Dynamic Permeability and Quantitative Susceptibility
Related Imaging Biomarkers in Cerebral Cavernous Malformations
Abdul Ghani Mikati, MD*; Huan Tan, PhD*; Robert Shenkar, PhD; Luying Li, MD; Lingjiao Zhang, MS; Xiaodong Guo, PhD; Henrik B.W. Larsson, MD, PhD; Changbin Shi, MD, PhD; Tian Liu, PhD; Yi Wang, PhD; Akash Shah, MD; Robert R. Edelman, MD; Gregory Christoforidis, MD; Issam Awad, MD

Background and Purpose—Hyperpermeability and iron deposition are 2 central pathophysiological phenomena in human cerebral cavernous malformation (CCM) disease. Here, we used 2 novel MRI techniques to establish a relationship between these phenomena.

Methods—Subjects with CCM disease (4 sporadic and 17 familial) underwent MRI imaging using the dynamic contrast-enhanced quantitative perfusion and quantitative susceptibility mapping techniques that measure hemodynamic factors of vessel leak and iron deposition, respectively, previously demonstrated in CCM disease. Regions of interest encompassing the CCM lesions were analyzed using these techniques.

Results—Susceptibility measured by quantitative susceptibility mapping was positively correlated with permeability of lesions measured using dynamic contrast-enhanced quantitative perfusion ($r=0.49; P≤0.0001$). The correlation was not affected by factors, including lesion volume, contrast agent, and the use of statin medication. Susceptibility was correlated with lesional blood volume ($r=0.4; P=0.0001$) but not with lesional blood flow.

Conclusions—The correlation between quantitative susceptibility mapping and dynamic contrast-enhanced quantitative perfusion suggests that the phenomena of permeability and iron deposition are related in CCM; hence, more leaky lesions also manifest a more cumulative iron burden. These techniques might be used as biomarkers to monitor the course of this disease and the effect of therapy. (Stroke. 2014;45:598-601.)

Key Words: biomarkers ■ cerebral cavernous malformations ■ cerebrovascular disorders ■ hemangioma, cavernous ■ hemorrhagic stroke ■ magnetic resonance imaging ■ vascular permeability

Cerebral cavernous malformations (CCM) are characterized by capillary dilatations with deficient blood–brain barrier and disrupted interendothelial tight junctions that may cause vessel hyperpermeability.1–3 This hyperpermeability may cause chronic blood leakage with neurological sequelae, including epilepsy and focal deficits and hemorrhagic stroke. We previously showed that Rho kinase inhibition by fasudil decreases iron deposition and lesion burden in murine CCM models,4 and mice haploinsufficient in Ccm gene demonstrated increased vascular permeability to Evan’s blue dye that is reversible by Rho kinase inhibition.5

With the advent of Rho kinase inhibition as a potential therapy, a method for assessing its effect is needed. Recent advances in MRI have provided 2 potential methods to accomplish this. The first being dynamic contrast-enhanced quantitative perfusion (DCEQP) is used to measure hemodynamic parameters such as permeability. Applicability of DCEQP has been demonstrated by Larsson et al6 and has subsequently been validated by comparisons with histology7 and quantitative autoradiography.8 The second method, quantitative susceptibility mapping (QSM),9,10 measures the magnetic susceptibility of the brain tissue, an intrinsic biophysical property of the tissue that is directly proportional to the local iron content. Both methods may be applied to assess characteristics of CCM lesions in humans. Given the common underlying pathophysiological mechanisms of the disease and the
potential to use these techniques as biomarkers for disease activity and response to treatment, we hypothesize that there is a positive correlation between permeability measured with DCEQP and iron burden measured by QSM in the same CCM lesions.

Materials and Methods

Subjects
After obtaining institutional review board approval and informed consent, 21 patients scheduled for routine clinical evaluation for CCM disease were recruited, including 1 case that included a second follow-up scan (characteristics in the Table).

