Real-Time Cerebral Angiography: Sensitivity of a New Contrast-Specific Ultrasound Technique

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Real-time imaging of the intracranial arteries with sonography was first described by Bogdahn et al\(^1\) in the early nineties. The main difference compared with conventional transcranial Doppler (TCD) is the color-coded representation of arterial blood flow to allow the unequivocal identification of the circle of Willis within the anatomic grayscale (B-mode) image of the brain parenchyma. Further, with the use of Doppler mode, the blood flow can be analyzed semiquantitatively, as in conventional TCD, but with the added advantage of visual control by tracking the target vessel using the color flow map. However, the major limitation of all transcranial sonography techniques has been the massive acoustic signal intensity absorption while insonating through the intact skull. Furthermore, the phase aberration of the sonography beam, as a result of the convexity of the temporal bone, its surface roughness, and the multiple impedances (from outside to inside of the skull: pars compacta–pars spongiosa–pars compacta), limits sonography imaging of the adult brain by significantly reducing the signal-to-noise ratio (SNR).\(^2,3\)

One approach to improving the SNR while imaging intracranial vasculature with color or power Doppler uses ultrasound contrast agents (UCAs). Intravenously injected, transpulmonary stable UCAs are well tolerated and allow the detection of the circle of Willis, peripheral branches of the anterior, middle, and posterior cerebral arteries, and the vertebrobasilar arteries.\(^4,5\) The diagnostic benefits of contrast-enhanced transcranial sonography have been demonstrated in multiple studies.\(^6-9\) However, besides the potential diagnostic benefits contrast-enhanced sonography of the intracranial arteries is limited because of UCA specific artifacts that occur mainly in the early phase after IV bolus injection. Although color and power Doppler mode—the common sonography techniques for vascular imaging—are sensitive to detect flow, the spatial resolution of the received acoustic signal is relatively poor. Strong acoustic signals, encoded as color pixels on the screen, may appear “outside” the anatomic delineation of the vessel, especially in the early phase after UCA microbubble injection. The enhancement appears as an overamplification of the color or power Doppler signals on the screen of the ultrasound machine and is termed “blooming” (Fig 1).\(^10\) The experience and skills of the sonographer are needed to adjust the machine settings and to optimize the image to control the effect of blooming. To overcome UCA-specific artifacts such as blooming, IV infusion is an option. A UCA infusion provides a prolonged useful enhancement with fewer artifacts compared with a bolus injection.\(^11\) However, in clinical practice, such as in an acute stroke setting with time limitations, an infusion technique might not be appropriate.

The purpose of this study was to develop a contrast-specific imaging technique that is easy to use and that enables visualization of the intracranial vessels in an angiography-like display with high spatial resolution and fewer UCA specific artifacts. We sought to validate the accuracy of physicians with little training in transcranial sonography, in preparation for wider clinical utility of the technique.

**BACKGROUND AND PURPOSE:** To test a new contrast-specific sonography imaging method that offers visualization of the intracranial vasculature in a manner similar to that seen on angiography.

**MATERIALS AND METHODS:** Thirty patients (35 sonography studies total) were included in the study after they provided written informed consent. The patients were scanned through the temporal bone window from both sides after intravenous injection of an ultrasound contrast agent (UCA; perfl发展阶段e lipid microspheres [Imagent]). The goal was to visualize the intracranial arteries, including the middle (M1–M3), anterior (A1 and A2), and posterior (P1–P3) cerebral arteries, using an axial scanning plane. The studies were performed using a contrast-specific imaging mode, based on a phase inversion technique (transcranial ultrasound angiography [tUSA]). For sensitivity, the results were compared with x-ray angiography as the “gold standard.” For interobserver reliability, 24 of 35 sonography studies were evaluated by 2 physicians with little training in transcranial sonography and by a seasoned sonographer.

**RESULTS:** The sensitivity of tUSA ranged between 0.778 (95% confidence interval [CI] of 0.577–0.914) and 0.963 (95% CI of 0.810–0.999). The sensitivities were similar among physicians with little training in transcranial sonography and the seasoned sonographer, indicating high inter-rater reliability. Overall, tUSA provided high anatomic resolution and vascular delineation even of small vessels in the millimeter range. At peak intensity, no UCA-related artifacts were observed.

