Impaired peri-nidal cerebrovascular reserve in seizure patients with brain arteriovenous malformations

Jorn Fierstra,1,2,3 John Conklin,1 Timo Krings,1 Marat Slessarev,4 Jay S. Han,1,4 Joseph A. Fisher,4 Karel terBrugge,1 M. Christopher Wallace,2 Michael Tymianski2 and David J. Mikulis1

1 Division of Neuroradiology, Joint Department of Medical Imaging, Toronto Western Hospital, The University of Toronto, Toronto, ON M5T 2S8, Canada
2 Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, The University of Toronto, Toronto, ON M5T 2S8, Canada
3 Rudolf Magnus Institute of Neuroscience, University Medical Centre, 3584 CG Utrecht, The Netherlands
4 Department of Anaesthesia, Toronto General Hospital, The University of Toronto, Toronto, ON M5G 2C4, Canada

Correspondence to: David John Mikulis, MD, Toronto Western Hospital, Joint department of Medical Imaging, McLaughlin Pavilion, 3rd Floor Room 431, 399 Bathurst St., Toronto, ON M5T 2S8, Canada
E-mail: mikulis@uhnres.utoronto.ca

Epileptic seizures are a common presentation in patients with newly diagnosed brain arteriovenous malformations, but the pathophysiological mechanisms causing the seizures remain poorly understood. We used magnetic resonance imaging-based quantitative cerebrovascular reactivity mapping and conventional angiography to determine whether seizure-prone patients with brain arteriovenous malformations exhibit impaired cerebrovascular reserve or morphological angiographic features predictive of seizures. Twenty consecutive patients with untreated brain arteriovenous malformations were recruited (10 with and 10 without epileptic seizures) along with 12 age-matched healthy controls. Blood oxygen level-dependent MRI was performed while applying iso-oxic step changes in end-tidal partial pressure of CO2 to obtain quantitative cerebrovascular reactivity measurements. The brain arteriovenous malformation morphology was evaluated by angiography, to determine to what extent limitations of arterial blood supply or the presence of restricted venous outflow and tissue congestion correlated with seizure susceptibility. Only patients with seizures exhibited impaired peri-nidal cerebrovascular reactivity by magnetic resonance imaging (0.11 ± 0.10 versus 0.25 ± 0.07, respectively; P < 0.001) and venous drainage patterns suggestive of tissue congestion on angiography. However, cerebrovascular reactivity changes were not of a magnitude suggestive of arterial steal, and were probably compatible with venous congestion in aetiology. Our findings demonstrate a strong association between impaired peri-nidal cerebrovascular reserve and epileptic seizure presentation in patients with brain arteriovenous malformation. The impaired cerebrovascular reserve may be associated with venous congestion. Quantitative measurements of cerebrovascular reactivity using blood oxygen level-dependent MRI appear to correlate with seizure susceptibility in patients with brain arteriovenous malformation.

Keywords: Cerebral arterio-venous malformations; seizures; epilepsy; cerebral autoregulation; cerebrovascular reserve; BOLD MRI; seizures; steal phenomenon; venous congestion

Abbreviations: BOLD = blood oxygen level-dependent; PETCO2 = end-tidal partial pressure of CO2
Introduction

Epileptic seizures are a common presentation in patients with newly diagnosed brain arteriovenous malformations (Stieg et al., 2007). They may be disabling and patients may require lifelong medication use. However, the aetiology by which brain arteriovenous malformations cause seizures remains poorly understood and cannot easily be explained by their morphology, as similar appearing brain arteriovenous malformations can present either with or without seizures. Thus, additional pathophysiological mechanisms may be involved.

