Clinical Significance of Intraluminal Contrast Enhancement in Patients with Spontaneous Cervical Artery Dissection: A Black-Blood MRI Study

Klinische Relevanz der intraluminalen Kontrastmittelaufnahme bei Patienten mit spontaner arterieller Dissektion der Halsgefäße: eine Black-Blood MRT-Studie

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ZUSAMMENFASSUNG

Material und Methoden 33 Patienten mit spontaner arterieller Dissektion der Halsgefäße (sCAD) erhielten ein MRT des Kopfes (Diffusion, T2w, T2*w, FLAIR) und eine 3T-MRT-Untersuchung der Halsgefäße mit hochaufgelösten fettgesättigten BB Sequenzen vor und nach Kontrastmittelgabe, sowie einer TOF-Sequenz. Nachweis oder Abwesenheit einer intraluminalen Kontrastmittelaufnahme (iCE), eines Gefäßverschlusses und eines Gefäßwandhämatoms (hyperintenses Signal in T1w vor Kontrastmittelgabe) wurden von zwei Radiologen im Konensus untersucht.

Ergebnisse In 44 von 132 bewerteten Gefäßen wurde ein Gefäßwandhämatom gefunden, vereinbar mit einer sCAD. Bei 17 von 44 dissezierten Gefäßen wurde in der Hirn-MRT ein akuter Schlaganfall auf derselben Seite diagnostiziert. 16 von 17 (94,1 %) dieser Gefäße ipsilateral des Schlaganfalls zeigten ein iCE, verglichen mit 9 von 44 (20,4 %) dissezierten Gefäßen ohne Nachweis eines Schlaganfall (p<0,001). Die Auswertung (Nachweises oder Abwesenheit von iCE) ergab eine Sensitivität, eine Spezifität, einen positiven bzw. negativen prädiktiven Wert sowie eine Accuracy von 0,94; 0,67, 0,64 und 0,95 und 0,77, sowie eine Odds ratio von 32,0.

Schlussfolgerung iCE scheint eine intraluminale Thrombosierung anzuzeigen, die streng korreliert ist mit ischämischen Symptomen bei Patienten mit einer sCAD.

Kernaussagen
- Bei Patienten mit arterieller Dissektion der Halsgefäße korreliert die intraluminale Kontrastmittelaufnahme mit einer umschriebenen Hirn-Ishämie im entsprechenden Gefäßterritorium.
Introduction

Cervical artery dissection (CAD) can provoke a variety of often nonspecific neurological symptoms such as headache/migraine, neck pain, Horner’s syndrome or other cranial nerve anomalies [1] and is an increasingly recognized cause of ischemic stroke, particularly in younger patients [2]. Although the majority of patients with CAD have a good prognosis, it is unclear why some patients suffer a stroke [3] and why some patients develop a stroke during follow-up [4]. Several hypotheses for the pathogenesis of spontaneous cervical artery dissection (sCAD) have been formulated:

One theory presumes a spontaneous rupture of the vasa vasorum of the artery which leads to pseudoaneurysms or rupture if the defect is located between the adventitia and media of the arterial wall [5, 6] or to stenosis or occlusion if located between the intima and media. Another theory suggests the creation of an intimal tear, which allows the entry of blood into the defect which then forms the vessel wall hematoma [7]. In sCAD abnormalities of the connective tissue [8] and association with vessel wall inflammation [9] have been discussed as predisposing factors for their occurrence.

Early diagnosis of CAD is of utmost importance and MRI has become a first-line diagnostic tool for CAD [10, 11]. Previous studies have shown that high-resolution black-blood (bb) MRI is ideally suited to visualize acute CAD, as it offers excellent visualization of the lumen, wall and peri-adventitial tissue and it allows visualization of the intimal tear noninvasively [12, 13]. The separation of the intimal layer of the vessel wall may lead to endothelium damage and the activation of blood clotting which ultimately may lead to thrombus formation [10, 14]. Thrombosis in the dissected arterial segment may then lead to vessel occlusion or embolization further downstream.

