Attenuation of cerebral venous contrast in susceptibility-weighted imaging of spontaneously breathing pediatric patients sedated with propofol

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Abstract

Purpose—Susceptibility-weighted imaging (SWI) is known for its detailed visualization of the cerebral venous system and seems to be a promising tool for early detection of cerebrovascular pathologies in children, who are frequently sedated for MRI. Since sedation influences cerebral hemodynamics, we hypothesized that it would affect cerebral venous contrast in SWI.

Material and Methods—SWI (125 examinations) of 26 patients (age: 2–16 years) were reviewed in this study. Images were acquired of patients sedated with propofol. Reviewers classified the images by weak or strong venous contrast. Physiological data, such as end-tidal CO₂ (etCO₂), blood pressure (BP), age, and cerebral blood flow (CBF) by arterial spin labeling, were monitored and collected during MRI. A generalized estimating equation approach was used to model associations of these parameters with venous contrast.

Results—EtCO₂ and CBF were found to correlate with venous contrast, suggesting that patients with high etCO₂ and CBF have weak contrast and patients with low etCO₂ and CBF have strong contrast. BP was also found to correlate with SWI’s venous contrast, suggesting that patients with high BP have strong venous contrast. No significant correlations were found for any other physiological parameters.

Conclusion—We found that the venous contrast in SWI is affected by propofol sedation in spontaneously breathing patients. We also found that low etCO₂, low CBF, and high BP are associated with strong venous contrast. Reviewing SWI data in light of physiological measures may therefore help prevent potential misinterpretations of weak venous contrast in SWI exams under propofol sedation.

INTRODUCTION

Susceptibility-weighted imaging (SWI) reveals the cerebral venous system with great anatomic detail. The signal, which determines the contrast of venous vessels in SWI, depends on the deoxyhemoglobin concentration in the blood and is referred to as the blood...
oxygenation level-dependent (BOLD) signal. Under normal physiological conditions, cerebral venous blood has an oxygenation level of about 50%, and venous vessels appear hypointense on SWI, with good contrast to their surrounding brain tissue. Variations of the BOLD signal depend mainly on changes in the cerebral blood flow (CBF). With increased global CBF due to carbogen (95% O₂, 5% CO₂) inhalation, the venous blood oxygenation level is increased, causing a higher venous BOLD signal. Therefore, cerebral veins appear almost isointense in SWI, and their contrast to the surrounding tissue vanishes. On the other hand, CBF can be easily decreased globally by e.g. common doses of caffeine, decreasing venous blood oxygen saturation, lowering their BOLD signal, and thereby increasing venous contrast in SWI. Detection of neuronal activation is also commonly achieved by repeated measurements of BOLD signal changes. Here, CBF in activated areas increases, exceeding the actual demand for oxygen of the activated neurons, resulting in a higher blood oxygenation level and consequently a higher BOLD signal.

SWI is a powerful diagnostic tool for early detection and better characterization of cerebrovascular malformations, hemorrhages, iron deposits, and calcifications in children. However, MRI examinations of very young children are frequently performed under sedation by using the common anesthetic propofol. It was shown by a 15O-PET study in propofol-sedated healthy men that cerebral metabolism and CBF were comparably decreased, keeping the oxygen extraction fraction constant. Therefore, venous blood oxygen saturation and BOLD signal should not be directly affected due to propofol sedation. However, CO₂ reactivity of cerebral vessels and autoregulation of brain perfusion are retained under propofol sedation. As pediatric patients breathe spontaneously during sedation while undergoing MRI, their respiration is depressed by propofol. Therefore, propofol indirectly increases the partial pressure of CO₂ in the arterial blood, causing cerebral vessel dilatation, leading to an increase in CBF and a consequent rise in the BOLD signal, which in turn attenuates the contrast of cerebral veins on SWI. This effect was recently observed in a limited number of cases without sufficient evidence. Although the authors hypothesized that this finding could be caused by a change of cerebral metabolism and arterial oxygen saturation due to sedation, they were not able to prove or refute this. Nevertheless, a correlation between sedation and venous contrast in SWI is likely, and this relation needs to be better understood to allow correct interpretation of SWI data. Even though it is not anticipated that prominent (i.e., clinically relevant) pathologies such as arterio-venous malformations or Sturge-Weber syndrome would be missed if venous contrast were attenuated due to propofol sedation, it is possible that the exact extent or degree of the disease could be underestimated. On the other hand, with SWI becoming more widely available, it is conceivable that different levels of venous contrast might be used in the future to better differentiate diagnoses or to stage diseases, as recently presented by Newbern et al. (2009) at this year’s annual meeting of the ASNR.

Therefore, purpose of this study was to investigate the effect of sedation with propofol on venous contrast in SWI. We hypothesized that physiological measures such as blood pressure, heart rate, respiration rate, and end-tidal carbon dioxide (etCO₂), which reflect the effect of sedation on respiration and the cardiovascular system, would correlate with the apparent contrast of cerebral veins in SWI. We thereby assumed that other physiological parameters such as patient age or time on treatment should not correlate with the venous contrast in SW images exhibiting healthy brain tissue. Testing these hypotheses should help to prevent potential misinterpretation of SWI images acquired under sedation.

**MATERIAL and METHODS**

SWI data were collected from 26 patients (14 female, 12 male; age at diagnosis, 2–16 years) who were enrolled between May 2006 and February 2009 in an institutional review board-
approved clinical phase I trial at our institution. The patients had diagnoses of diffuse pontine glioma and were being treated with local radiation therapy to the brain stem (n=25) or to the whole brain (n=1). Radiation was fractionated and administered over 6 weeks (30 fractions, 54 Gy total dose). During the study, patients received vandetanib (Zactima; ZD6474), an anti-angiogenic drug. A secondary objective of the phase I trial was to assess vascular changes during therapy by advanced MR imaging techniques. SWI images were acquired on a 3T clinical MRI scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany). Imaging parameters were: TE/TR/FA = 25 ms/56 ms/20°, FOV = 230×115×144 mm³, matrix = 512×254×72, voxel size = 0.45×0.45×2 mm³, parallel imaging acceleration factor 2. Six consecutive scans were acquired in 14 patients, and 12 patients received from one to five MRI examinations in our study. Follow-up examinations were performed about 2 weeks and about 1, 2, 4, and 6 months after the first scan. In total, 125 SWI examinations covering the whole brain were rated in consensus by two reviewers. The venous contrast in SWI was classified in two groups: group one showing good to strong contrast and group two showing weak to almost no venous contrast between cerebral veins and parenchyma (Fig. 1). The characteristic criterion for strong contrast was good delineation of cortical venous vessels. Examinations with missing contrast of cortical veins while maintaining intermediate deep venous vessel contrast were categorized as weak venous contrast.

As confirmed by radiation therapy dose maps, inferior parts of the brain (i.e., medulla oblongata, brainstem, and cerebellum) were subject to high doses, making radiation-induced vasculopathy likely. Therefore, only veins of the cerebrum were used for evaluation to minimize any compromising effect of high radiation doses.

The complete set of diagnostic images of the patient who received radiation to the whole brain was carefully reviewed for abnormal features that might be related to radiation therapy. Because no abnormalities were evident, this patient’s SWI examinations were not excluded from our study.

One patient presented with supratentorial and infratentorial tumor dissemination via CSF (leptomeningeal disease) at the time of the fourth MRI examination. Because of this, the patient was taken off the clinical trial and his last exam was also excluded from further evaluation in our study, since it is convincible that leptomeningeal tumor spread may compromise venous contrast on SWI through compromising venous outflow and causing congestion within transmedullary veins.

Of the 125 SWI scans performed, 114 were acquired under sedation with the patient breathing spontaneously. Eleven examinations were not performed with the patient under sedation and were not formally evaluated. Sedation was maintained by infusion of propofol (150–300 μg/kg/min). The individual doses were adjusted by the anesthesiologists to allow a smooth MRI examination with minimal risk for the patient. Due to different individual sensitivities to the anesthetic, the actual dose of propofol was not correlated with venous contrast. We instead investigated physiological measures, which are potential measure of the actual effect of propofol to the subject. During the SWI scan, the following physiological parameters were monitored and recorded: pulse, systolic and diastolic blood pressure (BP), respiration rate, and etCO₂. To further investigate whether non-sedation-related physiological parameters also affect venous contrast in SWI, we correlated patient age at examination and red blood cell count with venous contrast. As an additional measure of the effect of sedation on CBF, arterial spin labeling (ASL) perfusion data using a Q2TIPS sequence was evaluated along with the SWI data. ASL sequence parameters were: TE/TR = 23 ms/2280 ms, TI₁/TI₂ = 700 ms/1400 ms, FOV = 210×210 mm², matrix = 64×64, slice thickness = 5 mm, 11 slices. Quantitative CBF values were calculated for slices located.
above the anterior-posterior commissure line following a method proposed by Wang et al.\textsuperscript{31} The mean CBF value for gray matter was calculated using a histogram-based segmentation algorithm (i.e., thresholding technique) of the upper brain CBF values.

**Statistical Methods**

Logistic regression models\textsuperscript{32} were used to investigate the association of physiological measurements with venous contrast at single time windows (e.g., baseline, week-2 scans, and week-4 scans) in a cross-sectional fashion to guide the rest of the statistical analyses. In such models, venous contrast was a dichotomous response, and each physiological variable was investigated independently. After identifying physiological variables of interest that were associated with venous contrast in at least one time window, the investigation was performed in a longitudinal fashion, using generalized estimating equations (GEE) models,\textsuperscript{33} which take into account intra-patient variability as patients have serial examinations over time. In the GEE models, venous contrast in SWI was again a dichotomous response, assuming binomial distribution with a logit link function, which is commonly used for binary data. Since the time intervals between the subsequent examinations were not equally spaced and not identical between patients, a spatial-power covariance structure was used to take into account intra-patient correlations. As this was an exploratory analysis, $P$ values reported were not adjusted for multiplicity, and the results must be considered in the context of an exploratory analysis and should be confirmed with larger prospective studies.

**RESULTS**

All of the 11 MRI examinations acquired without sedation showed strong venous contrast. Because physiological data were not monitored during those scans, they were excluded from further statistical analysis. MRI examinations under sedation showed weak venous contrast by our classification in 55 SWI scans and strong contrast in 59. As shown in Figure 2, this variation of contrast was observed even in the same subjects on different examination dates. Only three patients showed consistently weak venous contrast for all examinations.

Figure 3 shows the variation in etCO\textsubscript{2} between the two contrast groups at all MRI examination dates. For etCO\textsubscript{2}, a clear trend was observed. The mean and median values were always smaller in the group with good venous contrast. The results of the cross-sectional analysis with logistic regression models for all physiological measures are summarized in Table 1. The previous visual finding for etCO\textsubscript{2} (Fig. 2) was supported by a significant association of etCO\textsubscript{2} at every time point. As also shown in Table 1, segmented gray matter CBF measures were significantly associated with low SWI contrast for the second to the fifth MRI examinations. Systolic and diastolic BP showed significance only at the second time point. All other parameters showed no significant association in the cross-sectional analysis and thus were not further evaluated with the GEE models. Systolic BP and gray matter CBF were also excluded from further evaluation because they were highly correlated with diastolic BP and etCO\textsubscript{2}, respectively. As expected, however, gray matter CBF was strongly associated with venous contrast in a univariate GEE model (odds ratio $= 0.94$, $P = 0.0003$). Here, the odds ratio suggests that patients with higher gray matter CBF have poorer venous contrast.