Data Acquisition and Processing
All scans were obtained during regular clinical follow-up. Permeability was measured using a $T_1$-weighted DCEQP protocol that included a precontrast $T_1$ scan followed by a dynamic scan using gadolinium contrast (gadodiamide or gadobenate dimeglumine). Images were then processed in MATLAB using the Patlak mathematical model to calculate the permeability, cerebral blood flow, and volume (CBF and CBV) maps. Regions of interest were selected encompassing entire

<table>
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<tr>
<th>Patient</th>
<th>Age at Scan/ Sex</th>
<th>Familial or Sporadic</th>
<th>Statin Use</th>
<th>Presence of Seizures</th>
<th>Hemorrhage Within 6 mo of Imaging</th>
<th>Contrast Used</th>
<th>No. of Lesions Analyzed</th>
<th>Mean Lesional Susceptibility (ppm)±Mean Lesional SD per Patient</th>
<th>Mean Lesional Permeability (mL/100 g per minute)±Mean Lesional SD per Patient</th>
<th>Average Lesional Volume per Patient, mL</th>
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<td>25 F</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<td>7</td>
<td>0.456±0.466</td>
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<td>Gadodiamide</td>
<td>16</td>
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<td>0.3947±0.364</td>
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<td>4</td>
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<td>No</td>
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<td>No</td>
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<td>0.294±0.423</td>
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<td>Gadobenate dimeglumine</td>
<td>1</td>
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<td>No</td>
<td>No</td>
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<td>No</td>
<td>Gadobenate dimeglumine</td>
<td>8</td>
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<td>No</td>
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<td>0.353±0.353</td>
<td>0.323±0.151</td>
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<td>1</td>
<td>0.49±0.56</td>
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<td>0.374±0.374</td>
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<td>Yes</td>
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<td>No</td>
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<td>Gadodiamide</td>
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<td>Gadobenate dimeglumine</td>
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<td>No</td>
<td>No</td>
<td>Gadodiamide</td>
<td>4</td>
<td>0.439±0.439</td>
<td>0.524±0.378</td>
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</tbody>
</table>

F indicates female; M, male; ppm, parts per million; and SD, standard deviation.
lesions as they appeared on T2-weighted images that were acquired simultaneously and were then superimposed on the maps.

A single 3-dimensional, multi-echo, T2*-weighted, spoiled gradient-echo sequence was used for data collection for QSM reconstruction. The QSM images were reconstructed with customized software using a morphology-enabled dipole inversion algorithm. Regions of interest included the same lesions identified on T2 images used for permeability. More detailed information is available in the online-only Data Supplement.

Statistics
The Pearson correlation was used to examine the correlation between QSM susceptibility and permeability, CBF, and CBV. Multivariate linear regression was used to assess the effect of potential contributing factors on the above-mentioned correlations, with susceptibility as the dependent variable, including permeability, the factor, and their interaction in the model. Bland–Altman plots were constructed to evaluate intraobserver and interobserver consistency, and coefficients of variation were calculated to look at interpatient and intrapatient variability.

Results
Figure 1 shows an example of a T2 image used for regions of interest selection, as well as a permeability map and QSM image of the same lesion. Intraobserver and interobserver consistency was demonstrated with both techniques in a subcohort of cases (see Results in the online-only Data Supplement). The Table illustrates the patients’ salient clinical features and summarizes imaging results for each case with both techniques. A positive correlation was found between mean QSM susceptibility of lesions and mean permeability of the same lesions (r=0.49; P≤0.0001; Figure 2A). This correlation between susceptibility and permeability was present predominantly in familial cases and was independent of lesion volume, the contrast agent used, and whether the patient was receiving statin therapy (see Results in the online-only Data Supplement). The correlation persisted when the data from cases with multiple lesions were pooled and averaged in each patient (r=0.46; P=0.038; Figure 2B).

There was a positive correlation between susceptibility and CBV in lesions (r=0.4; P≤0.0001) and no correlation between susceptibility and CBF in lesions (r=0.1; P=0.34; see Results in the online-only Data Supplement). Analyses using median values of susceptibility and permeability showed similar results (r=0.4; P=0.0001; data not shown).

Discussion
Vascular permeability is a hallmark of CCM disease, demonstrated as a result of loss of CCM gene expression in cultured endothelial cells and in the skin, lungs, and brain of CCM heterozygous mice. It has not been examined systematically in humans. Chronic iron deposition is also a cardinal feature of CCM lesions, demonstrated by imaging and histopathology. Here, we imaged human CCM lesions using 2 novel techniques examining dynamic permeability and the quantitative burden of iron deposit, respectively. The 2 techniques measure different and distinct features of the CCM lesion, yet these may be related biologically. We postulated and demonstrated that the more leaky CCM lesions also exhibited significantly greater mean susceptibility. This strong correlation was present, regardless of lesion volume, 2 different contrast agents, and whether the patient was using statin, a drug that may affect vascular permeability. The correlation was present mostly in familial cases, representing the vast majority of cases and lesions in our cohort. It will need to be examined in a larger group of sporadic cases. The correlation was present even when multiple lesions per case were averaged and analyzed by subject. Our results establish a proof of concept and help generate relevant hypotheses about the potential applicability of either technique to monitor CCM lesion behavior. The results may be interpreted using a transport model governed by mass conservation. Hence, permeability would reflect current ongoing rate of leaking, whereas susceptibility reflects the integral or historical accumulation of leaking. This and other hypotheses about QSM and DCEQP in CCM will need to be examined in prospective studies.

