

## **Intraplaque hemorrhage identifies patients at risk for new silent brain ischemia prior to carotid endarterectomy**

M.L. Rots<sup>a</sup>, N. Timmerman<sup>a</sup>, D.P.V. de Kleijn<sup>a</sup>, G. Pasterkamp<sup>b</sup>, M. Brown<sup>c</sup>, L.H. Bonati<sup>d</sup>, G.J. de Borst<sup>a</sup>  
Department of vascular surgery, University Medical Centre Utrecht, Utrecht the Netherlands

<sup>a</sup> Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands.

<sup>b</sup> Experimental Cardiology Laboratory, University Medical Center Utrecht, Utrecht, the Netherlands.

<sup>c</sup> Department of Neurology and Neurosurgery, University College London Hospitals, London, United Kingdom

<sup>d</sup> Department of Neurology and Stroke Center, Department of Clinical Research, University Hospital Basel, University of Basel

*Correspondence to:* Professor Gert J. de Borst, Department of Vascular Surgery, University Medical Center Utrecht, Room G04.129, PO Box 85500, 3508 GA Utrecht, the Netherlands; e-mail: [g.j.deborst-2@umcutrecht.nl](mailto:g.j.deborst-2@umcutrecht.nl); tel. +31887556965.

Article category: original research

Short title: *Intraplaque haemorrhage as risk factor for new silent brain ischemia*

Word count (introduction – references): 3359

*What this study adds:*

This study investigated the relation between histological apparent intraplaque haemorrhage (IPH) and presence of lesions on diffusion weighted imaging prior to carotid endarterectomy. We demonstrated that patients with IPH have an increased risk for development of new silent brain ischemia in the waiting period between index event and surgery. These results qualify IPH as a potential marker for identifying patients at risk for recurrent events.

## ABSTRACT

### OBJECTIVE

Intraplaque hemorrhage (IPH) has been independently associated with a higher risk of ipsilateral stroke in patients with carotid artery stenosis and is more often seen in patients with symptomatic than in patients with asymptomatic stenosis. Evaluation of plaque characteristics may be helpful for risk assessment of recurrent (silent) cerebrovascular events in order to help prioritizing patients for timing of treatment. It is unknown if patients showing histologically apparent IPH also have an increased risk of silent ischemic brain lesions in the time interval between index event and revascularization.

### METHODS

A retrospective analysis was performed based on prospectively collected data of patients included simultaneously in the MRI-substudy of the International Carotid Stenting Study and the Athero-Express biobank. Patients randomized for carotid endarterectomy (CEA) were operated between 2003-2008. Plaque was histologically examined for presence of IPH, MRI was performed 1-3 days prior to CEA. Primary outcome parameter was presence of silent ipsilateral ischemia on MR-DWI appearing hypo-/isointense on apparent diffusion coefficient, thereby excluding older lesions.

### RESULTS

A number of 53 patients with symptomatic carotid stenosis were included of which 13 showed  $\geq 1$  recent ipsilateral DWI lesion on pre-operative scan. Time between latest event and revascularization was 45 days (IQR 20-70) in DWI-negative patients versus 34 days (IQR 21-53,  $p=.16$ ) in DWI-positive patients. IPH was present in 24/40 (60.0%) DWI-negative patients versus 12/13 (92.3%) DWI-positive patients. Multivariate logistic regression analysis with correction for age and type of index event revealed that IPH was an independent predictor for development of new DWI lesions in the waiting period till surgery (OR: 10.8; 95% CI:1.17-99.9,  $p=.036$ ).

### CONCLUSION

In symptomatic carotid patients, IPH is associated with an increased risk of new silent brain ischemia on MR-DWI during the waiting period until revascularization. This identifies carotid IPH as a marker for identifying patients at risk for new silent brain ischemia.

**Key words:** carotid stenosis, intraplaque hemorrhage, silent brain ischemia, MR-DWI

## INTRODUCTION

The presence of carotid artery intraplaque hemorrhage is considered an important marker of plaque instability and associated with a high risk for clinically relevant events such as transient ischemic attack (TIA) or stroke due to the tendency to rupture. Signs of presence of IPH on magnetic resonance imaging (MRI) or duplex have been associated with an increased risk of future cerebrovascular events and IPH is more common in symptomatic patients compared to asymptomatic patients<sup>1,2</sup>. Moreover, IPH is associated with increased risk of secondary cardiovascular events in male patients<sup>3</sup>.

Risk assessment of recurrent cerebrovascular events based on plaque characteristics may be helpful for prioritizing patients for the timing of carotid revascularization. Current guidelines recommend that patients presenting with a symptomatic carotid stenosis should be considered (in case of 50-69% stenosis) or recommended (in case of 70-99% stenosis) for treatment within 14 days of the index event<sup>4</sup>. Nonetheless, these recommendations have been based on post hoc analyses of outdated RCT's and additionally may not always be feasible due to pre-hospital or in-hospital delay<sup>5</sup>. Identification of IPH may help to select patients that are most at risk for recurrent events and may help to select those in which urgent revascularization may be appropriate.