Previous reports suggest that patients with brain arteriovenous malformations located in the frontal and temporal lobes are more seizure-prone (Wilkins, 1985; Hoh et al., 2002), or that mass effect (Hacein-Bey et al., 1995) and cerebral haemorrhage (Stein and Wolpert, 1980; Turjman et al., 1995) in brain tissue surrounding brain arteriovenous malformations can be responsible for triggering seizure activity. Also, haemodynamic alterations caused by the complex angioarchitecture of brain arteriovenous malformations have been suggested as playing an aetiological role, although with varying results. For example, large arteriovenous malformation size and high flow through the arterial feeding vessels of the brain arteriovenous malformation have been related to seizure susceptibility on the assumption that the large nidus creates a low-resistance vascular bed redirecting blood away from the surrounding brain tissue, with higher vascular resistance towards the brain arteriovenous malformation. This is considered the classical definition of arterial ‘steal physiology’ (Spetzler et al., 1992; Norris et al., 1999; Taylor et al., 2002). However, the actual existence of steal physiology has been questioned, as it has been difficult to demonstrate quantitatively (Hacein-Bey et al., 1995, Mast et al., 1995a, b). Perhaps a more provocative component, such as a vasoactive stimulus (e.g. hypercarbia), has to be in place for steal physiology to occur. Others have raised the possibility that seizures are more often related to a disturbed venous outflow pattern rather than to an inadequacy of arterial blood supply (Kosnik et al., 1974; Lasjaunias et al., 1986; Hurst et al., 1992; Krings et al., 2010). Such studies were generally based on retrospective chart reviews or case reports and, while correlating the proposed risk factors to seizures, did not provide the mechanism.

Cerebrovascular reactivity, a measure of the existing cerebrovascular autoregulatory reserve in a vascular bed (Mandell et al., 2008; Kassner et al., 2010), can be measured as the change in blood oxygen level-dependent (BOLD) MRI signal in response to precise alterations in end-tidal partial pressure of CO₂ (PetCO₂; Vesely et al., 2001; Slessarev et al., 2007).

Here, we used this technique to determine whether seizure-prone brain arteriovenous malformations exhibit impaired cerebrovascular reserve in tissue surrounding the brain arteriovenous malformation. Also, we examined the angiographic brain arteriovenous malformation morphology to determine to what extent limitations of arterial blood supply or the presence of restricted venous outflow and tissue congestion correlated with seizure susceptibility.

Materials and methods

Subject enrolment

Patients were recruited from the neurovascular clinic at the University Health Network. The study protocol was approved by the University Health Network Research Ethics Board. We aimed to recruit 10 patients with brain arteriovenous malformation with seizures and 10 patients with brain arteriovenous malformation without seizures. Twenty-six patients with brain arteriovenous malformation met the inclusion criteria, of whom five declined to sign informed consent (three patients declined because of claustrophobia for an MRI exam and two declined as the travelling distance was too far). One patient could not be studied due to intolerance for the applied CO₂ stimulus during the MRI exam. The following inclusion criteria were used: the brain arteriovenous malformation had to be untreated and the nidus had to measure ≥3 cm in size to maximize the possibility that arterial steal physiology may be occurring due to high flow shunting through the large nidus. Seizure patients with a prior history of brain haemorrhage were not enrolled, to exclude patients with seizure activity unrelated to haemodynamic factors, such as prior cortical scarring or gliosis. Twelve age-matched healthy control subjects were also recruited for comparison of cerebrovascular reactivity patterns in the brain. These controls did not have a history of brain pathology. The investigators performing the BOLD-MRI cerebrovascular reactivity and morphological analyses were blinded to the patients’ past history of seizures.

MRI study protocol

All 32 subjects underwent MRI imaging consisting of 3D T₁-weighted inversion-recovery prepared fast spoiled gradient-echo acquisition (voxel size 0.86 × 0.86 × 1.0 mm) on a 3.0 Tesla HDX MRI system (Signa, GE Healthcare, Milwaukee, WI, USA). Cerebrovascular reactivity was then evaluated using BOLD echo planar gradient echo imaging (time to repetition 2000, echo time 30 ms, 3.75 × 3.75 × 5 mm voxels) and iso-oxic step Changes in PetCO₂ as the vasoactive stimulus.

Control of end-tidal CO₂ pressure

Controlled changes in PetCO₂ were implemented with a custom-built automated gas blender and breathing circuit combination (RespirAct™, Thornhill Research Inc., Toronto, Canada). The technique applies a model-based prospective end-tidal targeting method to precisely control PETCO₂ and end-tidal O₂ pressure independently of each other (Slessarev et al., 2007). The PetCO₂ and end-tidal partial pressure of O₂ in all subjects were adjusted to baseline values of 40 and 100 mmHg, respectively. Subjects then underwent two iso-oxic near-square wave increases in PetCO₂ to 50 mmHg. The first increase was of 45 s duration, followed by a return to baseline for 90 s and then a second increase for 130 s followed by a return to baseline. All PetCO₂ plateaus were maintained to within ± 1 mmHg.