We noted a range of susceptibility and permeability (as well as CBF and CBV) among CCM lesions. The correlates of this variation will be examined in a larger cohort of cases, including the potential effect of age, lesion features, genotype, and prior clinical activity. Statin use and other therapies can potentially modulate permeability in CCM lesions, and their effects will need more systematic study. Future research will also address the potentially different implications of CBV, CBF, permeability, and susceptibility in lesions themselves and in background brain.

Figure 1. MR images used for assessing cerebral cavernous malformation (CCM) lesions. Left, An example of a quantitative susceptibility mapping (QSM) image of a sporadic CCM lesion shown as a bright area highlighted within a yellow box. A color-coded map of the lesion itself is shown to indicate the potential distribution of iron within the lesion in parts per million (ppm). Middle, An example of a permeability map of the same lesion generated by MATLAB with areas of high permeability and low permeability indicated according to the color scale to the right of the image with units in mL/100 g per minute. Right, An example of a T2 image with the same lesion highlighted within a yellow box.
Conclusions
QSM and DCEQP are 2 unique imaging methods for quantitatively assessing CCM biological behavior. Strong correlation was observed between the 2 methods for measuring different end points of the same pathophysiological phenomena. This serves as proof of concept for these methods and the biological phenomena they measure. It also reflects their potential as biomarkers of CCM disease.

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Disclosures
None.

References
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http://stroke.ahajournals.org/content/suppl/2013/12/03/STROKEAHA.113.003548.DC1
Online Supplement

Dynamic Permeability and Quantitative Susceptibility: Related Imaging Biomarkers in Cerebral Cavernous Malformations

Abdul Ghani Mikati1*, MD; Huan Tan*, PhD; Robert Shenkar, PhD1; Luying Li2, Lingjiao Zhang1, MS; Xiaodong Guo3, PhD; Henrik BW Larsson9,10, MD, PhD; Changbin Shi1, MD, PhD; Tian Liu5, Ph.D; Yi Wang6,7, Ph.D; Akash Shah4, MD; Robert Edelman, MD8; Gregory Christoforidis4, MD; Issam Awad1, MD

1Section of the Neurosurgery, 3Brain Research Imaging Center, and 4Section of Neuroradiology, Department of Diagnostic Radiology, The University of Chicago, Chicago, IL  
2Department of Neurosurgery, West China Hospital of Sichuan University, Sichuan, China  
5MedImageMetric LLC, New York, NY  
6Department of Radiology, Weill Cornell Medical College, New York, NY  
7Department of Biomedical Engineering, Cornell University, Ithaca, NY  
8Department of Radiology, NorthShore University HealthSystem, Evanston, IL  
9Diagnostic Department Glostrup Hospital, University of Copenhagen, Denmark  
10Institute of Circulation and Medical Imaging, The Norwegian University of Technology and Science, Norway  
*Denote co-authors with equal contributions

Corresponding Author:  
Issam A. Awad, MD, Section of Neurosurgery, 5841 S. Maryland Ave., Room J325, M/C 3026, Chicago, IL, 60637, USA  
Fax: 1-773-702-3518, Tel.: 1-773-702-2123, iawad@uchicago.edu

Cover Title: QSM versus Permeability in CCM

Tables and figures:  
Supplemental Table I.  
Supplementary figure I.  
Supplementary figure II.  
Supplementary figure III.  
Supplementary figure IV.  
Supplementary figure V.  
Supplementary figure VI.  
Supplementary figure VII.  
Supplementary figure VIII.

Keywords: Quantitative Susceptibility Mapping, Dynamic Contrast Enhanced Quantitative Perfusion, Cerebral Cavernous Malformation, Cavernous Angioma, Magnetic Resonance Imaging

Subject Codes: [30], [58], [61]

Word Count: 1715
Supplemental Methods:

Subjects: After obtaining IRB approval and informed consent total of 21 patients have been recruited. The patients include 4 sporadic and 17 familial cases with a total of 89 lesions; this includes one sporadic case that has a second follow-up scan (table 1 of main manuscript). All QSM and DCEQP data acquisition was performed at the time of the clinical imaging studies obtained in the course of routine clinic evaluation or follow-up.