**CONCLUSION:** tUSA provides images of the intracranial arteries similar to those obtained at angiography with high anatomic resolution, reasonable sensitivity, and interobserver reliability.
could barely be seen. The transmit power ranged between 16% and at which known anatomic landmarks (ie, brain stem, third ventricle)
the bone window. The goal was to lower the acoustic power to a point
microbubble destruction as a result of high acoustic intensity imag-
band harmonic imaging to detect UCA microbubbles. To minimize
based on a phase-inversion technique using high-resolution wide-
visualization of the intracranial arteries with high spatial and tempo-
Transcranial Ultrasound Angiography (tUSA)
both devices are equipped with 2.5-MHz phased-array transducers
Sonography Devices and Study Design
Sonoline Elegra and a Sonoline Antares (Siemens, Erlangen, Ger-
study were available, 2 physicians with little sonography training
assessed. For the 24 of the 35 sonography studies for which videos of
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Table 1: Assessment of transcranial image quality

<table>
<thead>
<tr>
<th>Image quality</th>
<th>Contralateral Skull</th>
<th>3rd Ventricle</th>
<th>Brain stem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinically useful</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Insufficient</td>
<td>+/-</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

Note: Image quality was defined by the number of anatomic structures visualized precontrast.

cases of sufficient to optimal bone windows, the transmit frequency
was increased to a maximum of 2.0 MHz. This method of tUSA has
been described in detail recently.12

**UCA and UCA Administration**
We used AF0150 perflexane lipid microspheres (Imagent; IMCOR
Pharmaceutical, San Diego, Calif). Imagent was FDA approved for
endocardial border delineation, but as of June 2005, the agent is no
longer commercially available.

The agent was supplied as 200 mg of powder in a sealed vial. It was
reconstituted by adding 10 mL of water and gently mixing. The re-
sultant microbubble suspension encapsulated perfluoroethane vapor
and nitrogen in a thin phospholipid membrane and contained 5 ×
10⁶ microbubbles/mL with a mean diameter of 2–3 μm.

AF0150 was administered intravenously as a bolus injection into an
antecubital or forearm vein by using a 20G catheter, followed by a
5-mL saline flush. The UCA bolus dose was 0.5 mL if the intracranial
image quality was optimal, 1.0 mL if not optimal but clinically useful,
and 2.0 mL if the image quality was insufficient (Table 1). The UCA
dose injection was given twice, once for each hemisphere. Because the
maximum allowable dose for this agent is 0.2 mL/kg, an average 70-kg
adult can receive a total of 14 mL. If needed, up to 2 more UCA
injections were allowed in this study.

**Statistical Analysis**
The visualization (yes/no) of the cerebral artery segments (MCA: M1,
M2, M3, ACA: A1, A2, PCA: P1, P2, P3) was assessed by an experi-
enced sonographer who was blinded to the cerebral x-ray angiogra-
data. The presence of all cerebral artery segments was confirmed
on all x-ray angiograms. The sensitivity of visualizing the segments
was calculated using the x-ray angiogram as the “gold standard.” The
95% confidence intervals (CIs) were determined for each of these
values using an exact binomial distribution.13

In addition to sensitivity, the interobserver agreement was also
assessed. For the 24 of the 35 sonography studies for which videos of
the studies were available, 2 physicians with little sonography training
and an experienced sonographer evaluated the scans for bilateral
visualization. All 3 readers were blinded to the tUSA and x-ray data. The
sensitivity of visualization was calculated for all readers indepen-
dently. The McNemar χ² test for paired proportions was used to
 determine the difference in sensitivities between pairs of readers. The
Holm method was used to adjust for multiple comparisons.14

**Results**

**Overall Description**
Thirty patients (21 women, 9 men) were studied with tUSA. The age ranged between 18 and 81 years of age with a mean age
of 50 years. Three of 30 patients underwent 2 scans, and 1
patient underwent 3 scans. These 4 patients also underwent repeated neuroradiologic interventions, including preinter-
In 2 of 35 cases, a mild, transient event was described as a result of UCA administration; the volume of 2.8 mL of contrast agent per patient. No serious adverse effects were seen in the proximal vessel segments (M1, P1, and A1 segments), whereas the lowest values were reached in the peripheral vessel segments (M3, P3, and A2). Among the latter, the sensitivity for A2 was slightly lower compared with M3 and P3 segments.

### Sensitivity

On the right hemisphere, the sensitivity to visualize the aforementioned vessel segments ranged between 0.788 (A2 segment) and 0.970 (P1 and P2 segments). The corresponding 95% CIs were 0.798–0.993 (M1 and M2 segments) and 0.757–0.981 (M3 segment). For the left hemisphere, the results were comparable. The sensitivity ranged between 0.829 (A2 segment) and 0.971 (M1, P1, and P2 segments) with 95% CIs of 0.664–0.993 (A2 segment) and 0.851–0.999 (M1, P1, and P2 segments), respectively (Table 2). In both hemispheres, the highest sensitivities were seen in the proximal vessel segments (M1, P1, and A1 segments), whereas the lowest values were reached in the peripheral vessel segments (M3, P3, and A2). Among the latter, the sensitivity for A2 was slightly lower compared with M3 and P3 segments.