Morphological characterization of brain arteriovenous malformations on angiography

All patients with brain arteriovenous malformation underwent six-vessel cerebral angiograms that are used for detection of neurovascular...
abnormalities in and around the brain by injecting contrast into the internal and external carotid and vertebral arteries. The angiograms were evaluated by a neuroradiologist (T.K.) who was blinded as to the patient’s seizure history and cerebrovascular reactivity findings. The specific morphological evaluations were for:

(i) The nidal type of the brain arteriovenous malformations: either glomus type, fistulous type or combined (Berenstein et al., 2003).
(ii) Venous congestion: a pseudophlebitic pattern (Willinsky et al., 1999; Geibprasert et al., 2010), as shown in Fig. 1. This pattern is usually caused by rerouting of venous flow due to venous outflow restriction (i.e. thrombosis or stenosis), resulting in dilated cortical veins.
(iii) Morphological flow features of feeding arteries and draining veins: presence or absence of dilated arterial feeder(s) indicating high-flow shunting of blood through the brain arteriovenous malformation and susceptibility to venous congestion, and flow-related aneurysms that may indicate high flow through the arterial feeder(s) and possibly venous congestion.

MRI data analysis

MRI and P\textsubscript{ETCO\textsubscript{2}} data were imported to the Analysis of Functional Neuroimages software (Cox, 1996). BOLD images were automatically co-registered to the T\textsubscript{1}-weighted anatomical dataset (Saad et al., 2009). P\textsubscript{ETCO\textsubscript{2}} data was time-shifted to the point of maximum correlation with the whole-brain average BOLD signal to compensate for temporal offset between end-tidal gas sampling and the BOLD signal acquisition (circulatory delay). To minimize the effect of head motion, the BOLD time series at each voxel was orthogonalized to six rigid body motion parameters estimated from the volume-registration procedure. A linear least-squares fit of the BOLD-signal data series to the PETCO\textsubscript{2} data series was then performed. The cerebrovascular reactivity value was calculated as the percent change in BOLD signal per mmHg change in P\textsubscript{ETCO\textsubscript{2}}. Anatomical images and co-registered cerebrovascular reactivity maps were fitted to a 1 mm isotropic grid to facilitate subsequent analysis.

Tissue classification and regions of interest

Tissue probability maps for white and grey matter were generated from the anatomical images (SPM5; Wellcome Department of Imaging Neuroscience, University College, London, UK) with a threshold at a probability of 0.9 to construct categorical tissue masks for grey matter, white matter and ‘brain tissue’ (defined as either white or grey matter). The arteriovenous malformation was excluded from the white matter, grey matter and ‘brain tissue’ masks (Fig. 2).

To construct a 3D region of interest containing the brain arteriovenous malformation, a single rater blinded to the patient’s clinical history manually outlined the nidus of the arteriovenous malformation on all slices of the anatomical dataset in which the arteriovenous malformation was visible (Fig. 2D). The same rater then traced a 2 mm thick region of interest around the brain arteriovenous malformation nidus, which was automatically expanded by stepwise margins of \( \sim 2 \) mm up to a maximum expansion of 30 mm. (MATLAB, Image Processing Toolbox; Mathworks, Natick, MA, USA; Fig. 2G). These regions of interest were then combined with the previously generated white matter, grey matter and ‘brain tissue’ masks to categorize each voxel by both tissue class (white matter, grey matter or non-brain) and distance from the arteriovenous malformation nidus. Mean cerebrovascular reactivity was computed separately for grey matter, white matter and brain tissue, for each successive 2 mm region of interest.

Statistical analysis

Demographic data and cerebrovascular reactivity were compared between two patient groups (those with seizures and those without seizures) using independent sample t-tests and Fisher’s Exact test (\( P < 0.05 \) was considered significant; \( t(30) = 2.04 \)). Mean cerebrovascular reactivity values for white matter, grey matter and brain tissue in each consecutive ring were compared in patients with and without seizures using an independent sample t-test (\( P < 0.05 \) was considered significant; \( t(18) = 2.10 \)). A multivariate exact logistic regression was performed using the binary variable ‘seizures’ as the dependent variable, and cerebrovascular reactivity of adjacent brain tissue (0–6 mm) as the independent variable (LogXact 9.0, Cytel Software, Cambridge.