Data acquisition and Processing: All scans were obtained during regular clinical follow-up thus no additional imaging is needed. Permeability experiments were performed on a Philips Achieva Quasar Dual 16 Ch 3T MRI scanner (Philips Medical Systems, Best, The Netherlands) and an 8-channel SENSE head coil at the University of Chicago DCAM. A saturation recovery gradient recalled sequence is used both for an initial T1 measurement and for the subsequent dynamic imaging. Four slices cover the area of interest based on a whole brain susceptibility-weighted imaging, and another slice is perpendicular to the internal carotid artery, based on an MR angiography in order to obtain an arterial input function, with minimal partial volume. Each slice is acquired after application of a nonselective saturation prepulse with a saturation time delay (TD). The MRI parameters are: echo time TE = 1.9 ms, repetition time TR = 3.9 ms, flip angle = 30°, field of view = 230 x 182 mm², slice thickness = 8 mm, matrix size = 96×61, SENSE factor = 2, centric order phase encoding. Seven TD values (120 ms, 300 ms, 600 ms, 1 sec, 2 sec, 4 sec and 10 sec) are used to measure the T1 values of the brain tissue and arterial blood for calibrating the dynamic imaging data. The passage of the bolus of the contrast agent is imaged using a TD of 120 ms to minimize the effect of water exchange in such measurements. Total 250 dynamic volumes of images are acquired. A power injector (Medrad, Pittsburgh, PA, Spectris Solaris MR injector system) is used to create the bolus injection. The dose of contrast agent Omniscan (gadodiamide, 287 mg/mL equivalent to 0.5 mmol/mL) or Multihance (gadobenate dimeglumine, 529mg/mL equivalent to 0.5 mmol/mL) is 0.05 mmol/kg. The MR signal can be related to contrast concentration by:

\[
\left\{ \begin{array}{l}
s(t) = M_0 \sin \left[ 1 - \exp \left( -\frac{t}{\Delta R_1(t)} \right) \right] \\
\Delta R_1(t) = r_1 \cdot C(t)
\end{array} \right.
\]

Where \(s(t)\) is the MR signal at time point \(t\), \(M_0\) is the relaxed signal for a 90° RF pulse when TR>>T1, \(\alpha\) is the radiofrequency flip angle, \(R1 = 1/T\) is the relaxation rate, \(\Delta R_i\) is the change in relaxation rate caused by contrast agent, \(r_1\) is the T1 relaxivity. The \(r_1\) of Gd-DTPA at 3T is 4s⁻¹mM⁻¹, a value provided by the manufacturer. Assuming a constant relaxivity for the intravascular compartment and for the tissue in general, the signal equation for a saturation recovery (with \(\Delta R_i =0\)) is fitted to the data obtained for varying TD in order to determine T1 and \(M_0\). The MR signal is converted to \(\Delta R_i\) during the bolus passage as a single point resolved T1 determination. The pixel with the largest signal increase in the internal carotid artery is used for the arterial input function \(Ca(t)\). All post-imaging processing is completed on a computer running MATLAB software and final permeability values are obtained on MATLAB by applying the Patlak method represented by the following equation:

\[
c_i(t) = K_i \int_0^t \frac{C_a(t) dt}{C_a(t)} + V_b
\]

Where \(C(t)\) is the total tissue tracer concentration, \(C_o\) is the tracer concentration in arterial whole blood, \(V_b\) is the cerebral blood volume (CBV) and \(K_i\) is the unidirectional influx constant or permeability. \(K_i\) and \(V_b\) can be determined from the slope and the intercept in the Patlak plot, respectively. Following this computer processing, regions of interest (ROIs) encompassing entire CCM lesions are selected using ImageJ software on T2 weighted images acquired just prior to
the T₁ images and are then superimposed on the maps which provides measures of permeability, cerebral blood flow and cerebral blood volume.

QSM images were obtained using the same MRI machine during the same session. A single three dimensional, multi-echo, T2*-weighted, spoiled gradient echo sequence was used for data collection for QSM reconstruction. The imaging parameters were as follows: axial imaging plane with full brain coverage; 8 echo times with uniform spacing; TE [min, max] = [5.2, 51] ms; TR = 62 ms; flip angle = 15°; field of view = 224 mm, acquisition matrix = 224 x 224; slice thickness = 1 mm; number of slab encodings = 120. Data acquisition is accelerated by a factor of 2 with parallel imaging. The SWI and QSM images were reconstructed offline using customized software. QSM images were reconstructed using a morphology-enabled dipole inversion (MEDI) algorithm³,⁴. Regions of interest (ROIs) included the same lesions identified on the T₂ images used for permeability measures and were drawn on the QSM images using ImageJ software².