### Interobserver Reliability

Twenty-four of 35 tUSA studies were videotaped. These tapes were used for interobserver reliability and to assess the difference between inexperienced and experienced observers. The sensitivities for the visualization by the 2 physicians with little sonography training and an experienced sonographer are shown in Table 3. No statistically significant differences in sensitivities were detected between any pairs of the 3 readers, thus indicating a high interobserver agreement of visualization.

### Discussion

Contrast-specific brain imaging with sonography is currently a challenging research field. Unlike conventional cerebral x-ray angiography, because of arteriovenous malformation treatment, as well as postinterventional angiography. The individual study conditions, based on the quality of the temporal bone window, were as follows: 7 of 35, optimal; 21 of 35, clinically useful; and 7 of 35, insufficient study quality. Ten of the 35 scans were performed using a Sonoline Elegra sonography scanner and the remaining 25 with a Sonoline Antares system. The total UCA volume per single case ranged between 1.0 and 8.0 mL, with a mean volume of 2.8 mL of contrast agent per patient. No serious adverse events were described as a result of UCA administration; in 2 of 35 cases, a mild, transient (<60 seconds) metallic taste was reported immediately after UCA injection, and in 1 case of 35, the tUSA study failed because of IV catheter misplacement.

### Table 2: Transcranial ultrasound angiography sensitivity analysis in comparison to the "gold standard" cerebral x-ray angiography

<table>
<thead>
<tr>
<th>Vessel Segments</th>
<th>Sensitivity</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right MCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>0.96</td>
<td>0.798–0.993</td>
</tr>
<tr>
<td>M2</td>
<td>0.96</td>
<td>0.798–0.993</td>
</tr>
<tr>
<td>M3</td>
<td>0.92</td>
<td>0.757–0.981</td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>0.96</td>
<td>0.842–0.999</td>
</tr>
<tr>
<td>P2</td>
<td>0.96</td>
<td>0.842–0.999</td>
</tr>
<tr>
<td>P3</td>
<td>0.88</td>
<td>0.718–0.966</td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>0.96</td>
<td>0.757–0.981</td>
</tr>
<tr>
<td>A2</td>
<td>0.84</td>
<td>0.611–0.910</td>
</tr>
<tr>
<td>Left MCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>0.96</td>
<td>0.851–0.999</td>
</tr>
<tr>
<td>M2</td>
<td>0.96</td>
<td>0.808–0.993</td>
</tr>
<tr>
<td>M3</td>
<td>0.92</td>
<td>0.733–0.968</td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>0.96</td>
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</tr>
<tr>
<td>A1</td>
<td>0.96</td>
<td>0.808–0.993</td>
</tr>
<tr>
<td>A2</td>
<td>0.92</td>
<td>0.664–0.934</td>
</tr>
</tbody>
</table>

Note: MCA indicates middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery.
The significance of TCD in general is well displayed by its broad acceptance for various indications such as stroke,25–27 embolus detection,28–30 or vasospasm monitoring.31–33 The main benefits of TCD are well known: it is inexpensive, it can be used at the bedside, and it enables assessment of the intracranial flow dynamics in real-time. The main disadvantage of TCD is the dependency on the experience/skill of the operator, accompanied with the requirement for the sonographer to interpret flow spectra instead of direct visualization of intracranial vessels.

We believe that tUSA might reduce the dependency on the skill of the sonographer and therefore improve reliability. The results of the blinded reading of 2 physicians with little training in transcranial sonography and an experienced sonographer and the comparison of the 3 readings among each other show high interobserver agreement (Table 3). Although duplex sonography systems equipped with contrast-specific imaging techniques are decreasing in initial cost, they remain more expensive than TCD machines. However, the angiogram-like display of the circle of Willis and arterial branches and the ability to track vessels and acquire flow velocity data if desired should speed the training of inexperienced personnel, perhaps justifying the extra equipment costs.

**Conclusion**

tUSA using contrast-specific imaging techniques enables visualization of the major portion of the intracranial vasculature at the patient’s bedside. The clinical usefulness is the high sensitivity in visualizing the circle of Willis and the major branches of the anterior, middle, and posterior cerebral arteries without image artifacts and with little or no observer experience.

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