Figure 1  Angiographic signs of venous congestion in brain arteriovenous malformations in a seizure-prone patient. (A) Angiogram of brain arteriovenous malformation nidus (contrast injected in the right internal carotid artery). (B) The venous phase showing enlarged veins (indicating outflow obstruction) and absence of opacification of the cortical veins, indicating outflow obstruction-related retrograde flow (red arrow). (C) Pseudophlebitic pattern due to rerouting of venous flow to adjacent vascular territories (encircled in red).
Age and seizure-prone brain arteriovenous malformation location (i.e. a frontal or temporal lobe component to the brain arteriovenous malformation) were included as covariates in the regression model.

Results

Potential confounders affecting cerebrovascular reactivity in the current patient cohort

We evaluated comorbidities in our patients that could potentially impact on cerebrovascular reactivity findings. Evaluating the comorbidities such as smoking, diabetes, chronic obstructive pulmonary disease, asthma, hypercholesterolaemia and hypertension did not reveal significant differences in cerebrovascular reactivity readings between healthy subjects and patients with brain arteriovenous malformation ($P = 0.73$) nor between patients with brain arteriovenous malformation and seizures and patients with brain arteriovenous malformation and no seizures ($P = 0.88$).

Cerebrovascular reactivity findings between healthy subjects and patients with brain arteriovenous malformation

In order to determine whether the presence of a brain arteriovenous malformation impacted on cerebral vascular reserve, we compared cerebrovascular reactivity maps obtained from 12 age-matched healthy subjects (mean age 37 years, range 20–52; six females) with those of the 20 subjects harbouring a brain arteriovenous malformation (mean age 39.2 years, range 14–62; nine females; Fig. 2 and Table 1). Differences in cerebrovascular reactivity were calculated as the percent change in BOLD signal per mmHg change in $\text{PETCO}_2$. 

![Figure 2](image) 

Figure 2 Illustration of axial anatomical and cerebrovascular reactivity images, tissue segmentations and concentric expansion of peri-nidal region of interest. (A) An axial anatomical image of a brain arteriovenous malformation (red arrow) located in the posterior sylvian region. (B) The cerebrovascular reactivity (CVR) map overlaid on the same anatomical brain image. Cerebrovascular reactivity is calculated as the percent change in BOLD signal per mmHg change in $\text{PETCO}_2$. (C) An axial anatomical and cerebrovascular reactivity (CVR) map from a healthy volunteer. (D) Cerebrovascular reactivity analysis in patients with brain arteriovenous malformation, with the area overlying the arteriovenous malformation (AVM) masked out in order to avoid partial volume averaging from the lesion. (E) Further segmentation for calculation of cerebrovascular reactivity in grey and, in F, white matter. (G) Expansion of the region of interest (ROI; encircled in red) around the arteriovenous malformation nidus in concentric individual rings of 2 mm diameter each up to a maximum expansion of 30 mm from the lesion.
There were no global differences in mean cerebrovascular reactivity (as calculated from all voxels included in the ‘brain tissue’ mask) between patients with brain arteriovenous malformation and healthy subjects (0.231 ± 0.084 versus 0.210 ± 0.064, respectively; \( P = 0.538 \)). This suggests that brain arteriovenous malformations do not produce haemodynamic effects sufficient to modify cerebrovascular reactivity throughout the whole brain.

Cerebrovascular reactivity findings between patients with brain arteriovenous malformation with and without seizures

Further cerebrovascular reactivity analysis was performed between patients with brain arteriovenous malformation with seizures and those without seizures. There were no differences in age (\( P = 0.582 \)) and sex (\( P = 0.637 \)) between the two groups. The mean cerebrovascular reactivity values calculated from the entire brain volume did not exhibit a difference between the patients with brain arteriovenous malformation with seizures and patients with brain arteriovenous malformation without seizures (0.220 ± 0.086 versus 0.244 ± 0.087, respectively; \( P = 0.928 \)). More detailed analyses were undertaken in which the brain volume was further segmented by hemisphere, grey matter only and white matter only. None of these additional analyses of the data revealed any differences in mean cerebrovascular reactivity between patients with and without seizures (Supplementary Table 1).

These findings suggest that if cerebrovascular reactivity differences exist between these patient populations, they are not present across these entire brain segments and are seemingly independent of seizure characteristics.

