Quantitative Kinetic Analysis of Blood Vessels in the Outer Membranes of Chronic Subdural Hematomas

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Abstract
Dynamic biologic modeling was used to calculate the transfer rate constant for gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) and capillary permeability in the outer membrane of chronic subdural hematomas and effusions. Following intravenous Gd-DTPA injection, Gd concentrations in the subdural fluid and in timed arterial blood samples were measured by ion-coupled plasma emission spectrometry in 53 chronic subdural hematomas and 18 chronic subdural effusions. The capillary surface area in outer membrane was assessed morphometrically. Transfer rate constants for subdural hematomas and subdural effusions were 12.4 ± 1.0 and 20.6 ± 1.7 (×10^-4) min^-1, respectively. Capillary permeabilities for subdural hematomas and subdural effusions were 16 ± 1.2 and 19 ± 3.7 ml·min^-1·(mm^2/mm^3)^-1, respectively. The capillary surface areas for subdural hematomas and subdural effusions were 48 ± 3 and 77 ± 10 mm^2/mm^3, respectively. The high degree of infiltration of Gd into subdural effusions reflects the high capillary surface area in the outer membrane rather than greater permeability of individual capillaries. The value of transfer rate constant was correlated inversely with the duration of the chronic subdural fluid collection. Immature outer membrane has a high transfer rate constant which allows extravasation of plasma components into the subdural space, resulting in increasing volume of the subdural effusion. Delayed magnetic resonance imaging following Gd administration may be clinically useful for estimating the age of chronic subdural fluid accumulations.

Key words: chronic subdural hematoma, gadolinium, transfer rate constant, permeability, magnetic resonance imaging

Introduction
Chronic subdural hematoma is among the commonest entities encountered in neurosurgery. However, the mechanisms of occurrence and enlargement of chronic subdural hematomas are not completely understood. Traumatic subdural effusion is widely considered to be a precursor of chronic subdural hematoma. The key to understand these entities is that the outer membranes of these lesions contain capillaries and sinusoids. Capillaries begin to appear in the outer membrane 2 week after head injury, and the capillary endothelium has many fenestrations and open gaps which conceivably could allow extravasation of plasma components into the subdural space, enlarging the subdural effusion. We previously reported that the rate constant of gadolinium (Gd) transfer into chronic subdural effusion was significantly higher than that of chronic subdural hematoma. We also showed that the Gd transfer rate constant became lower as subdural hematomas matured. These results suggest that the ingress of plasma from blood vessels in the outer membrane correlates with the increase of hematoma (effusion) volume and aging of the outer membrane.

The present study measured Gd concentrations in the arterial blood and subdural hematomas (effusions), and calculated the permeability of the blood vessels in the outer membrane by quantitative kinetic analysis, to investigate the mechanism of increase of hematoma (effusion) volume and whether magnetic resonance (MR) imaging can be used to assess the age of the outer membrane.

Materials and Methods
The subjects consisted of 58 patients (40 males and...
18 females. All diagnoses were confirmed by computed tomography (CT) and MR imaging. To simplify mathematical analysis, only patients with homogeneous hematomas and effusions were studied. CT was used to measure the volume and Hounsfield number of the subdural fluid. MR imaging used a 0.5 T Hitachi MRH-500 imager (Hitachi Ltd., Tokyo) with spin-echo sequences to obtain T₁-weighted images of repetition time/echo time 470/23 msec. Baseline signal intensity (SI-baseline) was measured using computer-drawn regions of interest (ROIs) in the subdural fluid on the T₁-weighted images. The character of the subdural fluid was confirmed by centrifugation of the subdural fluid, with a dark red pellet (old blood) signifying hematoma and xanthochromic fluid with no pellet indicating effusion. Thirty-five patients had unilateral hematoma and nine had bilateral hematomas. Ten patients had unilateral effusion and four had bilateral effusions. The clinical and radiological characteristics of the chronic subdural hematomas and effusions are summarized in Table 1.

### Table 1 Clinical and radiological characteristics of chronic subdural hematomas and effusions

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age (yrs)</th>
<th>Interval (wks)</th>
<th>CT number</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematomas</td>
<td>53 (44 patients)</td>
<td>86 ± 3</td>
<td>8.3 ± 0.7</td>
<td>52 ± 1.5</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>Effusions</td>
<td>18 (14 patients)</td>
<td>70 ± 3</td>
<td>5.3 ± 0.8*</td>
<td>32 ± 2.3*</td>
<td>62 ± 9</td>
</tr>
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</table>

Interval (wks) refers to weeks from head injury to operation. Values are mean ± SEM. *Significant at p<0.05, by unpaired Student's t-test. **Significant at p<0.01, by unpaired Student's t-test. CT: computed tomography.

To quantitatively estimate the transfer capacity of Gd-DTPA into the subdural space, the rate constant for transfer of Gd-DTPA from blood vessels in the outer membrane to the subdural cavity was derived from a dynamic model of Gd-DTPA influx into the subdural fluid. The transfer rate constant (K) of Gd-DTPA is the concentration of Gd in subdural fluid at the time of fluid evacuation [Cl(T)] divided by the timed integral of the Gd concentration of arterial blood [∫₀^t Ca(t) dt].

\[
K = \frac{Cl(T)}{\int_0^t Ca(t) dt} \tag{1}
\]

where t is any time (minute) after intravenous administration of Gd-DTPA and T is the time (minute) when the subdural fluid is evacuated. Equation (1) is the operational equation for calculating the transfer rate constant.

According to Fick's law of diffusion, the definition of capillary permeability (P) is

\[
dAi/dt = PS \cdot dC/dX \tag{2}
\]

where S is the capillary surface area (mm²/mm³) in the outer membrane, and dAi/dt is the amount of tracer (Gd) that diffuses into the subdural cavity per unit time, equal to the volume of the subdural cavity (V) x dCi/dt. dC/dX is a concentration gradient proportional to Ca(t). The relationship between transfer rate constant and the concentration gradient is given by

\[
dCi/dt = K \cdot Ca(t) \tag{3}
\]

From equations (2) and (3),

\[
P = \frac{K \cdot V}{S} \tag{4}
\]

Equation (4) is the operational equation for calculating the permeability of blood vessels in the outer membrane.
The rate constant of Gd transfer into chronic subdural hematoma (effusion) is influenced by both the permeability of the blood vessels in the outer membrane and the amount of intervening fibrous tissue between the blood vessels and the hematoma cavity. To estimate the latter, the percentage of the volume of the outer membrane consisting of blood vessels (volume fraction) was measured as follows. Photographs of sections of the outer membrane were taken at a magnification of ×200. A MCID system (Microcomputer Imaging Device; Imaging Research Inc., St. Catharines, Ontario, Canada) was used for quantitative analysis of the total tissue area and area of blood vessels within the measured area of the outer membrane. From the morphometric data, the capillary surface area and the volume fraction were calculated according to stereologic theory.17,18

Results were analyzed for statistical significance using the unpaired Student's t-test and linear regression analysis, with p < 0.05 considered significant. Data are shown as mean ± SEM.

Results

The quantitative kinetic parameters of the blood vessels in the outer membrane of the chronic subdural hematomas and effusions are summarized in Table 2.

The Gd concentrations in subdural hematomas and subdural effusions were measured in samples 150–210 minutes after intravenous injection of Gd-DTPA. The mean Gd concentrations in the subdural hematomas (n = 53) and subdural effusions (n = 18) were 42 ± 3 and 85 ± 10 nmol/ml, respectively. The mean Gd concentration in subdural effusions was significantly higher (p < 0.01) than in subdural hematomas.

The transfer rate constant for Gd into subdural fluid was calculated from equation (1), using the measured arterial blood concentrations and subdural fluid Gd concentrations. The mean values for subdural hematomas (n = 53) and subdural effusions (n = 18) were 12.4 ± 1.0 and 20.6 ± 1.7 (×10⁻⁴)min⁻¹, respectively. The mean value for subdural effusions was significantly higher (p < 0.01) than for subdural hematomas.

The volume fractions and capillary surface areas were determined in the outer membranes. The mean volume fractions (%) for subdural hematomas (n = 53) and effusions (n = 18) were 10 ± 0.8% and 18 ± 2.5%, respectively, with the mean volume fraction of effusions being significantly higher (p < 0.01). The mean capillary surface area of subdural hematomas and effusions were 48 ± 3 and 77 ± 10 mm²/mm³, respectively, with the mean capillary surface area of subdural effusions being significantly higher (p < 0.01).

The permeabilities of capillaries in the outer membrane of chronic subdural hematomas and effusions were calculated from equation (4), using data for transfer rate constants, capillary surface area, and volume of the chronic subdural fluid. The mean permeability values for subdural hematomas (n = 53) and effusions (n = 18) were 16 ± 1.2 and 19 ± 3.7 ml·min⁻¹(mm²/mm³)⁻¹, respectively, and were not significantly different.

Thirty patients with hematomas and 11 with effusions had a definite history of head injury. The corre-

Table 2  Kinetic parameters of blood vessels in outer membranes of chronic subdural hematomas and effusions

<table>
<thead>
<tr>
<th></th>
<th>Gd concentration (nmol/ml)</th>
<th>Gd transfer rate constant (×10⁻⁴)min⁻¹</th>
<th>% Volume of blood vessels</th>
<th>Capillary surface area (mm²/mm³)</th>
<th>Permeability of capillary [ml·min⁻¹(mm²/mm³)⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematomas</td>
<td>42 ± 3</td>
<td>12.4 ± 1.0</td>
<td>10 ± 0.8</td>
<td>48 ± 3</td>
<td>16 ± 1.2</td>
</tr>
<tr>
<td>Effusions</td>
<td>85 ± 10*</td>
<td>20.6 ± 1.7*</td>
<td>18 ± 2.5*</td>
<td>77 ± 10*</td>
<td>19 ± 3.7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *Significant at p<0.01, by unpaired Student's t-test. Gd: gadolinium.
lation between the transfer rate constant values and the interval from head injury to operation in weeks are shown in Fig. 1. Regression analysis revealed the regression curve as \( Y = 21.7 \times e^{-0.08X} \). The coefficient of determination \( (R^2) \) was 0.187 and was statistically significant \( (p < 0.005) \).

Correlation by linear regression analysis between transfer rate constant values and \% enhancement on MR images revealed a regression equation of \( Y = 11.5 + 0.123X \) (Fig. 2). The \( R^2 \) was 0.318 and was statistically significant \( (p < 0.001) \). Chronic subdural fluid tended to have a high \% enhancement on MR images when transfer rate constant was high.

Correlation by linear regression analysis between the interval from head injury to operation and the \% enhancement on MR images revealed a regression equation of \( Y = 44.8 - 3.3X \). The \( R^2 \) was 0.155 and was statistically significant \( (p < 0.0001) \). Those data show that delayed Gd-enhancement MR imaging was clinically useful for estimating the age of the lesion.

Representative photomicrographs of outer membranes of chronic subdural effusion and hematoma show that the outer membrane of effusion contains numerous capillaries whereas the capillaries in the outer membrane of the hematoma have largely been replaced by fibrous tissue (Fig. 3).

**Discussion**

Previously, quantitative studies of the function of capillaries in the outer membrane have been rare. Study of the dynamics of technetium-99m (\(^{99m}\text{Tc}\))-pertechnetate flux into chronic subdural hematomas following intravenous injection of \(^{99m}\text{Tc}\) showed that peak \(^{99m}\text{Tc}\) radioactivity in the subdural fluid was detected 1.5 hours after injection. Therefore, diagnostic sensitivity to chronic subdural hematomas could be increased by using delayed \(^{99m}\text{Tc}\) scanning. Examination of delayed MR images obtained 4 hours after intravenous injection of Gd-DTPA in cases of subdural effusion and hematoma showed that Gd-DTPA leaks into the subdural space, which is isolated from the subjacent subarachnoid space. Such delayed-enhancement phenomena suggest that the influx of tracers into subdural fluid is cumulative. Recently, we presented a dynamic biologic modeling analysis to calculate the transfer rate constant for Gd-
DTPA influx into the chronic subdural hematomas and effusions and found that the Gd transfer rate constant for effusions were significantly higher than for subdural hematomas. We concluded that the immature outer membrane of subdural effusion has a high transfer rate constant, allowing extravasation of plasma components into the subdural space and increasing the volume of the subdural effusions; this rate constant decreases with aging of the subdural hematomas. However, the related issue of capillary permeability was not examined.

