Vessel Wall Inflammation in Spontaneous Cervical Artery Dissection

A Prospective, Observational Positron Emission Tomography, Computed Tomography, and Magnetic Resonance Imaging Study

Thomas Pfefferkorn, MD; Tobias Saam, MD; Axel Rominger, MD; Maximilian Habs, MD; Lisa-Ann Gerdes, MD; Caroline Schmidt, MD; Clemens Cyran, MD; Andreas Straube, MD; Jennifer Linn, MD; Konstantin Nikolaou, MD; Peter Bartenstein, MD; Maximilian Reiser, MD; Marcus Hacker, MD; Martin Dichgans, MD

Background and Purpose—Vessel wall inflammation (VWI) may be a pathogenetic factor in cervical artery dissection (CAD). We used contrast-enhanced high-resolution MRI (hrMRI) and positron emission tomography CT (PET-CT) to systematically investigate VWI in spontaneous CAD.

Methods—In this monocentric, prospective, observational study, all consecutive patients with acute, MRI-confirmed, spontaneous CAD admitted to our center between August 2007 and August 2009 were included. VWI was defined as perivascular contrast enhancement in hrMRI and increased perivascular [18F]-fluorodesoxyglucose uptake in PET-CT. VWI was further differentiated between local (restricted to the site of dissection) and generalized (exceeding the site of dissection).

Results—A total of 37 patients were included. Multiple dissections were seen in 10 patients (27%). Twenty-five patients received both modalities as planned, 8 received only PET-CT, and 4 received only hrMRI. A subset of patients showed signs of a generalized VWI in hrMRI (4/29 patients, 14%) and PET-CT (8/33 patients, 24%). In patients who received both modalities, all with hrMRI signs of generalized VWI were PET-CT positive (3/3), whereas some PET-CT–positive patients were hrMRI-negative (4/7). If present, generalized VWI in hrMRI completely resolved within 6 months. The presence of >2 simultaneous dissections (seen in 2 patients) was significantly associated with generalized VWI in hrMRI (P=0.015) but marginally not in PET-CT (P=0.053).

Conclusions—A subset of patients with spontaneous CAD showed signs of a generalized transient inflammatory arteriopathy in contrast-enhanced hrMRI and PET-CT. This subset of patients may be more prone to multiple dissections. (Stroke. 2011;42:1563-1568.)

Key Words: cervical artery dissection ■ inflammation ■ positron emission tomography

Cervical artery dissection (CAD) is a relevant cause of stroke in younger patients. Its pathophysiology is poorly understood. Possible constitutional factors include connective tissue disorders1 and genetic predisposition.2 Environmental factors include major3 and minor4,5 trauma but also recent infection.6,7 A possible causal role of recent infection is supported by a seasonal peak of CAD in autumn.8 Consistent with that, several studies have demonstrated elevated serum markers of inflammation in patients with CAD.9,10 Furthermore, evidence for a generalized arteriopathy in spontaneous CAD patients has been previously provided by microscopic signs of tissue weakening in biopsy specimens of the superficial temporal artery.11

Modern imaging modalities are capable to demonstrate vessel wall inflammation. Specifically, [18F]-fluorodesoxyglucose positron emission tomography CT (PET-CT) is able to detect large vessel inflammation with high sensitivity12 and may be used to predict the risk of unfavorable outcome in acute aortic dissection.13 Moreover, PET-CT and MRI are increasingly used to image atherosclerotic plaque inflammation and morphology.14–16 High-resolution MRI (hrMRI) recently has been applied to characterize cervical and intracranial artery

Received August 9, 2010; accepted January 5, 2011.
From the Department of Neurology (T.P., L.A.G., C.S., A.S., M.S.), Department of Clinical Radiology (T.S., M.H., C.C., K.N., M.R.), Department of Nuclear Medicine (A.R., P.B., M.H.), and Department of Neuroradiology (J.L.), Klinikum Grosshadern, University of Munich, Munich, Germany; Institute for Stroke and Dementia Research (M.D.), University of Munich, Germany.
The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.599548/DC1.
T.P. and T.S. contributed equally to this work.
Correspondence to Thomas Pfefferkorn, MD, Klinikum Grosshadern, Department of Neurology, University of Munich, Marchioninistrasse 15, 81377 Munich, Germany. E-mail Thomas.Pfefferkorn@med.uni-muenchen.de
© 2011 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.599548
pathology, including inflammatory vessel wall alterations.\textsuperscript{17,18} In another recent study, hrMRI demonstrated increased periarterial edema in spontaneous compared to traumatic CAD.\textsuperscript{19} To further elucidate the role of vessel wall inflammation (VWI) in spontaneous CAD, we performed a monocentric, prospective, observational rater-blinded PET-CT and hrMRI study focusing on perivascular [18F]-fluorodesoxyglucose uptake (PET-CT), perivascular contrast enhancement (hrMRI), and perivascular edema (hrMRI).

Patients and Methods

Patients

All consecutive patients with the first manifestation of spontaneous cervical artery dissection treated at our center between August 2007 and August 2009 were included in the study if the following inclusion criteria were fulfilled: (1) unequivocal MRI evidence of cervical artery dissection (hyperintense signal in fat-suppressed T1 sequences demonstrating intramural met hemoglobin); (2) written informed consent; and (3) admission at our center within 4 weeks after symptom onset, which enabled us to perform PET-CT and hrMRI within 5 weeks. The date of dissection was estimated from the first appearance of ≥1 of the following symptoms or signs: acute cervical pain; local symptoms such as cervical swelling or Horner syndrome; and clinical features of cerebral ischemia. Patients with a history of a related trauma, a preexisting diagnosis of arteritis, or an underlying disease clearly associated with CAD were excluded. Standard diagnostic procedures included laboratory investigations for markers of inflammation (C-reactive protein on admission) and extracranial and intracranial Duplex sonography. VWI was assessed by hrMRI and PET-CT as described. All patients were seen 3 to 6 months after the initial presentation for a clinical and sonographic follow-up. If patients showed signs of a generalized VWI in the initial hrMRI, then a second hrMRI investigation was performed at follow-up. The study was approved by the local institutional Ethics Committee and complied with the declaration of Helsinki.

MRI

Patients underwent hrMRI at 3.0 T (Magnetom Verio; Siemens Healthcare). Sequences included fat-suppressed and blood-suppressed T1 sequences with and without contrast agent, T2 sequences, and time of flight angiography. Further details of the MRI sequences are given in the online supplement (http://stroke.ahajournals.org). Coverage reached from the shoulders to the base of the skull. Therefore, contrast enhancement in the common carotid arteries, internal carotid arteries, external carotid arteries, and vertebral arteries could be analyzed. Off-line, 2 experienced radiologists blinded to clinical and PET-CT data rated contrast enhancement (yes/no) and perivascular edema (yes/no). If contrast enhancement was restricted to the site of the dissection, then this alteration was rated as local VWI. If it was observed not only in the dissected but also in any other not dissected artery, then it was rated as generalized VWI.

PET-CT

PET-CT studies were performed on 2 different scanners. Initially, the PET-CT scanner Philips Gemini (Philips Healthcare) was used, which was substituted during the study by the Siemens Biograph 64 (Siemens Healthcare). Further details on the PET-CT sequences are given in the online supplement. Coverage reached from the diaphragm to the base of the skull. Off-line, 2 experienced reviewers blinded to clinical and hrMRI data rated increased perivascular glucose metabolism (yes/no). If these alterations were restricted to the site of the dissection, then they were rated as local VWI. If the alterations were observed not only in the dissected but also in any other artery not dissected, then they were rated as generalized VWI. Additionally, standardized uptake values were quantified in the aorta and both carotid and both vertebral arteries. From these, target-to-blood pool ratios (TBR) were derived (arterial standardized uptake values\textsubscript{max}/venous standardized uptake values\textsubscript{mean}).\textsuperscript{20} These can be reproducibly obtained scanner-independently.\textsuperscript{21}

To match the PET-CT and MR images, we used several landmarks, such as the carotid bifurcation, the further course of the carotid and vertebral arteries, and the vertebral bodies. All these structures clearly can be identified both on MR and PET-CT images.

Statistical Analysis

Values are given as mean±SD. Groups were compared by univariate analysis using the independent t test for comparison of continuous variables and the Fisher exact test for comparison of proportions. Because of the relatively low number of patients, we did not perform a logistic regression analysis.

Results

Patients Characteristics

A total of 44 patients were screened. Seven of them were not enrolled in the study because of delayed presentation (>35 days). Basic data of the 37 enrolled patients is presented in the Table. In 4 patients, PET-CT was not performed because of withdrawn consent after the MRI examination. In 8 patients, MRI was not performed because of logistical prob-
lems at the beginning of the study. This resulted in 25 patients who received both modalities. Eight patients only had PET-CT and 4 had only hrMRI performed. All patients received standard therapy with heparin, which was later switched to oral anticoagulation (phenprocoumon; international normalized ratio, 2.0–3.0) for at least 6 months. No patient had a CAD or stroke recurrence within 6 months after the initial presentation. Thirty-four patients (92%) had a good functional outcome after 6 months, defined as a modified Rankin scale score of ≤2.