Ischemic brain lesions on magnetic resonance diffusion weighted imaging (MR-DWI) are increasingly being used as a surrogate marker of ischemic events for postoperative outcome after revascularization as they are associated with an increased risk of future cerebrovascular events<sup>6</sup>. To date, few studies have focused on the role of new DWI lesions in the preoperative period. One of the major advantages of assessment of presence of new DWI lesions is that they can be seen within few hours after a thrombo-embolic event and are therefore sensitive to recent changes. By assessing diffusion restricted brain areas with MR-DWI in combination with apparent diffusion coefficient (ADC), lesions of less than ten days of age can be identified. This method to estimate the age of an ischemic lesion can be useful to distinguish lesions accessory to the index event from recurrent thrombo-embolism prior to revascularization. Until now, it is unclear if carotid plaque characteristics are associated with these brain lesions identifying them

as their potential source. For this, we investigated whether patients with characteristics of plaque instability have an increased risk of recurrent preprocedural ischemic brain lesions during their waiting period for carotid intervention.

Since thrombo-embolic events are the most common underlying cause of ischemic brain lesions in carotid patients, we hypothesize that patients showing histologically apparent signs of IPH in the atherosclerotic plaque (excised during carotid endarterectomy) have an increased risk of recurrent silent ischemic brain lesions in the time interval between index event and revascularization.

## METHODS

A retrospective analysis was performed based on prospectively collected data of patients included simultaneously in the MRI-substudy of the International carotid stenting study (ICSS)<sup>7</sup> and the Athero-Express (AE). Patients that underwent carotid endarterectomy (CEA) between October 2003 and October 2008 were included. Patients included in the ICSS were symptomatic carotid stenosis patients with stenosis >50% deemed to require treatment with the following exclusion criteria: previous revascularization in the randomized artery, contraindications for either treatment and planned major surgery<sup>8</sup>. As the atherosclerotic plaque was collected in the AE biobank, only patients that were randomized for endarterectomy were included in this study. No additional exclusion criteria were asserted.

### *Atherosclerotic plaque assessment*

After CEA, all atherosclerotic plaques were immediately processed. The culprit lesions were divided into segments of 5-mm thickness along the longitudinal axis. The segment with the largest plaque burden was chosen as a culprit lesion and subjected to histological examination. A more detailed description can be found in the supplemental methods. The investigated plaque characteristics resulting from immunochemical staining were: presence of IPH, presence of lipid core ( $\geq 40\%$ ), moderate/heavy calcifications, moderate/heavy collagen, mean number of microvessels per hotspot, percentage of positive macrophage staining per plaque and percentage of positive smooth muscle cell (SMC) staining per plaque<sup>9</sup>.

### *MRI*

Primary outcome parameters include ipsilateral ischemic lesions on MR-DWI appearing hypo-/isointense on apparent diffusion coefficient (ADC), thereby excluding lesions > 10 days old, and its correlation to intraplaque hemorrhage (see figure 1 for an illustrative timeline)<sup>10</sup>. Secondary outcome parameters include presence of white matter lesions (WML), semi-quantitatively assessed on FLAIR sequences by

use of the sum of the ipsilateral age-related-white matter changes (ARWMC) score (see supplemental table SI)<sup>11</sup>.

### *Statistics*

Data were inspected for patterns of missing values. The proportion of randomly missing values for baseline characteristics did not exceed 2%. Differences in binary characteristics were analyzed with Pearson's Chi square. Differences in continuous parameters were calculated with a student's t-test when data were normally distributed and otherwise using a Mann-Whitney U test. For the ARWMC score a binary outcome parameter was used based on median ipsilateral ARWMC score (sum score  $\leq 2$  compared to sum score  $> 2$ ). To investigate independent associations between histological plaque characteristics and presence of fresh DWI lesions as well as ARWMC score, we conducted a multivariable binary logistics regression analysis correcting for age and type of index event as well as any baseline characteristics with  $p < 0.1$  in univariate analysis. In case of ARWMC score, estimated-packyears was identified as an additional potential confounder and therefore included in multivariate analysis. Non-normally distributed quantitative histological parameters including number of microvessels and percentages of macrophage and SMC staining required logarithmic transformation before entering into regression models. SPSS 25.0 (SPSS Inc, Chicago, Illinois, USA) was used for all statistical analysis.

