will be necessary to prove the prediction value of the determined risk factors and to eventually incorporate the new findings in clinical practice. Already, a large longitudinal study (European Carotid Surgery Trial-2) has started which also includes MR and ultrasound plaque imaging.

References

Buisman LR, Tan SS, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Hospital costs of ischemic stroke and TIA in the Netherlands. Neurology 2015;84:2208-2215.

Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, Stern B, Wilterdink J, Therapeutics, Technology Assessment Subcommittee of the American Academy of N. Carotid endarterectomy--an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65:794-801.

Koopman C, van Dis I, Vaartjes I, Visseren FLJ, Bots ML. Hart- en vaatziekten in Nederland 2014, cijfers over kwaliteit van leven, ziekte en sterfte. 2014

Meinders JM, Brands PJ, Willigers JM, Kornet L, Hoeks AP. Assessment of the spatial homogeneity of artery dimension parameters with high frame rate 2-D B-mode. Ultrasound Med Biol 2001;27:785-794.

Nederlandse vereniging voor Neurologie. Richtlijn Diagnostiek, behandeling en zorg voor patienten met een beroerte. 2008

Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. European cardiovascular disease statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis 2012;

Park JH, Ovbiagele B. Optimal combination secondary prevention drug treatment and stroke outcomes. Neurology 2015;84:50-56.