Affected Arteries and Clinical Manifestations
A total of 49 cervical artery dissections (30 carotid and 19 vertebral artery dissections) were detected in the 37 patients. In 10 patients (27%), multiple arteries were affected; in 2 patients (5%), 3 arteries were affected. Most patients presented with signs of cerebral ischemia (TIA, 14%; stroke, 54%). A minority of patients (32%) only showed local symptoms such as cervical pain or Horner syndrome.

MRI and PET-CT Findings
In the majority of patients (27/33; 82%), PET-CT showed increased [18F]-fluorodeoxyglucose accumulation at the site of the dissection (Figures 1–3). In a limited number of patients (8/33; 24%), these alterations exceeded the site of the dissection (Figures 1, 2), suggesting generalized VWI.

A similar pattern was observed with hrMRI. In the majority of patients (21/29; 72%), perivascular contrast enhancement...
was found at the site of the dissection (Figures 2, 3). And, again, in a limited number of patients (4/29; 14%), perivascular contrast enhancement exceeded the site of the dissection (Figure 2). Perivascular edema at the site of the dissection was observed in approximately half of the patients (15/29; 52%). It exceeded the site of the dissection in the same 4 patients who showed generalized contrast enhancement (4/29; 14%; Figure 2). In these 4 patients, control hrMRI 3 to 6 months later showed complete resolution of contrast enhancement and perivascular edema (Figure 4). Intramural hematoma also regressed over time (Supplemental Figure S1, at http://stroke.ahajournals.org).

All patients with hrMRI signs of generalized VWI (3/3) also had PET-CT signs of generalized VWI, whereas 4 out of 7 PET-CT–positive patients were hrMRI-negative. In 3 of these 4 patients, generalized VWI in PET-CT was deducted from increased [18F]-fluorodesoxyglucose uptake in the aortic arch, a region that was not captured by hrMRI. This left only 1 patient in whom PET-CT and hrMRI provided conflicting results with regard to generalized VWI.

Quantitative PET-CT analyses revealed higher mean TBR values in dissected than in nondissected arteries (1.48 ± 0.56 versus 1.12 ± 0.25; P < 0.001; Figure 5A). Patients with multiple dissections tended to have higher mean TBR values in the (never dissected) aortic arch (1.55 ± 0.20 versus 1.41 ± 0.20; P = 0.08; Figure 5B). Mean TBR values were also increased in arteries in which hrMRI had demonstrated perivascular contrast enhancement (1.58 ± 0.64 versus 1.41 ± 0.20; P < 0.001; Figure 5C) or perivascular edema (1.56 ± 0.64 versus 1.16 ± 0.33; P < 0.001; Figure 5D).

In univariate analysis, generalized VWI in PET-CT was associated with younger age (Table). Patients with multiple dissections tended to more often show signs of generalized VWI in hrMRI and PET-CT; however, these trends were not statistically significant (Table). The presence of ≥2 dissections (seen in 2 patients) was significantly associated with signs of generalized VWI in hrMRI but marginally not in PET-CT (Table). Mean C-reactive protein values on admission tended to be higher in patients with signs of generalized VWI in hrMRI and PET-CT, yet these trends were not statistically significant (Table).

![Figure 3.](image-url) Axial fat-suppressed black-blood precontrast and postcontrast T1-weighted images (A, B), T2-weighted images (C), and positron emission tomography CT images (D) of the vertebral arteries of a 48-year-old patient with left-side vertebral artery dissection (imaging 3 weeks after symptom onset). A, Weak hyperintense signal (arrow) on precontrast T1-weighted imaging demonstrating left vertebral artery dissection. B, Perivascular contrast enhancement of the left vertebral artery. Of note, no contrast enhancement is seen in the right vertebral artery, confirming that local vessel wall inflammation was confined to the site of the arterial dissection. C, Local perivascular edema. D, Pathological [18F]-fluorodesoxyglucose uptake at the site of the dissection. CE indicates contrast enhancement; PET, positron emission tomography; CT, computed tomography.

![Figure 4.](image-url) Axial MR images in black-blood technique of the same patient as in Figures 1 and 2 at baseline (A, B) and 4 months later (C, D). The arrows in (A) and (B) point to areas of perivascular contrast enhancement and edema in both internal carotid arteries, consistent with vessel wall inflammation. At follow-up (C, D), the inflammatory changes had completely resolved. CE indicates contrast enhancement.
Discussion

In our prospective observational imaging study, local signs of VWI were a frequent finding in patients with spontaneous CAD. However, in approximately one-fifth of our patients, signs of VWI exceeded the site of CAD, suggesting a generalized inflammatory arteriopathy.