The first GEE model (Table 2) resulted in a significant ($P < 0.0001$) odds ratio of 0.75, which suggests that, for high etCO\textsubscript{2} values, strong venous contrast is less likely than weak contrast in SWI. In the second analysis, etCO\textsubscript{2} and diastolic BP were investigated in one multivariate GEE model, which again led to significant odds ratios of 0.78 ($P = 0.0018$) for etCO\textsubscript{2} and 1.09 ($P = 0.0056$) for diastolic BP. Here, the odds ratio greater than one implies
that patients who presented with higher diastolic BP were more likely to show strong venous contrast in SWI.

Both GEE models showed that venous contrast did not change significantly over treatment time. This observation is important because it implies that there were probably no therapy-induced effects on venous contrast in the cerebrum, which was not directly targeted by conformal radiation and, thus, received only minor doses. In agreement with this is the finding that the red blood cell count did not correlate with venous contrast, because any therapy-induced changes in the red blood cell count would have to be corrected by blood transfusions. No correlation of venous contrast with patient age was found in our study.

DISCUSSION

Our analysis of SWI data from sedated patients showed that such imaging studies should be conducted under well adjusted physiological conditions to achieve a good venous contrast and to be able to make reliable comparisons between patients or between scans of an individual patient over time. In particular, etCO$_2$ was strongly associated with venous contrast and should be well controlled.

We feel confident that the radiation treatment of our patients did not compromise the validity of our study, because the observed associations of venous contrast in SWI with etCO$_2$, CBF, and BP were already obvious in the first scan, which was acquired before onset of radiation and anti-angiogenic therapy (Table 1, first examination).

We concluded from our pediatric patients (age: 2–16 years), who were sedated during MRI, that age-related changes in physiology have no effect on the observed venous contrast in SWI. There is, however, no evidence based on our results that there is an age-dependency of venous contrast for healthy non-sedated subjects, in particular, when considering a significant drop in CBF over several decades of life.

Since we argued that sedation affects respiration, it was interesting that no correlation of respiration rate with venous contrast was found. However, respiration rate is not a measure of the actual tidal volume and thus cannot give evidence of the actual depression of respiration. A similar finding was reported by Iwama et al., who observed a decrease in tidal volume but not in respiration rate while increasing the propofol infusion rate. The only measure of respiration attenuation available to the anesthesiologist is etCO$_2$, which was found in our study to be strongly associated with the observed venous contrast in SWI. Based on that finding, it might be possible to ensure good venous contrast in SWI by controlling sedation in such a way that etCO$_2$ is kept as low as possible. Karsli et al. reported a maximal etCO$_2$ value of 30–35 mmHg for which CBF in sedated children is not artificially elevated. This is also in agreement with our findings for CBF, where lower CBF values were accompanied by lower etCO$_2$ and good venous contrast. Conversely, higher CBF was associated with higher etCO$_2$ and weak venous contrast, which was confirmed by the consistent odds ratios less than one for CBF in Table 1 and for the univariate GEE model (see results part). All these findings are in perfect agreement with our introductory argument and support our hypothesis that etCO$_2$ reflects respiration attenuation due to intravenous propofol sedation and correlates with venous contrast in SWI.

The observed correlation between diastolic BP and venous contrast suggests that higher BP is associated with good venous contrast, lower etCO$_2$, and lower CBF and that lower BP is linked with weak venous contrast, higher etCO$_2$, and higher CBF, which was confirmed by the consistent odds ratios larger than one for diastolic BP (Table 1 and 2). This finding is very interesting, because one would expect high BP to cause high CBF and low BP to cause low CBF. However, it was shown that the autoregulatory mechanism of brain perfusion...
works more efficiently for lower etCO₂ than for higher etCO₂. This could explain the contradictory association between BP and CBF.