In CAD fat-suppressed T1w sequences reveal the characteristic hyperintense signal which represents the vessel wall hematoma (crescent sign) [15, 16]. bb-MRI suppresses the signal of flowing blood which allows differentiation of the vessel wall and its components from the lumen, which appears dark. This technique has been used successfully for carotid plaque imaging [17], for the detection of venous thrombi [18] and for the visualization of CAD [13, 19 – 21]. It has also been used successfully to image plaque rupture and local blood coagulation in carotid atherosclerotic plaques [12, 17, 18, 22, 23].

Our own observations of occluded vessels in patients with spontaneous cervical artery dissection (sCAD) and Takayasu vasculitis and recent studies in venous thrombi (look for venous thrombosis of the intracranial veins with the SPACE sequence) have suggested that intra-luminal thrombi are characterized by intraluminal contrast enhancement (iCE) on T1w-bb-MRI. The aim of the study was to evaluate the association of iCE with ischemic stroke in patients with sCAD.
Materials and Methods

Patients

Patients with sCAD treated at our center between August 23rd 2007 and June 29th 2010 were prospectively included in the study if the following inclusion criteria were fulfilled:
1. Clinical suspicion of CAD and evidence of vessel wall hematoma on standard neck MRI (hyperintense signal on fat-suppressed T1w sequences demonstrating intramural methemoglobin accumulation and stenosis or occlusion in contrast-enhanced (CE) MR angiography)
2. Performance of standard brain MRI consisting of fluid-attenuated inversion recovery sequence (FLAIR), T2-weighted sequence (T2w), diffusion-weighted sequences (Diff), 3D time-of-flight sequence (TOF)
3. Written informed consent, and
4. Performance of high-resolution fat-suppressed T1w-bb-MRI within 1 week after standard brain and neck MRI diagnostics.

The study was approved by the local institutional ethics committee and complied with the Declaration of Helsinki.

MRI

Patients with clinical suspicion of sCAD were routinely examined with a 1.5 T Symphony® (Siemens Medical Solutions, Erlangen, Germany) or a 3.0 T GE scanner (Signa® HDxt, GE Healthcare, Milwaukee, WI, USA) using a standard head and neck coil.

Standard neck sequences included fat-suppressed (fs) T1w sequences with a slice thickness of 3.5 mm (1.5 T) or 3.0 mm (3 T) in the coronal and axial plane and contrast-enhanced MR angiography (CE-MRA) with a pixel size of 0.84 × 0.84 mm² (1.5 T) or 1.0 × 1.0 mm² (3 T) (fs T1w and CE-MRA = standard neck MRI). Maximum intensity projections (MIP) were carried out for the representation of CE-MRA. The contrast medium Gadobutrol (Gadovist®, Bayer Vital, Leverkusen, Germany) was applied in a dose of 0.1 mmol/kg body weight. In the same examination a 1.5 T Symphony® (Siemens Medical Solutions, Erlangen, Germany) o ra 3 . 0 TG Es c a n n e r( S i g n a ® HDxt, GE Healthcare, Milwaukee, WI, USA) using a standard head and neck coil.

Within one week a multi-sequence 3 T high-resolution MRI scan (Verio®, Siemens Medical Solutions, Erlangen, Germany) with a flexible 4-channel carotid surface coil (Machnet BV, Eelde, ND) [9] was executed consisting of fat-saturated T1w-bb-sequences pre- and post-contrast. High resolution was defined as a spatial resolution with an in-plane pixel size of 0.5 × 0.5 mm² and a slice thickness of 2 mm. The image parameters are listed in ▶ Table 1.