In the absence of histopathology, one may question whether the observed hrMRI and PET-CT alterations really demonstrate VWI. The concept of an underlying inflammation, however, is strongly supported by the fact that our 4 patients with generalized perivascular contrast enhancement also showed generalized perivascular edema in hrMRI and (if examined) generalized increased [18F]-fluorodesoxyglucose uptake in PET-CT. An underlying transient inflammatory process is further supported by the observation that these generalized vessel wall alterations (detected by hrMRI) resolved within weeks. It is important to note that time intervals from symptom onset to hrMRI and PET-CT were similar in patients with and without signs of generalized VWI. This argues against the conception that the observed hrMRI and PET-CT findings may be a regular time-dependent feature of CAD.

An underlying transient inflammatory arteriopathy may explain the frequently observed occurrence of multiple dissections at 1 point in time and the relatively low risk of late CAD recurrence in affected patients.22,23 In our study, more than one-quarter of patients were affected by multiple dissections. These patients tended to have higher mean TBR values in the (not dissected) aortic arch than those with only 1 dissection. They also tended to more often show signs of generalized VWI in PET-CT and hrMRI. Interestingly, the presence of >2 dissections, as seen in 2 of our patients, was in fact significantly associated with signs of generalized VWI in hrMRI. These findings support the idea of an inflammatory pathogenetic factor in a subset of CAD patients.

Our study may have been underpowered to demonstrate an association between signs of generalized VWI and serum markers of inflammation. We can only provide trends for higher C-reactive protein values in patients with signs of generalized VWI. This finding should be tested in larger patient populations.

Arteries showing contrast enhancement or perivascular edema in hrMRI had higher TBR values in PET-CT, suggesting that both methods can be used to assess VWI. The observed higher rate of generalized VWI in PET-CT compared to hrMRI may, in part, be explained by the additional PET-CT assessment of the aortic arch, which could not be covered by hrMRI. Surprisingly, signs of generalized VWI in PET-CT were associated with younger age. The hrMRI did not demonstrate a similar association. This may be explained by a decreasing sensitivity of PET-CT with age caused by a higher atherosclerosis-related background activity in older individuals.15

Because of the good functional outcome in most of our patients, we cannot provide much information on the clinical, therapeutic, and prognostic relevance of generalized VWI in CAD. Because the hrMRI signs of generalized VWI resolved in all affected patients within a few months, long-term consequences may not arise. However, it remains unclear whether affected CAD patients may benefit from short-term anti-inflammatory or antibiotic therapy. Only trials much larger than ours could possibly answer this question. Because MRI is increasingly used in the routine diagnostic work-up of CAD patients,24 high-resolution, contrast-enhanced, T1-weighted sequences easily could be included in a respective study protocol.

Conclusions

In conclusion, a subset of patients with spontaneous CAD showed signs of a generalized transient inflammatory arteriopathy in PET-CT and contrast enhanced hrMRI. This subset
of patients may be more prone to multiple dissections. Multicenter efforts are needed to confirm our findings in larger patient populations.

Acknowledgments
The authors thank K. Ogston for language editing of the manuscript.

Disclosure
None.

References
Vessel Wall Inflammation in Spontaneous Cervical Artery Dissection: A Prospective, Observational Positron Emission Tomography, Computed Tomography, and Magnetic Resonance Imaging Study

Thomas Pfefferkorn, Tobias Saam, Axel Rominger, Maximilian Habs, Lisa-Ann Gerdes, Caroline Schmidt, Clemens Cyran, Andreas Straube, Jennifer Linn, Konstantin Nikolaou, Peter Bartenstein, Maximilian Reiser, Marcus Hacker and Martin Dichgans

Stroke. 2011;42:1563-1568; originally published online April 21, 2011; doi: 10.1161/STROKEAHA.110.599548

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/6/1563

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/04/21/STROKEAHA.110.599548.DC1
http://stroke.ahajournals.org/content/suppl/2012/02/28/STROKEAHA.110.599548.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Vessel Wall Inflammation in Spontaneous Cervical Artery Dissection: A Prospective Observational PET-CT and MRI Study

Expanded materials and methods: Details on MRI and PET-CT sequences

Supplemental Figure S1: Resolution of intramural hematoma over time
Expanded materials and methods: Details on MRI and PET-CT sequences

High-resolution MRI: To improve signal-to-noise performance and optimize spatial resolution, a dedicated four-channel surface coil (Machnet, Eelde, Netherlands) for bilateral carotid scans was used in combination with the head and neck coil. All patients obtained a multi-sequence protocol without ECG gating or motion correction using Parallel Imaging techniques (PAT factor = 2). The protocol included a fat- and blood suppressed 2D-T1 Turbo Spin Echo (TSE) sequence [TR=800 ms, TE=12 ms, Field of View (FOV)=160 x 120 mm] with and without contrast agent [intravenous injection of 0.1 mmol/kg Gadobutrol (Gadovist®, Bayer Schering, Leverkusen, Germany)], a fat- and blood suppressed 2D-T2 TSE sequence (TR=3000 ms, TE=65 ms, FOV=160 x 120 mm) and a 3D-GRE time-of-flight angiography (TOF; TR=21 ms, TE=3.96 ms, FOV=160 x 120 mm). Best in plane resolution was 0.5 x 0.5 mm² with a slice thickness of 4 mm for T1- and T2- weighted images and 1 mm for TOF images. Number of slices was 20 – 30 for T1-, 24-36 for T2- and 104 for TOF images. Total scan time was on average 35 minutes.

PET-CT: Patients fasted for 6h to ensure a blood glucose level below 130mg/ml. Five MBq of [18F]-FDG per kg body weight were injected one hour before scanning. The patients rested in a comfortable sitting position and then were brought to the scanning suite. First, transmission data were acquired by means of a low-dose CT scan (20 mAs, 140kV, 512 x 512 matrix, 6-mm slice thickness, increment of 5 mm/s, rotation time of 0.5 s, pitch index of 1.5). PET emission scans were acquired afterwards in caudocephalad direction in 3D-mode with a 144 x 144 matrix. After scatter and decay-correction, PET data were reconstructed iteratively with and without attenuation correction and then reoriented in axial, sagittal and coronal slices with a slice thickness of 4 mm (Philips scanner) and 5 mm (Siemens scanner) respectively, yielding a spatial resolution of 6 mm.
Axial MR images in a patient with left carotid artery dissection (arrows). Time of flight (TOF) angiography and T1 demonstrate typical lumen narrowing (A) and intramural hematoma (B) in the acute phase. Four months later these alterations have regressed (C, D). Additional images of the same patient are presented in the manuscript (figures 2 and 4).
表3 脳組織低酸素およびメタボリック・クライシスの多変量予測因子

<table>
<thead>
<tr>
<th>変数</th>
<th>OR(95% CI)</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>入院時 Hunt-Hess grade 5</td>
<td>5.1 (1.6 〜 16)</td>
<td>0.006</td>
</tr>
<tr>
<td>入院時 CT 時の IVH</td>
<td>5.4 (1.5 〜 20)</td>
<td>0.009</td>
</tr>
<tr>
<td>1 時間の血清グルコース&lt; 6.6 mmol/L</td>
<td>1.4 (1.1 〜 1.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>呼気終末 CO2 ≦ 35</td>
<td>1.2 (0.9 〜 1.5)</td>
<td>0.071</td>
</tr>
<tr>
<td>CPP &gt; 90 mmHg</td>
<td>1.1 (0.8 〜 1.5)</td>
<td>0.406</td>
</tr>
<tr>
<td>CPP 80 〜 90 mmHg</td>
<td>1.2 (1.0 〜 1.5)</td>
<td>0.023</td>
</tr>
<tr>
<td>CPP 70 〜 80 mmHg</td>
<td>1.6 (1.1 〜 2.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>CPP 60 〜 70 mmHg</td>
<td>2.1 (1.2 〜 3.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>CPP 50 〜 60 mmHg</td>
<td>2.8 (1.5 〜 5.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>CPP &lt; 50 mmHg</td>
<td>6.7 (2.6 〜 17)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

一覧の変数について補正した多変量ロジスティック回帰モデル(GEE)を示す。メタボリック・クライシスとは、乳酸/ピルビン酸の比が 40 を超え、脳内グルコース濃度が 0.7 mmol/L 以下である場合を指す。脳組織低酸素は PbtO2 が 20 mm Hg 未満である場合を指す。CPP は CPP > 90 を対照群として用いて 6 段階でモデル化した脳灌流圧を指す。

CI: 信頼区間, CPP: 脳灌流圧, CT: コンピュータ断層撮影, IVH: 脳室内出血, OR: オッズ比, GEE: 一般化推定方程式。