Cerebrovascular reactivity in brain tissue adjacent to the brain arteriovenous malformations distinguishes patients with and without seizures

Because brain arteriovenous malformation-related seizures are thought to originate focally in the brain, differences in cerebrovascular reactivity might appear in closer approximation to the brain arteriovenous malformation. Therefore, cerebrovascular reactivity analysis was performed in concentric 2 mm thick regions of interest drawn around the brain arteriovenous malformation nidus (see Methods section; Fig. 2G). Analysis of the region of interest immediately adjacent to the arteriovenous malformation revealed that seizure-prone patients showed a markedly impaired perinidal cerebrovascular reactivity as compared with those without seizures (0.11 ± 0.10 versus 0.25 ± 0.07, respectively; \( P < 0.001 \); Fig. 3). In a further analysis, this 2 mm region of interest was expanded in concentric rings with steps of 2 mm up to a maximum expansion of 30 mm. The difference in cerebrovascular reactivity was greatest in the 2 mm closest to the brain arteriovenous malformation and became smaller at each more distal region of interest (Table 3; Fig. 4). Analyses of cerebrovascular reactivity changes in grey and white matter separately within the same individual concentric

### Table 1 Patient demographics and general arteriovenous malformation characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Feeding artery</th>
<th>Size (cm)</th>
<th>Grade</th>
<th>Location</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>+</td>
<td>&gt;6</td>
<td>4</td>
<td>Right temporal</td>
<td>GTCS</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>+</td>
<td>3</td>
<td>4</td>
<td>Right temporal–occipital</td>
<td>Headaches</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>M</td>
<td>+</td>
<td>&gt;6</td>
<td>5</td>
<td>Left fronto-parietal</td>
<td>GTCS</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>F</td>
<td>+</td>
<td>3</td>
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<td>GTCS</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>2</td>
<td>Left occipital</td>
<td>Headaches</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>F</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>Left fronto-temporal</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>F</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>Left fronto-temporal</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>M</td>
<td>+</td>
<td>5</td>
<td>4</td>
<td>Left parietal</td>
<td>GTCS</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>F</td>
<td>+</td>
<td>3</td>
<td>2</td>
<td>Left parietal</td>
<td>Headaches</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>F</td>
<td>+</td>
<td>4</td>
<td>3</td>
<td>Right fronto-parietal</td>
<td>Seizures (unknown)</td>
</tr>
<tr>
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<td>+</td>
<td>&gt;6</td>
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<td>GTCS</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>M</td>
<td>+</td>
<td>4</td>
<td>3</td>
<td>Right fronto-parietal</td>
<td>GTCS</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>M</td>
<td>+</td>
<td>5</td>
<td>3</td>
<td>Left thalamic</td>
<td>Headaches</td>
</tr>
<tr>
<td>14</td>
<td>24</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>Left frontal</td>
<td>Headaches</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>Right parietal</td>
<td>GTCS</td>
</tr>
<tr>
<td>16</td>
<td>47</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>2</td>
<td>Right frontal</td>
<td>GTCS</td>
</tr>
<tr>
<td>17</td>
<td>53</td>
<td>M</td>
<td>+</td>
<td>5</td>
<td>3</td>
<td>Left temporal–occipital</td>
<td>Focal seizures</td>
</tr>
<tr>
<td>18</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>Right frontal</td>
<td>Headaches</td>
</tr>
<tr>
<td>19</td>
<td>42</td>
<td>F</td>
<td>+</td>
<td>3</td>
<td>2</td>
<td>Left frontal</td>
<td>Focal seizures</td>
</tr>
<tr>
<td>20</td>
<td>49</td>
<td>F</td>
<td>+</td>
<td>5</td>
<td>3</td>
<td>Right occipital</td>
<td>Headaches</td>
</tr>
</tbody>
</table>

a Grading according to the Spetzler–Martin grading scale.

ACA = anterior cerebral artery; F = Female; GTCS = generalized tonic clonic seizures; M = Male; MCA = middle cerebral artery; PCA = posterior cerebral artery.
regions of interest revealed that cerebrovascular reactivity differences for both tissue types exist between seizure-prone and non-seizure-prone arteriovenous malformations (Supplementary Table 2). Also, the method of concentric regions of interest was applied to the contralateral brain region mirroring that encompassing the brain arteriovenous malformation and the same analysis repeated for all brain tissue, grey matter and white matter in every individual concentric region of interest (Supplementary Tables 3 and 4). This additional analysis only revealed a significant cerebrovascular reactivity difference in the first 4 mm for the contralateral versus ipsilateral cerebrovascular reactivity comparison in the seizure group (all brain tissue and grey matter; Supplementary Table 4).