Image Analysis

The presence or absence of iCE, vessel occlusion and vessel wall hematoma on T1w-bb images pre- and post-contrast of both carotid and both vertebral arteries were reviewed by two experienced radiologists in consensus decision (T.S; E.C.). The radiologists were blinded to all clinical information and the standard brain MRI. Image quality was rated as followed: 4 = excellent, uniform image; 3 = good, minimal heterogeneity, only minor flow artifacts; 2 = satisfactory, delineated lumen, noticeable flow artifacts; 1 = not suitable for diagnosis. Diagnostic confidence was rated as 4 = excellent, exact diagnosis possible; 3 = good, with definite diagnosis possible; 2 = fair, judgement of major findings possible; 1 = poor with definite diagnosis not possible. A vessel wall hematoma was defined as an area of hyperintense signal intensity on pre-contrast T1w-bb images in the vessel wall. Additional criteria for vessel wall hematoma were a crescent-shaped hyperintensity and/or an intimal flap best seen on TOF images. ICE was defined as an area of intraluminal contrast enhancement on post-contrast T1w-bb images. Vessel occlusion was identified by a filling defect on MRA images.

Statistics

Statistical analysis was carried out with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). To correlate the parameters “ICE/stroke”, “ICE/vessel occlusion”, and “vessel occlusion/stroke”, standard 4x4 contingency tables were used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, accuracy and odds ratio. Differences in distribution regarding catego-
rical variables, such as risk factor profiles, were analyzed using the Fisher’s exact test. A p-value of < 0.05 was considered to be statistically significant.

Results

33 patients with sCAD fulfilled the inclusion criteria. ► Table 2 gives an overview of the demographics, clinical presentation and cardiovascular risk factors. The mean age was 47 ± 12.1 years. Dissections were found in 19 men and 14 women (58/42 %). In 33 patients 132 vessels were evaluated (2 carotid and 2 vertebral arteries per patient). 44 out of 132 analyzed vessels showed a vessel wall hematoma consistent with CAD. 23 patients had one dissection, 9 patients two and one patient three dissections (► Table 3).

The location of the dissected arterial segments is given in ► Table 4 using the Bouthillier classification. About two-thirds of the dissections were located in the internal carotid artery (p = 0.07, not significant, ► Table 3). Women were more likely to present with more than one dissection (3 men with ≥ two dissections compared to 7 women with ≥ two dissections, p < 0.05).

The image quality of T1w-bb sequences was found to be good or very good (mean: 3.7, range: 3 – 4). Diagnostic confidence was rated even better (mean: 3.9, range: 3 – 4). 17 strokes were found in the corresponding vessel territory of sCAD. There was a tendency to a higher prevalence of ischemic stroke in vessel territories of the internal carotid artery compared to the vertebral arteries (48 % vs. 20 %, p = 0.068, n.s.). 16 of these dissected arteries showed iCE in the dissected vessel segment, and one vessel showed no ICE. In 9 dissected vessels without a stroke, iCE was detected in the dissected vessel segments. In 18 dissected vessels neither a stroke nor iCE could be found in the dissected vessel segments ( ► Table 5). Fisher’s exact test for association of iCE and stroke was highly significant (p < 0.001). iCE in the prediction of stroke showed a sensitivity of 94 %, a specificity of 67 %, a positive predictive value of 64 %, a negative predictive value of 95 % and an accuracy of 77 %. The odds ratio was 32.0 (confidence interval 3.6 – 281).

In the 44 dissected vessel segments of our study, 15 segments showed occlusion. In 14 out of 15 occluded vessel segments, iCE could be found. Stroke was detected in the vessel territory of 12 occluded vessels and in 5 non-occluded dissected vessel segments. In three occluded vessel segments, no stroke was found, 24 dissected vessels were not occluded and did not reveal a stroke. In the Chi-square test a significant test result was observed for vessel occlusion/contrast enhancement and vessel occlusion/stroke (p < 0.001).

