Background and Purpose—A recent study showed a dramatic increase in cerebral hemorrhage comprising atypical locations with low-frequency ultrasound–mediated recombinant tissue plasminogen activator–thrombolysis in humans. Here, we provide a possible explanation for this phenomenon by a side effect observed in a study using the similar ultrasound device.

Methods—The study was originally undertaken to investigate by transcranial Doppler sonography, positron emission tomography and perfusion MRI whether transcranial application of wide-field low-frequency ultrasound (300 kHz) improves cerebral hemodynamics in patients with cerebral small vessel disease.

Results—Showing no clear positive effect on cerebral hemodynamics in 4 patients and on cerebral perfusion (positron emission tomography) in 2 patients, the study has been terminated early because of a remarkable side effect in the first patient (a 62 year-old man) undergoing perfusion-MRI: detection of frontoparietal extravasation of Gadolinium contrast agent (applied during MRI perfusion imaging preinsonation) on MRI immediately postinsonation.

Conclusions—Abnormal permeability of the human blood-brain barrier can be induced by wide-field low-frequency insonation. The observed excessive bleeding rate with low-frequency sonothrombolysis might thus be attributable to primary blood-brain barrier disruption by ultrasound. (Stroke. 2006;37:1546-1548.)

Key Words: blood-brain barrier  ■  hemodynamic phenomena  ■  leukoaraiosis  ■  side effect  ■  ultrasound

A recent study showed a dramatic increase in cerebral hemorrhage with ultrasound-mediated recombinant tissue plasminogen activator (rtPA)-thrombolysis in humans using low-frequency ultrasound.1 We provide a possible explanation for this phenomenon by a side effect observed in a lately performed study using the similar ultrasound device.

In that study, we originally aimed to investigate whether transcranial application of low-frequency ultrasound improves cerebral perfusion and hemodynamics in chronically hypoperfused brains such as of patients with cerebral small vessel disease. The investigation was stimulated by animal data showing NO-mediated flow recovery in ischemic tissue by low-frequency ultrasound.2,3

Methods

Four men (aged 62 to 73 years) with severe cerebral small vessel disease were studied after approval by the local Ethics committee. Within different sessions, cerebral hemodynamics before and immediately after application of low-frequency ultrasound were to be assessed by transcranial Doppler (TCD) measurements in the middle cerebral artery (for details see Table),15O-H2O positron emission tomography (PET) studies, and MRI perfusion measurements (including application of Gadolinium-DTPA [Gd-DTPA] before and after insonation).

Low-frequency ultrasound was applied through the right temporal bone window using an array transducer fixed by a headband. The insonation system (NeuroFlow, Walnut Technologies, Inc) was the same used in the sonothrombolysis study.1 It consisted of an array transducer emitting low-frequency ultrasound (∼300 kHz) with 700 mW/cm² temporal-average-spatial peak intensity. The transducers were arranged to cover a large bilateral target region around the basal ganglia and periventricular white matter. The peak rarefational pressure was significantly below 1 atmosphere, thereby avoiding cavitation. The mechanical index was <0.5. The low intensity levels combined with the low frequency resulted in a thermal index soft tissue of <1.0 and a thermal index cranial of ∼5.0. The higher thermal index cranial was addressed through the use of heat sinking, which wicks heat away from the transducer array, and the use of a gel pad between the transducer and the skin. A thermal sensor was placed at skin level to control for excessive heating.

Results

The majority of cerebral hemodynamic parameters measured by TCD remained unchanged after 30 to 60 minutes of insonation in 4 patients (Table). A univocal decrease was only found for transfer function gain. PET studies performed in 2 patients before the early termination of the study showed no areas of better perfusion after the ultrasound intervention (Figure 1).

The first and only patient undergoing MRI perfusion imaging showed abnormalities on MRI immediately after 60 minutes of
insonation before reapplication of Gd-DTPA (Figure 2). These were at first sight indicative of subarachnoid hemorrhage. The patient was, however, completely asymptomatic, and cerebrospinal fluid taken shortly afterward revealed a high concentration of Gd-DTPA (18.9 mmol/L) and no erythrocytes. MRI follow-up at 2 weeks did not show any new lesions. On repetition of insonation in the same patient, the effect was not observed again, whereas perfusion analysis did not show any changes after insonation. For reasons of security it was decided to stop the study early, and no other patient underwent insonation with perfusion MRI or PET imaging.

Discussion

The majority of TCD parameters and PET results do not indicate an improvement of cerebral hemodynamics and perfusion by therapeutic ultrasound. Yet, this series was clearly too small to exclude any hemodynamic benefit, and the significant reduction of transfer function gain after insonation which points to improved damping of blood pressure oscillations in the cerebral circulation obviously merits further research.