Finally, using the exact logistic regression model with seizures being the dependent variable and adjacent cerebrovascular reactivity (0–6 mm) being the independent variable, the cerebrovascular reactivity of adjacent brain tissue demonstrated a significant effect on seizures (P = 0.03). The effect of the other covariates (seizure-prone location and age) did not reach significance, although there was a trend towards a positive association between seizure-prone brain arteriovenous malformation location and seizures (P = 0.08). Finally, two similar models were calculated by confining the cerebrovascular reactivity measurements to white matter only and grey matter only. Cerebrovascular reactivity of both white and grey matter within 6 mm of the arteriovenous

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**Figure 3** Axial anatomical images and cerebrovascular reactivity in adjacent tissue of brain arteriovenous malformation patients with and without seizures. Axial anatomical acquisitions of patients with brain arteriovenous malformation with no history of seizures (top) and seizure-prone patients with brain arteriovenous malformation (bottom). Each image shows the cerebrovascular reactivity (CVR; calculated as the percent change in BOLD signal per mmHg change in P\textsubscript{ETCO\textsubscript{2}}) in brain tissue surrounding the brain arteriovenous malformation nidus. The peri-nidal cerebrovascular reactivity of the patients with brain arteriovenous malformation with seizures exhibits impaired cerebrovascular reserve compared to that of the brain arteriovenous malformation patients without seizures (P < 0.001).
malformation were both significantly associated with seizures \((P=0.045\) and \(P=0.022\), respectively). Also, a brain arteriovenous malformation nidal size of \(>3\, \text{cm}\) showed a difference between the two groups \((P=0.02)\). This may comprise a reason for haemodynamic differences between the groups.

Considering the seizure patients with a brain arteriovenous malformation, the frequency of seizures \((P=0.86)\), duration of seizures \((P=0.61)\), seizure medication \((P=0.61)\) and whether the seizures were medically refractory or controlled \((P=0.93)\) did not demonstrate a significant effect on the cerebrovascular reactivity readings.

Our cerebrovascular reactivity measurements indicate that cerebrovascular reserve is reduced in brain tissue adjacent to brain arteriovenous malformations of seizure-prone patients. However, peri-nidal cerebrovascular reserve in this brain arteriovenous malformation patient cohort was not so impaired as to reach negative values, which would have implied arterial steal from the affected tissue.

### Morphological evaluation of brain arteriovenous malformations on angiography

Since our cerebrovascular reactivity results did not reveal changes compatible with peri-nidal steal physiology, other brain arteriovenous malformation features may be associated with seizure susceptibility. Therefore, morphological evaluation of the angiographic features of each brain arteriovenous malformation was undertaken by a blinded neuroradiologist. In the seizure group, all brain arteriovenous malformations exhibited venous congestion by the criteria listed in Table 2, whereas the brain arteriovenous malformations in patients without seizure susceptibility did not. Seven brain arteriovenous malformation lesions in the seizure group and two in the no seizure group had fistulous components, indicating a high-blood flow shunting through the nidus. Other brain arteriovenous malformation characteristics that would indicate shunting of blood flow are dilated arterial feeder(s) and flow-related aneurysms, and were mainly found in the seizure group (Table 2). Morphological characterization of the brain arteriovenous malformation lesions revealed venous congestion in all seizure-prone brain arteriovenous malformations.

### Table 2 Morphological brain arteriovenous malformation features evaluated on angiography

<table>
<thead>
<tr>
<th>Feature</th>
<th>Seizures ((n=10))</th>
<th>No seizures ((n=10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous congestion</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Pseudophlebitic pattern</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Outflow-restriction draining vein</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Outflow-restriction remote</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nidus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomus</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Fistulous</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Feeding arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant dilatation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Moderate dilatation</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Flow-related aneurysm</td>
<td>2</td>
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</tr>
</tbody>
</table>

The difference in morphological features between brain arteriovenous malformations presenting with and without seizures.
Discussion

Our study highlights a strong association between impaired cerebrovascular reserve in brain immediately surrounding the brain arteriovenous malformation nidus and the tendency for epileptic seizures, a finding that was also closely associated with venous congestion in all seizure-prone patients with brain arteriovenous malformation. In contrast, patients without seizures did not show impaired cerebrovascular reserve in the tissue surrounding the brain arteriovenous malformation and did not have concomitant venous congestion. The observed impairment in cerebrovascular reactivity implies that venous congestion impairs reserve capacity for microvascular autoregulation in brain tissue surrounding brain arteriovenous malformations in patients with seizures.