The present study showed that Gd concentrations and the transfer rate constant in subdural effusions were significantly higher than in subdural hematomas, but there were no significant differences in the permeability of capillaries in the outer membrane between subdural hematomas and effusions. Also, the % volume consisting of blood vessels and the capillary surface area in the outer membranes was significantly higher in subdural effusions than in subdural hematomas. The high infiltration rate of Gd into subdural effusions is related to the high capillary surface area per unit volume of outer membrane (with less tissue intervening between blood vessels and the effusion cavity) rather than the degree of permeability of individual capillaries. We believe that enhanced transport of plasma components into the subdural cavity increases the volume of chronic subdural effusion until repeated bleeding from degenerating capillaries, accompanied by locally increased fibrinolysis, transforms the effusion into chronic subdural hematoma.

This study showed that the transfer rate constant value correlates negatively with the age of the subdural fluid accumulation (that is, the interval from head injury to operation). The transfer rate constant value also correlates with the percentage of delayed enhancement on MR imaging, which is more prominent in immature lesions. Figure 4 shows a representative T1-weighted MR image before and the corresponding T1-weighted MR image (delayed MR imaging) 1 hour after intravenous administration of Gd-DTPA. Delayed MR imaging may be clinically useful for estimating the age of chronic subdural effusions and hematomas. For example, in an asymptomatic patient with a small chronic subdural fluid collection after head injury which is strongly enhanced by Gd, it is advisable to defer surgery until after maturation of the subdural effusion to avoid reaccumulation of subdural fluid after operation.

Acknowledgment

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References


Fig. 4 T1-weighted magnetic resonance (MR) images showing hypointense subdural fluid (upper row), and 1 hour after intravenous injection of gadolinium (Gd)-diethylenetriaminepenta-acetic acid (delayed MR image) showing influx of Gd into the subdural fluid (lower row).
Commentary

We have known since the introduction of CT and MRI that a chronic subdural hematoma can very often develop following a traumatic subdural effusion. However, the mechanisms of occurrence and enlargement of a chronic subdural hematoma are not clearly understood. This article provides convincing evidence that Gd concentrations and the transfer rate constant in subdural effusions were significantly higher than in subdural hematomas. The authors suggest that this high infiltration rate in subdural effusions is related to the high capillary surface per unit volume of outer membrane rather than the degree of permeability of individual capillaries. More interestingly, the value of transfer rate constant was correlated inversely with the duration of the chronic subdural fluid collection. They suggest that delayed MRI may be clinically useful for estimating the age of chronic subdural effusions and hematomas. Such information will shed valuable light on the mechanism or pathogenesis underlying the association between a traumatic subdural effusion and a chronic subdural hematoma. Hopefully, the results of Mori and co-workers will serve as the groundwork for further clinical investigation of chronic subdural hematoma.

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Mori et al. have utilized an extremely precise and elegant method to demonstrate the capillary permeability of the outer membrane of chronic subdural and traumatic effusions, using a quantitative kinetic analysis, in order to elucidate the mechanism of hematoma and effusion volume growth; and also to calculate the age or maturity of the hematoma/effusion membrane through magnetic resonance. They demonstrated that the more immature membrane of subdural effusion has a higher transfer rate constant of gadolinium, and a more pronounced extravasation of plasma components into the subdural space, responsible for the increasing volume of effusions; this phenomenon decreasing with aging of the expanding lesion, local fibrinolysis transforming an effusion into a chronic subdural. This is an important contribution for the care of these patients, since it will be possible to postpone the surgery in asymptomatic patients with small traumatic collections if strongly entranced by gadolinium, until maturation of the subdural effusion, in order to prevent reaccumulation of fluid, thus preventing a precocious intervention.

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The etiology of subdural hematoma and subdural effu-
sion, and the mechanism of their increase and differentiation are still controversial. Mori et al. used quantitative kinetic analysis to measure the Gd concentrations in arterial blood and subdural hematomas (effusions) and calculated the permeability of the blood vessels in the outer membrane. The high degree of infiltration of Gd into subdural effusions reflected the high capillary surface area in the outer membrane rather than the greater permeability of individual capillaries. The immature outer membrane had a high transfer rate constant, allowing extravasation of plasma components into the subdural space, resulting in an increased volume of subdural effusion. These results suggest the clinical usefulness of delayed magnetic resonance imaging following Gd administration for estimating the age of chronic subdural fluid accumulations. The reliability of the method for measurement of the capillary surface area in the resected outer membrane which has collapsed, and the issue of informed consent from patients for serial blood extraction appear to be problematic. Prospectively, magnetic resonance imaging using intravascular infusion of contrast material will be replaced by a less invasive method for the diagnosis of chronic subdural hematoma (effusion).

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