Discussion

In this mono-centric, prospective and observational study, we were able to show that the presence of ICE in patients with sCAD on T1w-bb images is highly associated with ischemic stroke in the corresponding vessel territory. In fact 16 out of 17 vessels with CAD and stroke in the corresponding vessel territory had iCE which in our opinion shows that iCE is indicative of intraluminal thrombus formation. This is supported by the finding that nearly all occluded vessels (14 out of 15) had ICE. However, ICE also occurred in non-occluded vessels and further studies are warranted to investigate the association of ICE in non-occluded vessels with sCAD and the risk of ischemic stroke or its reoccurrence.
Patient age and characteristics in our sCAD study were similar to previous studies [24]. In our investigation stroke was found in 52 % of patients, which is consistent with the literature in which the stroke incidence in sCAD patients ranges from 20 – 60 % [24, 25]. MRI is ideally suited to diagnose vessel wall hematoma. Although fat-suppressed T1w images without the use of contrast media are able to visualize the vessel wall hematoma, addition of bb-pre-pulses (e. g. double or quadruple inversion recovery = DIR or QIR) offer the advantage of the simultaneous assessment of intraluminal changes and the vessel wall [13]. This study showed that the combined assessment of the vessel wall and intraluminal changes with T1w-bb MRI is feasible and that this technique results in good to excellent image quality and yields a high diagnostic confidence level for the diagnosis of sCAD. In addition, to differentiate iCE from intraluminal flow artifacts, sufficient flow suppression is mandatory.

Previous observations in patients with sCAD and in patients with occluded vessels in Takayasu disease led us to believe that iCE on T1w-bb-MRI represents thrombus formation. In this study we therefore sought to evaluate the significance of iCE in patients with sCAD on clinical symptom status. The high correlation between iCE in the dissected vessel segments and stroke is in

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Table 4 Dissected arterial segments (Bouthillier classification).

Dissected arterial segments (Bouthillier classification).

sex | age | vessel | side | location
--- | --- | --- | --- | ---
m | 42  | ICA    | right | C1     |
m | 62  | ICA    | right | C2     |
m | 45  | ICA    | left  | C1/C2  |
m | 44  | ICA    | right | C1/C3  |
m | 56  | ICA    | left  | C1/C6  |
m | 50  | ICA    | left  | C1     |
m | 66  | ICA    | left  | C1     |
m | 34  | ICA    | left  | C2/C3/BIF |
m | 55  | ICA    | left  | C1/C2  |
m | 55  | ICA    | left  | C1/C2  |
m | 52  | ICA    | left  | C1/C2  |
m | 45  | ICA    | left  | C1      |
m | 62  | VA     | right | V3     |
m | 62  | VA     | left  | V3     |
m | 48  | VA     | left  | V3/V4  |
m | 59  | VA     | right | V3     |
m | 50  | ICA    | right | C1     |
m | 72  | VA     | right | V4     |
m | 47  | ICA    | left  | C1     |
m | 43  | ICA    | right | C1/C2/BIF |
w | 45  | ICA    | right | C2     |
w | 44  | ICA    | right | C2     |
w | 24  | ICA    | right | C1     |
w | VA | right  | V1     |
w | VA | left   | V1     |
w | 41  | ICA    | left  | C1     |
w | VA | left   | V2/V3  |
w | 34  | ICA    | right | C1     |
w | VA | left   | V2/V4  |
w | 35  | ICA    | right | C1/C2/BIF |
w | ICA| left  | C1/C2/BIF |
w | 43  | ICA    | right | C1/BIF |
w | 35  | VA     | left  | V2/V3  |
w | 45  | ICA    | right | C2/C3  |
w | 46  | VA     | right | V2     |
w | 63  | ICA    | right | C1/C2  |
w | ICA| left  | C1/C2  |

Table 5 Intraluminal contrast enhancement in dissected vessels and stroke.

Intraluminal contrast enhancement

<table>
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<th>vessel</th>
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<td>w</td>
<td>33</td>
<td>ICA</td>
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<tr>
<td>w</td>
<td>31</td>
<td>VA</td>
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<td>V3/V4</td>
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<td>w</td>
<td>44</td>
<td>ICA</td>
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1 in dependent vessel territory.