Since our ultimate goal is to monitor therapy-induced changes in tumor tissue of pediatric patients, we have to further investigate to what extent sedation compromises CBF or SWI measurements of tumor tissue. Our study showed that respiration attenuation due to propofol sedation can alter CBF and SWI contrast in healthy brain tissue. Thus, it might be necessary to correct for sedation-induced effects while monitoring tumors. Future studies that involve CBF and SWI measurements should be acquired under controlled physiological conditions during sedation. It is also conceivable that the observed sedation effect could be used to assess CO₂ reactivity as a pathophysiological marker of tumor vessels.

We feel confident that this effect does not degrade the detection of hemorrhages in sedated patients as reported by Tong et al., because the hemorrhagic contrast is caused by extravascular deoxyhemoglobin and methemoglobin rather than by the presence of intravenous deoxyhemoglobin. It should also be noted that findings of passive functional MRI studies might be compromised by the respiratory attenuation of propofol since the magnitude of the BOLD signal responses are most likely lowered due to elevated resting state perfusion of the brain. Therefore, an increased variation over different subjects or multiple examinations of the same subjects are anticipated for quantitative findings such as the magnitude of BOLD signal responses or numbers of activated voxels.

CONCLUSION

Based on the results of our analysis, we conclude that it is necessary to acquire SWI data of sedated patients under well controlled physiological conditions to achieve a good venous contrast and to be able to make reliable comparisons between different patients or follow-up scans. It was found that etCO₂ was strongly associated with venous contrast and must be kept below 30–35 mmHg, as reported by Karsli et al., to achieve good venous contrast in SWI. If etCO₂ cannot be well controlled in sedated, spontaneously breathing, patients, we strongly recommend reviewing SWI data in light of etCO₂, BP, and CBF measures acquired at the same physiological state to prevent potential misinterpretation of venous contrast in SWI.

Acknowledgments

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ABBREVIATION KEY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SWI</td>
<td>Susceptibility-weighted imaging</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood oxygenation level-dependent</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<tr>
<td>etCO₂</td>
<td>end-tidal carbon dioxide</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>RR</td>
<td>respiration rate</td>
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RBC: red blood cell count
Q2TIPS: Quantitative imaging of perfusion using single subtraction, second version, with thin-slice T1 periodic saturation
ASL: arterial spin labeling
GEE: generalized estimating equations

References


Figure 1.
Example SWI data demonstrating venous contrast classification. All images were generated and visualized using identical parameters. Examinations with obviously vanished veins (A) as well as examinations showing missing contrast of cortical veins (thin arrow) while maintaining intermediate contrast of deep veins (thick arrow) (B) were categorized as weak venous contrast. Examinations showing strong contrast of deep veins while maintaining intermediate contrast of cortical veins (C) and examinations with obviously strong venous contrast for all veins (D) were categorized as strong venous contrast.
Figure 2.
Example SWI data of a 7-year-old patient on two different examination dates to demonstrate the intra-subject variation of venous contrast. The patient was sedated for both MRI examinations. Physiological measures (BP – blood pressure, RR – respiration rate, etCO$_2$ – end tidal CO$_2$, CBF – cerebral blood flow, RBC – red blood cell count) at both examinations are shown for comparison. The images were generated and visualized using identical parameters.
Figure 3.
Scatter and box plots shown for etCO$_2$. Exhaled CO$_2$ is plotted for both groups of different venous contrast in SWI and separately for all six time points of consecutive MRI examinations. The asterisk within the box plot denotes the mean value of the particular etCO$_2$ distribution.
Table 1