After the initial analysis, a subcohort of ten patients was selected for intraobserver (AGM repeat measures of QSM and DCEQP) and interobserver (AGM and HT) consistency measures of the two techniques. These included all patients with single lesions and two patients with multiple lesions selected randomly.

Statistics: Pearson correlation was used to examine the correlation between QSM susceptibility vs. permeability (Figure 2 of main manuscript), CBV (supplementary figure V), and CBF (Supplementary figure VI). Multivariate linear regression was applied to assess the impact of some factors including whether the lesion is familial (supplementary figure I), contrast agent used (supplementary figure II), lesion volume (dichotomized using median volume) (supplementary figure III) and whether the patient was on statins (supplementary figure IV) on the susceptibility-permeability correlation. Susceptibility as the dependent variable, including permeability, the factor and their interaction in the model. Bland-Altman plots were constructed to evaluate intra-observer and inter-observer consistency (supplemental figures VII and VIII respectively). Coefficients of variation were calculated for interpatient and intrapatient variability (supplemental table I).
Supplemental Tables:
Supplemental Table I. Interpatient and Intrapatient variation of QSM and Permeability Measures

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<th>QSM</th>
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<tr>
<td><strong>Intrapatient coefficient of variation</strong></td>
<td>0.67</td>
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<td><strong>Interpatient coefficient of variation</strong></td>
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Supplemental Figures:

Supplementary figure 1. Correlation between susceptibility and permeability of CCM lesions in familial and sporadic patients

This graph illustrates the relationship between susceptibility (ppm) and permeability (mL/100g/min) when separating lesions into sporadic (in blue) \( r=-0.37, p=0.12 \) and familial (in red) \( r=0.5, p=<0.0001 \) groups, with the combined correlation shown in black.

Supplementary figure II. Impact of contrast agent on lesional susceptibility vs. permeability correlation

This graph illustrates the relationship between susceptibility (ppm) to permeability (mL/100g/min) using gadodiamide (Omniscan) in blue \( r=0.48, p=<0.0001 \) and gadobenate dimeglumine (Multihance) in red \( r=0.52, p=0.003 \), with the combined correlation (in black).
Supplementary figure III. Impact of lesion size on lesional susceptibility vs. permeability correlation

This graph illustrates the relationship between susceptibility (ppm) and permeability (mL/100g/min) when separating lesions into groups of small (in blue) \((r=0.41, p=0.006)\) and large (in red) \((r=0.38, p=0.01)\) lesions, with the combined correlation shown in black.

Supplementary figure IV. Impact of statin on lesional susceptibility vs. permeability correlation

This graph illustrates the relationship between susceptibility (ppm) and permeability (mL/100g/min) when separating patients into groups of those taking statins (red) \((r=0.42, p=0.12)\) and those not taking statins (blue) \((r=0.50, p=<0.0001)\), as well as the combined correlation in black.
Supplementary figure V. Lesional QSM susceptibility vs. lesional CBV

Linear regression illustrating the correlation between lesional QSM susceptibility in ppm and lesional CBV in mL/100g. (r=0.40, p=0.0001)

Supplementary figure VI. Lesional QSM susceptibility vs. lesional CBF

Graph illustrating the relationship between lesional QSM susceptibility in ppm and lesional CBF in mL/100g/min. (r=0.1, p=0.34)
Supplementary figure VII. Bland-Altman plot of intraobserver consistency

Bland-Altman plot of intraobserver consistency in QSM measures showing a bias of only 0.004 (95%CI=[-0.04-0.05]) between measurements of the same lesions at two different times. Bland-Altman plot of intraobserver consistency in permeability measures showing a bias of only 0.015 (95%CI=[-0.12-0.09]) between measurements of the same lesions at two different times.

Supplementary figure VIII. Bland-Altman plot of interobserver consistency

A. Bland-Altman plot of interobserver consistency in QSM measures showing a bias of only 0.03 (95%CI=[-0.02-0.09]) between two observers analyzing the same lesions. B Bland-Altman plot of interobserver consistency in permeability measures showing a bias of only -0.07 (95%CI=[-0.28-0.13]) between two observers analyzing the same lesions.
Supplemental References: