Detecting misery perfusion in patients with cerebrovascular disease by susceptibility of draining veins using quantitative susceptibility mapping

Poster No.: C-1408
Congress: ECR 2018
Type: Scientific Exhibit
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Keywords: Computer Applications-Detection, diagnosis, MR, Neuroradiology brain, Ischaemia / Infarction
DOI: 10.1594/ecr2018/C-1408

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Aims and objectives

Oxygen extraction fraction (OEF) is a powerful index for misery perfusion in patients with cerebrovascular disease [1,2]. Most reliable approach to measure OEF is using positron emission tomography (PET) with radioactive $^{15}$O$_2$ generated by cyclotron. $^{15}$O PET available hospital is limited, therefore OEF measurement is not generally used in clinical purpose. Recently, several OEF estimation methods have been reported using susceptibility effect of deoxygenated hemoglobin in MRI. MRI is widely available in most stroke center. It may have the potential in clinical routine. One of the OEF estimation methods in MRI is using quantitative susceptibility mapping (QSM) [3]. Although QSM is a novel quantitative technique for estimating magnetic susceptibility [4-7], assumptions of several unknown parameters were needed for the OEF quantification from QSM, e.g. susceptibility difference per unit hematocrit, correction factor for partial volume effect. In spite of the quantitative OEF value comparison, direct evaluation of susceptibility difference in the draining veins may be enough for clinical purpose. Therefore, we investigate the relationship between quantitative susceptibility of the draining veins and OEF evaluated by PET.
Methods and materials

Subjects

Twenty-six patients (7 females and 19 males) with unilateral chronic major cerebral artery steno-occlusive disease were selected for this study. Their age ranged from 37 to 80 (mean 62.9) years-old. Ten patients had internal cerebral artery (ICA) stenosis or occlusion, 16 patients had middle cerebral artery (MCA) stenosis or occlusion. MRI and $^{15}$O PET scans within two days.

Twelve normal subjects (6 females and 6 males) were also added for the determination of normal range of susceptibility value of draining veins. Their ages ranged from 29 to 59 (mean 45.7) years-old. They were confirmed to have no past history of neurological diseases. Informed consent was obtained from all normal subjects in this study.

MRI

MRI scans were performed using a 3.0 Tesla scanner with a 32-channel head coil. MRI protocol included T2WI, SWI, 3D TOF MRA, 3D-T1 structural image and QSM. A three-dimensional (3D) gradient echo recalled (GRE ) sequence with flow compensation was used for phase image acquisition. The scan parameters for QSM included repetition time (TR) of 33 ms, echo time (TE) of 25 ms, flip angle of 15 degree, number of excitation of 1, acquisition matrix of 352 × 286, field of view (FOV) of 230 mm, slice thickness of 3 mm, and number of partitions of 30. The acquisition time was 3 min and 30 s. The magnitude and phase images were reconstructed by the software installed in the MRI console.

QSM images were created using MATLAB-based software package of STI Suite version 3 (University of California, Berkeley, USA) [7]. 3D V-SHARP method was used for background phase removal, and STAR method was used for QSM calculation [7].

PET

$^{15}$O PET measurements were performed for gas inhalation of $^{15}$O, $^{15}$O$_2$ and bolus injection of H$_2$O. In $^{15}$O PET study, parameters of CBF, CMRO2, OEF and CBV were measured [8].
**Data processing**

Schematic of data processing was shown in figure 1. Comparison between QSM and PET-OEF was performed in the two slabs of basal ganglia and corona radiata level. Six QSM images (total thickness 18 mm) were included in the slab. PET-OEF value in the slab is evaluated by the mean intensity after co-registration from PET-OEF images to the MRI T1 structural image by using SPM 12 software [9]. The mean value in eight square (20 × 20 mm) regions-of-interests (ROIs) in the slab was evaluated. ROIs was manually placed along the parenchymal surface at MCA territory. Evaluation for QSM, maximum intensity projection (MIP) in the slab (QSM-MIP) was calculated. Extracted draining veins maps (QSM-VEINs) were extracted from QSM-MIP value which is higher value than magnetic susceptibility of 0.04 ppm. Mean value of QSM-VEINs in the ROIs was evaluated as mean susceptibility value in draining veins (MRI-SDV). Image processing except for co-registration was performed using ImageJ software (https://imagej.nih.gov/ij/).

**Statistical analysis**

Contralateral ratio correlation between PET-OEF and MRI-SDV was evaluated the mean value of the two slabs in each patient. Each hemisphere value was evaluated by the average of 4 ROIs in each hemisphere. PET-OEF and MRI-SDV ratio were calculated between affected (OEF\textsubscript{affected}, SDV\textsubscript{affected}) and contralateral value (OEF\textsubscript{contralateral}, SDV\textsubscript{contralateral}) in the patients as equation 1 and 2.

\[
\text{OEF ratio} = \frac{\text{OEF}_{\text{affected}}}{\text{OEF}_{\text{contralateral}}} \quad \text{[Equation 1]}
\]

\[
\text{SDV ratio} = \frac{\text{SDV}_{\text{affected}}}{\text{SDV}_{\text{contralateral}}} \quad \text{[Equation 2]}
\]

Normal range of MRI-SDV ratio was defined as mean ± 2 × (standard deviation; SD) in the 12 normal subjects in this study. Normal range of PET-OEF ratio was also defined as mean ± 2 × SD (1.00± 0.08) from our previous reports [8]. Increased value was defined as above the normal range and preserved value as in the normal. The numbers of increased or preserved value were evaluated. The sensitivity, specificity, and accuracy of PET-OEF and MRI-SDV were also calculated.

Correlation analysis was accessed by linear regression analysis and Pearson's correlation coefficient.
Direct value correlation was analyzed using 16 ROIs from all patients and correlation coefficient was calculated for increased PET-OEF and preserved patients separately.
**Fig. 1:** Schematic of data processing. Two slabs of basal ganglia and corona radiata level was used for evaluation of PET-OEF and QSM comparison. Orange squares showed example of ROIs.

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Results

Upper limit of normal ranges in MRI-SDV ratio was 1.12. The scatter plot of PET-OEF and MRI-SDV is shown in figure 2. Nine patients had significant increase in PET-OEF and others have normal PET-OEF. Among seven patients who had significant increase in MRI-SDV, six had also significant increase in PET-OEF (true-positive). There was a significant and moderate correlation between PET-OEF and MRI-SDV (p<0.01 and r=0.85).

Number of patients who had increased and preserved value was shown in table 1. According to these data, the sensitivity of MRI-SDV was 0.67 (6/9), the specificity was 0.94 (16/17), and the accuracy was 0.85 (22/26).

The scatter plot of direct value correlation was shown in figure 3. Figure 3a was the plot of increased PET-OEF patients (n=9) and Figure 3b was preserved patients (n=17). Significant and moderate correlation was observed (p<0.01, r=0.46) in increased PET-OEF patients. In contrast, there was no correlation (p=0.20, r=-0.11) in preserved PET-OEF patients.

A typical image with chronic occlusion of the right MCA was shown in figure 4. MRA disclosed occlusion of the proximal M1 segment of the right MCA (Figure 4a). PET-OEF showed increased value in the right MCA territory suggesting misery perfusion (Figure 4b). QSM-MIP shows prominent superficially hyperintense signals in the superficial cerebral veins (Figure 4c) corresponding to increased PET-OEF region. Hyperintense signals at QSM-MIP might indicate deoxygenation due to an increase in OEF.
Fig. 2: Comparison of contralateral ratio between PET-OEF and MRI-SDV ratio. Red and yellow circle indicate increased and preserved PET-OEF patients, respectively. Three patients had false-negative in MRI-SDV (small arrows) and one did not have increase in MRI-OEF (false-positive, large arrows). Threshold value of 1.08 (PET-OEF) and 1.12 (MRI-SDV) was defined as mean + 2 # (standard deviation) in normal value. Equation of linear regression analysis and Pearson's correlation coefficient (r) were indicated in the figure.

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**Fig. 3:** Direct value correlation between PET-OEF and susceptibility of draining veins. Correlation of increased PET-OEF patients (a) and preserves PET-OEF patients (b) were shown. ROIs number and equation of linear regression analysis and Pearson's correlation coefficient were indicated in the figure.

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Fig. 4: A typical image with chronic occlusion of the right MCA. (a) MRA image with indication of occlusion in the proximal M1 segment of the right MCA (arrow). PET-OEF (b) and QSM-MIP(c) in basal ganglia level (upper) and corona radiate level (lower). Prominent superficially hyperintense signals in the superficial cerebral veins between arrows.

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<table>
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<tr>
<th>PET-OEF</th>
<th>MRI-SDV</th>
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<tr>
<td></td>
<td>Increased</td>
<td>Preserved</td>
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<tr>
<td>Total</td>
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<td>19</td>
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Sensitivity = \( \frac{6}{9} = 0.67 \)
Specificity = \( \frac{16}{17} = 0.94 \)
Accuracy = \( \frac{22}{26} = 0.85 \)

**Table 1:** Number of patients who had increased / preserved PET-OEF and mean susceptibility value in draining veins (MRI-SDV).

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Conclusion

Discussion

In our study, contralateral ratio of magnetic susceptibility was well correlated with PET-OEF. Higher contralateral ratio of MRI-SDV indicate increased PET-OEF in affected tissue. However, the direct value correlation between PET-OEF and MRI-SDV was not strong even in patients with increased PET-OEF. This may be related to the partial volume effect in the voxel. The voxel size of the MRI-SDV is 0.7 × 0.7 × 18 mm, whereas the diameter of draining veins frequently ranged from 0.1 to 1.0 mm [10]. Therefore, the susceptibility value in the vein may be underestimated. The variance in the magnetic susceptibility value (shown in figure 3) may reflect the diameter of the vein in the voxel. Correct MRI-SDV may be higher than the value in the study. Venous engorgement prominently appeared in the increased PET-OEF region. Partial volume underestimation may be corrected by enlarged veins than preserved PET-OEF patients. Estimation of contralateral ratio just reflects the difference between affected and non-affected hemisphere. Partial volume effect is less sensitive than direct value comparison.

We hypothesized that direct evaluation of susceptibility difference in the draining veins may be enough for clinical purpose. For the estimation of contralateral ratio, assumed parameters for OEF quantification in QSM is canceled out in the equation of division. Therefore the contralateral ratio in this study indicates useful clinical value. If the magnetic susceptibility in the vein can be correctly estimated, OEF value could be useful. However, estimated variance of magnetic susceptibility is large and the acquisition from small voxel for partial volume correction is very difficult. Therefore exact MRI-SDV and OEF estimation from the QSM is not easy. In these reason, contralateral ratio evaluation by susceptibility difference may be enough for clinical purpose.

Conclusion

Feasibility of contralateral ratio of susceptibility for patients with cerebrovascular disease was confirmed. Higher value of susceptibility in draining veins may indicate increased OEF. Mean susceptibility in draining veins using QSM technique is useful for detecting misery perfusion in patients with cerebrovascular disease.
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