Odds ratio estimates ($P$ values) from logistic regression models for individual time points of consecutive MRI examinations. Asterisks denote odds ratios significant to a level of $P < 0.1$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First exam (n=23)</th>
<th>Second exam (n=21)</th>
<th>Third exam (n=21)</th>
<th>Fourth exam (n=19)</th>
<th>Fifth exam (n=16)</th>
<th>Sixth exam (n=13)</th>
</tr>
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<tbody>
<tr>
<td>CBF</td>
<td>0.97 (0.25)</td>
<td><strong>0.90 (0.016)</strong></td>
<td><strong>0.95 (0.071)</strong></td>
<td><strong>0.94 (0.051)</strong></td>
<td><strong>0.90 (0.050)</strong></td>
<td>0.97 (0.26)</td>
</tr>
<tr>
<td>sys BP</td>
<td>1.03 (0.29)</td>
<td><strong>1.16 (0.048)</strong></td>
<td>1.00 (0.99)</td>
<td>1.01 (0.83)</td>
<td>0.93 (0.25)</td>
<td>0.96 (0.48)</td>
</tr>
<tr>
<td>dia BP</td>
<td>1.07 (0.14)</td>
<td><strong>1.23 (0.037)</strong></td>
<td>1.01 (0.83)</td>
<td>1.08 (0.14)</td>
<td>1.01 (0.93)</td>
<td>1.04 (0.54)</td>
</tr>
<tr>
<td>Pulse</td>
<td>1.00 (0.98)</td>
<td>0.99 (0.70)</td>
<td>0.96 (0.26)</td>
<td>0.98 (0.7)</td>
<td>1.03 (0.49)</td>
<td>0.97 (0.50)</td>
</tr>
<tr>
<td>etCO$_2$</td>
<td><strong>0.72 (0.050)</strong></td>
<td><strong>0.8 (0.036)</strong></td>
<td><strong>0.84 (0.066)</strong></td>
<td><strong>0.68 (0.062)</strong></td>
<td><strong>0.65 (0.071)</strong></td>
<td><strong>0.60 (0.089)</strong></td>
</tr>
<tr>
<td>RR</td>
<td>1.04 (0.67)</td>
<td>1.26 (0.15)</td>
<td>1.07 (0.49)</td>
<td>1.08 (0.44)</td>
<td>1.02 (0.82)</td>
<td>0.81 (0.26)</td>
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<tr>
<td>Age</td>
<td>1.06 (0.59)</td>
<td>0.93 (0.54)</td>
<td>0.89 (0.28)</td>
<td>0.98 (0.87)</td>
<td>1.15 (0.26)</td>
<td>1.16 (0.28)</td>
</tr>
<tr>
<td>RBC</td>
<td>4.34 (0.36)</td>
<td>0.42 (0.49)</td>
<td>0.27 (0.25)</td>
<td>1.16 (0.85)</td>
<td>0.67 (0.71)</td>
<td>2.39 (0.62)</td>
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</table>

Note – CBF indicates cerebral blood flow; sys BP, systolic blood pressure; dia BP, diastolic blood pressure; etCO$_2$, end-tidal carbon dioxide; RR, respiration rate; RBC, red blood cell count.
Table 2

Odds ratio estimates with confidence intervals and \( P \) values from general estimating equation (GEE) models for the parameters of interest. To describe the longitudinal nature of the data, the actual time points of the follow-up MRI examinations were taken into account by the GEE models.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
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<tbody>
<tr>
<td>etCO(_2)</td>
<td>0.75</td>
<td>0.65–0.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time points</td>
<td>0.27</td>
<td>0.02–4.24</td>
<td>0.34</td>
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<table>
<thead>
<tr>
<th>Model 2</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>etCO(_2)</td>
<td>0.78</td>
<td>0.66–0.91</td>
<td>0.0018</td>
</tr>
<tr>
<td>dia BP</td>
<td>1.09</td>
<td>1.03–1.15</td>
<td>0.0056</td>
</tr>
<tr>
<td>Time points</td>
<td>0.41</td>
<td>0.02–10.1</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Note – CI indicates confidence interval; etCO\(_2\), end-tidal carbon dioxide; dia BP, diastolic blood pressure.