The cerebrovascular reactivity in the seizure-prone group was smaller than that observed in patients with brain arteriovenous malformation without seizures and in controls, but still exhibited an increase in BOLD signal in response to hypercarbia. The cerebrovascular reactivity technique, by its nature, does not measure arterial flows and, therefore, is not a direct measure of arterial physiology. Nonetheless, if steal were present, cerebrovascular reactivity could not exhibit an increase in BOLD signal but would have demonstrated a ‘paradoxical’ decrease in BOLD signal in response to hypercarbia (Fierstra et al., 2010). For this reason, it is unlikely that seizures in these patients with brain arteriovenous malformation can be explained based on arterial steal physiology, as was suggested by Taylor and Spetzler in patients with large brain arteriovenous malformations (Spetzler et al., 1992; Taylor et al., 2002). Although our study includes a relatively small number of patients, we do not believe that our inability to demonstrate arterial steal is due to methodological limitations of the cerebrovascular reactivity technique, as this quantitative method has proven itself capable of identifying even subtle reductions in cerebral blood flow to a vasodilatory stimulus (Mandell et al., 2008).

Our findings, however, are more in keeping with the suggestion first proposed by Kosnik in 1974, that venous congestion, not arterial steal physiology, adversely affects neuronal function in the tissue surrounding brain arteriovenous malformations.

Several studies have reported an association between venous congestion and seizures in brain arteriovenous malformations (Krings et al., 2010), dual arteriovenous malformations (Kosnik et al., 1974; Lasjaunias et al., 1986; Hurst et al., 1992) as well as in relation to venous sinus thrombosis (Varelas, 2010). Although association does not imply causation, the consistent findings of venous congestion and peri-nidal impaired cerebrovascular reserve in seizure-prone patients with brain arteriovenous malformation indicate a possible pathophysiological association.

The role of venous congestion in the impaired cerebrovascular reactivity might be explained as follows: the area of impaired cerebrovascular reserve being present in a shell surrounding the lesion rather than confined to a specific arterial territory (such as the territory of the feeding artery) indicates that the impaired cerebrovascular reactivity is not entirely related to an increased flow through the artery into the brain arteriovenous malformation since different vascular territories (such as deep and superficial arteries) were involved in the supply of the tissue surrounding the brain arteriovenous malformation. High arterial inflow through the brain arteriovenous malformation nidus may overwhelm the venous drainage capacity, leading to venous congestion. The accordingly high intravascular pressures in the venous system then limit the ability of arterioles in the peri-nidal tissue to vasodilate, thus limiting cerebrovascular reactivity. This pressure-related inability to respond to a vasoactive stimulus (CO₂) would be detectable as a decrease in cerebrovascular reactivity. The association between peri-nidal impaired cerebrovascular reserve and seizures will require further investigation.

From a clinical perspective, it is well-known that seizures are associated with venous congestion. Detection of venous congestion, however, is based on subjective criteria set out by the neuroradiologist and requires an invasive angiographic assessment, whereas cerebrovascular reactivity measurements are quantitative and non-invasive.

Other methods may also be used for measuring cerebrovascular reactivity in relation to brain arteriovenous malformations including, for example, dynamic single-photon emission computed tomography, xenon CT and PET. A similar finding of regionally impaired cerebrovascular reserve in seizure patients with a brain arteriovenous malformation was made by Van Roost and Schramm in a xenon CT study (Van Roost et al., 2001). This finding, however, did not reach statistical significance in the 12 non-haemorrhagic patients with epilepsy who were studied, which might have been related to the non-quantitative imaging technique used. The reasons we have chosen BOLD-MRI include the wide availability and relatively high spatial resolution of MRI. Furthermore, prior work has validated BOLD-MRI cerebrovascular

Table 3 Cerebrovascular reactivity findings in the concentric regions of interest in brain tissue surrounding the brain arteriovenous malformation