## RESULTS

### *Patient characteristics*

A number of 53 patients met the inclusion criteria. Thirteen patients had preoperative ipsilateral DWI lesions that appeared hypo- or isointense on ADC. Baseline characteristics of patients with and without recent DWI lesions are presented in table 1, no statistical differences in baseline features were found between the two groups. The median time between the latest symptom and revascularization was 45 days (IQR 20-70) in the DWI-negative group and 34 days (IQR 21-53,  $p=0.16$ ) in the DWI-positive group.

### *DWI lesions*

In patients with preoperative ipsilateral DWI lesions, median number of DWI lesions was 1 (range 1-6). The investigated histological plaque characteristics are shown in table 2 for DWI-negative and DWI-positive patients. 24 out of 40 (60.0%) DWI-negative patients showed intraplaque hemorrhage on histological assessment, versus 12 out of 13 (92.3%) in DWI-positive patients. A lipid-core of  $\geq 40\%$  was present more often in the DWI-negative group (23/40; 57.7%) compared to the DWI-positive group (3/13; 23.1%). For other plaque characteristics, incidences were similar between DWI-positive and DWI-negative patients. Of the total of 36 patients with IPH, 12 (33.3%) had preoperative DWI lesions, of 17 patients without IPH 1 (6%) showed DWI lesions. Univariate binary logistic regression showed an odds ratio (OR) of 8.0 (95% CI: 0.95 – 67.7,  $p=.056$ ) for presence of DWI lesions in IPH-positive patients compared to IPH-negative patients. Multivariate logistic regression analysis with correction for age and type of index event revealed that IPH was an independent predictor for development of new DWI lesions in the waiting period till surgery (OR: 10.8; 95% CI: 1.17-99.9,  $p=.036$ ). Univariate analysis showed decreased odds for presence of DWI lesions in patients with a large ( $>40\%$ ) lipid core (OR: 0.22; 95% CI: 0.05 – 0.93,  $p=.040$ ) which remained significant after correction for age and type of index event (OR: 0.184; 95%-CI: 0.041-0.836,  $p=.028$ ). Other plaque characteristics did not show any significant association with development of new lesions in uni- or multivariate analysis. Median number of ipsilateral DWI lesions in IPH positive patients ranged from 0-6 versus 0-1 DWI lesions in IPH negative patients ( $p=0.032$ ). Of the complete cohort, two patients had a (single) contralateral DWI lesion, one of them was IPH positive and one was IPH negative.



### *ARWMC score*

Median ipsilateral ARWMC sum score was 2. Patients with an ipsilateral ARWMC sum score of  $\leq 2$  (n=30) were compared to those with a score  $>2$  (n=23). Patients with a high ARWMC sum score were significantly older ( $72.5 \pm 6.46$ ) compared to patients with a low score ( $65.3 \pm 8.63$ ,  $p=.002$ ), other baseline characteristics did not differ between the two groups (see supplemental table SII). Univariate analysis showed fewer macrophage staining in the high-ARWMC group (OR: 0.19; 95% CI: 0.05 – 0.75,  $p=.017$ ), which was no longer significant after adjustment for confounders in multivariate logistic regression (OR: 0.232 95% CI: 0.052 – 10.02  $p = .053$ ), see supplemental table SIII.

### *Postoperative course*

The median follow-up period was 3.0 years (IQR: 2.9-3.2). Of the 53 included patients eight had a major cardiovascular event: four developed stroke (two ischemic and two hemorrhagic) stroke; three suffered from myocardial infarction (MI) and one additional patient died of cardiovascular origin. All but one of these patients were IPH-positive, of the IPH-negative patients one patient had MI, no IPH-negative patients suffered from stroke or died of cardiovascular disease during follow-up period.

## DISCUSSION

This study investigated the presence of recent silent ischemic lesions in patients with IPH compared to those without IPH. We demonstrated that presence of MR-DWI ischemic brain lesions in the time interval between symptom onset and revascularization is associated with carotid IPH, irrespective of type of index event, identifying IPH as the potential pathological substrate for such lesions.

This finding is in agreement with pathological and imaging studies on plaque instability, showing that intraplaque hemorrhage is an independent risk factor for future stroke or TIA in patients with carotid artery atherosclerosis<sup>12,13</sup>. This study, relating histological data to the development of new ischemic lesions, provides unique insight in natural course and pathology up until revascularization. The results suggest that revascularization of patients with IPH should be prioritized over patients without IPH in terms of averting the risk of recurrent ischemia, also in case of hospital presentation of >14 days after the index event. Moreover, a broad consensus on urgent versus 'delayed' treatment is still lacking<sup>5,14-17</sup>. This study contributes to the ongoing discussion on this matter by stressing the importance of eliminating an unstable plaque prior to any recurrent event. A more tailored therapy for symptomatic patients based on amongst others plaque imaging may be a solution for risk reduction of individual patients.