ICA: internal carotid artery; VA: vertebral artery; BIF: carotid bifurcation Bouthillier classification of dissected arterial segments (C1 = cervical segment, C2 = petrous segment, C3 = lacerum segment, C4 = cavernous segment, C5 = clinoid segment, C6 = suprACLINOID [ophthalmic] segment, C7 = terminal [communicating] segment of ICA; V1 = preforaminal segment, V2 = foraminal segment, V3 = atlantic [extradural] segment, V4 = intradural segment of VA)
accordance with our hypothesis, although our study group is small. Information about the presence/absence of intraluminal thrombus is important as previous studies have shown that large infarcts causing death or severe disability were associated with a thrombus in the internal carotid artery and distal emboli [26]. Although the risk of recurrent stroke in CAD is generally considered to be low (stroke recurrence rates of 1–3% have been reported [4, 27]), one could assume that patients with iCE have a higher risk for stroke recurrence compared to patients without iCE. One subgroup in our patient cohort without stroke might be particularly interesting: asymptomatic patients with iCE. These patients could have a higher risk of stroke compared to asymptomatic patients without iCE. It is known that a subset of patients with initially stroke-free sCAD suffer a stroke within the first weeks after occurrence of sCAD [28] which could be caused by thrombus formation. Whether certain subgroups of patients could profit from more aggressive anti-thrombotic therapy remains to be evaluated in future studies. Only trials much larger...
than ours could possibly answer this question. Because MRI is increasingly used in the routine diagnostic workup of CAD patients, high-resolution, contrast-enhanced, T1-weighted sequences could easily be included in a respective study protocol.

sCAD and severe ischemic stroke were more closely associated in the internal carotid compared to the vertebral arteries. This finding is consistent with the literature [29]. One possible explanation for this is that even in the case of total vessel occlusion the vertebral artery has good collateralization over the contralateral side. However, our results missed the level of significance (p = 0.07), probably due to the small number of patients.

Limitations

Our study is relatively small and larger studies are necessary to confirm these initially very promising results. Because of the good functional outcome in most of our patients, we cannot provide much information on the clinical, therapeutic, and prognostic relevance of iCE in sCAD patients in the long term. However, the association of iCE with ischemic stroke in the corresponding vessel territory suggests that iCE could be a potential imaging biomarker to identify patients with a possibly higher risk of adverse outcomes. The current study used 2D pre- and post-contrast T1w sequences which have a relatively large slice thickness of 2 mm and are time-consuming. For future studies of arterial dissection, 3D-T1w black-blood sequences such as 3D-T1w-VISTA or 3D-T1w-SPACE seem to be promising candidates as they provide superior coverage and sub-mm resolution. These sequences have already been applied successfully for thrombus imaging [18] and for vasculitis imaging [30]. Furthermore, we cannot provide histological proof that iCE represents thrombus formation which is due to the fact that histology is usually not obtained in sCAD patients. iCE can also be found in stenosed vessels or when slow flow occurs although – based on our clinical experience – the contrast enhancement in slow flow is lower and more focal and can therefore in most cases be easily differentiated from iCE in thrombi.

Conclusion

The presence of iCE in T1w-black-blood MR imaging is strongly correlated with ischemic events in the corresponding vessel territory in patients with sCAD, which is highly suggestive that iCE represents intraluminal thrombus formation. Future prospective studies will have to determine whether patients with iCE are at greater risk for recurrent stroke or a worse clinical outcome.

**CLINICAL RELEVANCE**

- Intraluminal contrast enhancement is correlated with ischemic events in patients with spontaneous cervical artery dissection.
- T1-w-black-blood MR imaging provides a novel tool to detect intravascular thrombus formation.
- The results may be beneficial to triage patients with impending stroke.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