<table>
<thead>
<tr>
<th>Distance from arteriovenous malformation nidus (mm)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>0–30</th>
</tr>
</thead>
<tbody>
<tr>
<td>S+ CVR</td>
<td>0.120 (0.08)</td>
<td>0.127 (0.08)</td>
<td>0.140 (0.09)</td>
<td>0.149 (0.08)</td>
<td>0.155 (0.09)</td>
<td>0.178 (0.08)</td>
<td>0.183 (0.08)</td>
<td>0.166 (0.006)</td>
</tr>
<tr>
<td>S0 CVR</td>
<td>0.232 (0.09)</td>
<td>0.231 (0.07)</td>
<td>0.233 (0.09)</td>
<td>0.236 (0.09)</td>
<td>0.234 (0.09)</td>
<td>0.242 (0.08)</td>
<td>0.232 (0.08)</td>
<td>0.247 (0.01)</td>
</tr>
<tr>
<td>P-value</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
<td>P = 0.06</td>
<td>P = 0.10</td>
<td>P = 0.20</td>
<td>P = 0.07</td>
</tr>
</tbody>
</table>

Cerebrovascular reactivity calculated for every individual concentric ring and the mean cerebrovascular reactivity for the overall region of interest (0–30 mm).

Statistically significant P-values are highlighted in bold.

CVR = cerebrovascular reactivity; S+ = seizure group; S0 = non-seizure group.

Values depicted as mean (± SD).
reactivity as a surrogate of cerebral blood flow changes using arterial spin labelling (Mandell et al., 2008). The use of model-based prospective end-tidal targeting also enabled precise and reproducible PETCO2 changes, permitting quantification of cerebrovascular reactivity. A second advantage of our gas-control method is that it maintains iso-oxia while changing PETCO2, thus preventing the T1 effects of O2 pressure from influencing the BOLD signal (Prisman et al., 2008). Finally, only with the model-based prospective end-tidal targeting does the subjects’ PETCO2 equal the arterial CO2 pressure, which is the independent stimulus affecting the Cerebral Blood Flow (Ito et al., 2008).

Although the cerebrovascular reactivity findings appear to discriminate between patients with brain arteriovenous malformation with seizures and patients with brain arteriovenous malformation without seizures, possible confounders such as co-morbidities and brain arteriovenous malformation and seizure characteristics, might have influenced cerebrovascular reactivity readings. Even though these influences did not demonstrate a statistically significant effect, these analyses are underpowered in this cohort, with a relatively small sample size of 20 patients, to reveal possible statistical differences. Also, the effect of age, pulmonary disease and history of chronic cigarette smoking, which may ordinarily increase the arterial to end-tidal gradient in spontaneously breathing subjects, might influence the cerebrovascular reactivity readings. However, Ito et al. (2008) have argued that, with model-based prospective end-tidal targeting, the gradient will nevertheless, be small, even in the presence of lung disease, over a large range of induced PETCO2 and end-tidal O2 pressure. Finally, the significant difference of larger nidus size in the seizure group may have contributed to more pronounced changes in local blood flow and haemodynamics as evaluated by BOLD-MRI cerebrovascular reactivity. However, the difference in nidus size is anticipated to be an underlying cause of haemodynamic changes (Spetzler et al., 1992; Norris et al., 1999; Taylor et al., 2002) and thus does not contradict our conclusions that cerebrovascular reactivity can demonstrate those alterations in cerebral haemodynamics that make epilepsy more likely.

In summary, seizure-prone patients with brain arteriovenous malformation exhibit impaired peri-nidal cerebral blood reserve and concomitant venous congestion. There was no evidence for arterial steal physiology in our patient cohort. Therefore, venous congestion is the probable factor associated with the pathophysiology of seizures. Quantitative measurements of cerebrovascular reactivity using BOLD-MRI appear to correlate with seizure susceptibility in patients with brain arteriovenous malformation and may provide an objective test to detect brain arteriovenous malformations with seizure susceptibility in the future. Further studies in this regard may yield clinically useful predictive criteria for seizure propensity in treated and untreated patients with brain arteriovenous malformations.

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Conflict of interest

Three of the study authors (M.S., J.A.F. and D.J.M.) contributed to the development of RespirAct™. These authors stand to gain financially if the device is successfully commercialized by Thornhill Research Inc., a University of Toronto/University Health Network-related company.

Supplementary material

Supplementary material is available at Brain online.

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