The present study, however, has been terminated early because of a remarkable side effect: frontoparietal extravasation of contrast agent. This passage of 0.5 kDa Gd-DTPA

<table>
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<tr>
<th>Results of TCD Hemodynamics</th>
<th>Preinsonation n=8 Sides</th>
<th>Postinsonation n=8 Sides</th>
<th>P Values* Pre vs Post</th>
<th>Controls n=24 Sides</th>
<th>P Values** Patients vs Controls</th>
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<tr>
<td>Phase shift at 0.1 Hz (°)</td>
<td>81.6±28.2</td>
<td>87.7±40.5</td>
<td>ns</td>
<td>60.5±28.3</td>
<td>ns</td>
</tr>
<tr>
<td>Gain at 0.1 Hz (%/%)</td>
<td>1.15±0.17</td>
<td>0.93±0.10</td>
<td>P=0.025</td>
<td>0.97±0.17</td>
<td>Preinsonation: P=0.040</td>
</tr>
<tr>
<td>Autoregulatory index Dx</td>
<td>0.20±0.16</td>
<td>0.10±0.26</td>
<td>ns</td>
<td>0.04±0.13</td>
<td>Preinsonation: P=0.012</td>
</tr>
<tr>
<td>Pulsatility Index</td>
<td>0.69±0.07</td>
<td>0.68±0.09</td>
<td>ns</td>
<td>0.72±0.09</td>
<td>ns</td>
</tr>
<tr>
<td>Mean MCAFV (cm/s)</td>
<td>38.7±7.7</td>
<td>39.8±6.8</td>
<td>ns</td>
<td>51.3±8.4</td>
<td>Pre and Post: P&lt;0.001</td>
</tr>
<tr>
<td>CO₂ reactivity (%/mm Hg)</td>
<td>2.68±0.86</td>
<td>2.50±1.03</td>
<td>ns</td>
<td>3.12±1.19</td>
<td>ns</td>
</tr>
</tbody>
</table>

Standard TCD parameters were averaged over 10 minutes before and after insonation. MCAFV indicates middle cerebral artery flow velocity. Dynamic cerebral autoregulation was assessed from regular breathing at 0.1 Hz (phase/relative gain between blood pressure and MCAFV oscillations) or 10 minutes of spontaneous blood pressure oscillations (Dx) measured by noninvasive fingerplethysmography as described previously. CO₂ reactivity was assessed by inhalation of 7% CO₂ mixed with room air. Controls were free from cerebrovascular disease and sex/age-matched. *Wilcoxon test, **Mann–Whitney test.

Figure 1. PET studies. Patient 1 showed small hypoperfused areas (biparietal, left temporal, left frontal and in the left caudate nucleus). Visually and by statistical comparison, there were no differences in the perfusion before and after ultrasound exposure. In patient 2, the hypoperfusion was located in the right frontal area and in multiple areas of the left temporal lobe. There were also no changes after insonation.
indicates abnormal permeability of the blood-brain barrier (BBB) after insonation. Such a phenomenon has not been directly observed in humans so far. It indicates that the observed excessive bleeding rate with low-frequency sonothrombolysis comprising also atypical locations (like the intraventricular or subarachnoid space) might in fact be attributable to primary disruption of the BBB.1

In comparison to routine 2 MHz Doppler devices (as also used in another large sonothrombolysis study without hemorrhagic side-effects4), the applied device had a wider sonification field but comparable power. Transient disruption of the BBB by focused ultrasound has been described recently in animals when applied in the presence of preformed gas bubbles.5 Furthermore, ultrastructural animal studies have, among other mechanisms, proposed endothelial injury with high power, but partly opening of tight junctions already with low-power insonation.6

A clue to the mechanism of BBB disruption in our patient might be that it occurred distant to the target volume: standing waves near the bone at the border zone of the large insonation field may have occurred during continuous insonation and lead to local heating or mechanical effects disrupting the BBB. Small-field insonation should thus be preferred for sonothrombolysis in acute ischemic stroke.

Patients with cerebral small vessel disease may well already have an impaired BBB (vascular leakage),7 and this precondition might have contributed to an increased ultrasound vulnerability in our case and also in patients experiencing hemorrhagic complications after sonothrombolysis.

Though the transient BBB disruption could also bear a therapeutic potential by facilitating drug delivery of macromolecules, it has to be tentatively regarded as a negative effect of wide-field low-frequency ultrasound on the cerebral endothelium outweighing any potential benefit on thrombolysis or cerebral perfusion.

Acknowledgments

The ultrasound device used in this study was provided by Walnut Technologies Inc, Andover, Mass, USA.

References


Figure 2. Cranial MRI after insonation. Sixty-two year-old man with small-vessel disease indicated by periventricular white matter lesions. Upper line: The FLAIR MRI immediately after insonation revealed a hyperintensity (arrows) in the right frontal and parietal area indicating a subarachnoid hemorrhage or extravasation of contrast agent. Cranial CT performed shortly afterward was normal. Lower line: Control MRI 12 hours later showed normalization of the hyperintense areas. T2* imaging gave no indication for subarachnoid hemorrhage.
Blood-Brain Barrier Disruption By Low-Frequency Ultrasound
Matthias Reinhard, Andreas Hetzel, Sebastian Krüger, Stefan Kretzer, Jochen Talazko, Sargon Ziyeh, Johannes Weber and Thomas Els

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