One other clinical study showed that patients with symptomatic carotid stenosis with IPH are more likely to develop recurrent cerebrovascular events in the waiting period until revascularization<sup>18</sup>. This study did not use histological data but MR T1-weighted 3-dimensional gradient echo sequence to demonstrate IPH. Reliable methods for preoperative assessment of IPH on imaging are essential for clinical applicability. Over the years, several studies investigating IPH-imaging on MR have been performed using various sequences and protocols<sup>19,20</sup>. More recent articles propose magnetization-prepared rapid acquisition gradient-echo (MPRAGE) as one of the most promising for sequence identification of IPH, with high sensitivity, specificity and k-values when validated with histological data<sup>21</sup>. However, reliability of MR imaging of IPH in the plaque is still limited in case of smaller hemorrhages or coexisting calcifications<sup>21</sup>.

We found that presence of a large lipid core was negatively associated with new DWI lesions whereas hypercholesterolemia and statin use did not differ between groups. One might expect a lipid rich necrotic

core to be positively associated with plaque instability and therefore recurrent events. Nonetheless, our results are in agreement with earlier research showing that large lipid core and macrophages are not associated with vascular events although no subanalysis was done for cerebrovascular events<sup>22</sup>. Another study comparing symptomatic to asymptomatic arteries within patients with unilateral symptomatic carotid stenosis, also found that IPH but not a large lipid core was seen more often on the symptomatic side<sup>23</sup>. Perhaps the presence of a large lipid core shows that plaque rupture has not yet occurred and therefore at this time does not characterize an acute risk for thrombo-embolisms.

This study used MR-DWI in combination with ADC imaging as our primary outcome parameter. Presence of DWI lesions as a surrogate marker for cerebral ischemia may become increasingly important, especially considering the evidence that DWI lesions are associated with a higher risk for recurrent cerebrovascular events<sup>6</sup>. As the rate of recurrent cerebrovascular events in the period up until revascularization is relatively low, the use of DWI lesions as a surrogate marker (occurring in 28% of patients) provides the opportunity to detect statistically significant differences in relatively small patient cohorts. We did not find a difference in ARWMC score between IPH positive and IPH negative patients. Although one might hypothesize that plaque instability can contribute to development of age related white matter lesions via embolic events<sup>18</sup>, convincing evidence of a causal relation between the two was not demonstrate in earlier studies either <sup>24,25</sup>. A shared etiology for atherosclerosis and white matter lesions may be more likely<sup>25</sup>.

### *Limitations*

Intraplaque hemorrhage was determined histologically after exciding the plaque during CEA. As the time interval between symptom onset and surgery was quite large this does not necessarily mean that IPH was already present on moment of index event. Relation to signs of IPH on preoperative imaging (MRI/duplex) may have improved the clinical applicability of our data. Additionally, we did not perform analyses to differentiation older (healed) IPH from acute IPH; although identification of healed IPH on histology is technically possible as shown in studies of coronary arteries<sup>26</sup>.

In the context of clinical relevance, the impact of DWI-lesions on future cerebrovascular events would have been of interest. However, MR-DWI performed within few days after revascularization revealed that several patients developed (new) periprocedural DWI-lesions. Hence, any correlation between presence of DWI-lesions on preoperative imaging and future events is clouded by the carotid intervention shortly after and thus no statements can be made on the clinical impact of preprocedural silent ischemic lesions.

We are aware of the chance of type II statistical error or overfitting of our statistical model as a result of the small patient cohort. Patients of this study were included between 2004 and 2007 when, under current standards, substantial delay between hospital presentation and intervention was common practice. Considering the gained insights and ensuing guidelines on timing of carotid revascularization it would not be feasible or ethical to repeat a similar study in this day and age and we will therefore not be able to extend our population. We do believe that the obtained knowledge is of surplus value as prioritizing patients may be challenging when multiple patients qualify for treatment at the same time. Also, patients with a late hospital-presentation may sometimes be postponed in favor of patients with more recent events. This study emphasizes the relevance of prompt acting even after passing of 14 days since index events. This small patient cohort also limits statistical comparison of the clinical course of IPH-positive versus IPH-negative as well as DWI-positive versus DWI-negative patients. Future research should focus on validation of the found results in a large cohort using both histological data as well as MRI-plaque data to compare to development of future cerebrovascular events. Identification of histological IPH as a potential source for early ischemic brain lesions shows the importance of plaque characteristics on cerebral events that may also be used as indication for treatment in asymptomatic carotid stenosis patients. Studies on imaging of carotid plaque IPH and follow-up in asymptomatic patients are needed to confirm this.

### *Conclusion*

In this study, we demonstrated that carotid plaque IPH is associated with increased silent cerebral ischemia on MR-DWI prior to revascularization. This qualifies IPH as a potential marker for identifying patients at risk for these ischemic brain lesions.

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