Intracranial Aneurysms Treated With Endovascular Coils
Detection of Recurrences Using Unenhanced and Contrast-Enhanced Transcranial Color-Coded Duplex Sonography

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Background and Purpose—Because neck recurrence after endovascular treatment of intracranial aneurysms (IAs) is not uncommon, surveillance to assess long-term stability of occlusion is clearly important. This study evaluated unenhanced and contrast-enhanced transcranial color-coded duplex sonography (TCCS) in detecting refilling of IAs treated with detachable coils.

Methods—Patients with coiled IAs were imaged before and after contrast enhancement. The results were compared with those of a surveillance digital subtraction angiogram (DSA). The operator was blinded to the results of the DSA. Aneurysms were classed as either occluded or with residual flow and quantified as minor, moderate, or extensive. There were 208 studies performed in 4 neurosurgical centers. Of those, 141 studies received ultrasonic contrast enhancement with Levovist, and 68 had an additional enhanced study with SonoVue.

Results—We excluded 44 studies. Of the 164 unenhanced studies, TCCS correctly identified 52 of 67 cases defined as completely occluded by DSA (sensitivity 78%; specificity 77%), 13 of 50 aneurysms with minor refilling (sensitivity 26%; specificity 88%), 15 of 27 aneurysms with moderate refilling (sensitivity 56%; specificity 95%), and 9 of 20 aneurysms with extensive refilling (sensitivity 45%; specificity 100%). TCCS correctly identified an additional 10 aneurysms with minor refilling after Levovist enhancement and 3 with SonoVue. Both SonoVue and Levovist enhancement identified an additional 1 aneurysm with moderate refilling and 3 with extensive refilling.

Conclusions—TCCS could be used to selectively monitor IAs, which would reduce the requirement for long-term invasive monitoring. The detection of neck refilling is improved with contrast enhancement.

Key Words: endovascular therapy • imaging techniques • intracranial aneurysm

Endovascular detachable coils are increasingly being used for the treatment of intracranial aneurysms (IAs). However, neck recurrence after endovascular treatment is not uncommon. Indeed, Raymond et al1 examined 501 aneurysms and reported a neck recurrence in 33% of endovascular-treated aneurysms attracting a 0.8% recurrence of bleed over 31 months, with major recurrences in ≈21% of cases. Similarly, Cognard et al2 reported a 14% recurrence in a study of 148 initially occluded aneurysms. Extended surveillance to assess the long-term stability of aneurysm occlusion is clearly important.

Digital subtraction angiography (DSA) remains the gold standard for aneurysm surveillance.3,4 The method is expensive, time consuming, and carries a risk of disability (transient neurological complication, 0.8%; permanent neurological complication, 0.07%).5 Previous studies have reported the limitations of MRI angiography (MRA) and computerized tomography angiography for visualizing IAs.6–8 With the advances in ultrasound and in contrast agents, transcranial color-coded duplex sonography (TCCS) is an alternative imaging modality. Whereas work has previously explored TCCS for the detection of IAs,9–12 the use of TCCS for the surveillance of coiled aneurysms remains largely unexplored.

The use of ultrasonic contrast agents in TCCS may be particularly relevant for intracranial vessels because of the low velocities encountered and limitations of the bone window. Indeed, previous work has shown that visualization of the vascular anatomy can be significantly improved by the use of contrast enhancement.13,14 Two contrast agents have been specifically developed for use in neurosonology: Levovist (Schering, AG), a suspension of air-filled microbubbles, and the more recent SonoVue (Bracco), a solution of sulfur hexafluoride microbubbles.

This study is a continuation of our previous published work, which explored the use of TCCS in a cohort of 48
patients in a single center. The aim of the current study was to evaluate the use of TCCS in a large multicenter cohort of patients and to assess the effects of 2 contrast agents in detecting aneurysm refilling after an endovascular procedure.

Methods
Ethical approval was sought and approved by the Cambridge Local Research Ethics Committee (LREC 00/436). Written informed consent was obtained from all of the subjects.

Patient Selection
Patients were recruited from 4 UK neurosurgical centers: Cambridge, Newcastle, Oxford, and Oldchurch. The same operator (who has 5 years of experience in transcranial imaging) performed all of the studies. Ultrasound examinations were performed within 2 months of a surveillance DSA. There was no preselection in patient recruitment. Where possible, all of the patients due to undergo a surveillance DSA were approached for recruitment and were only excluded because of either patient refusal (eg, unavailability or incapacity) or an inability to perform the TCCS within the time period. The operator was blinded to the results of the current DSA, although the aneurysm size, location, and morphology were known.

A total of 166 subjects were recruited, with a mean age of 52 years (range, 24 to 83 years), of which 14 subjects had multiple aneurysms. All of the subjects had an IA embolized with endovascular coils (162 with Guglielmi detachable coils, 11 with Micrus Anatomically Compliant Three-Dimensional microcoils, 3 with Matrix coils, 3 with Guglielmi detachable coils and Matrix coils, and 1 with Guglielmi detachable coils and Micrus Anatomically Compliant Three-Dimensional coils). Patient and aneurysm characteristics are seen in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total No. of Aneurysms</th>
<th>Unruptured/Ruptured</th>
<th>Men/Women</th>
<th>Mean Age</th>
<th>Coils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acomm</td>
<td>42</td>
<td>3/39</td>
<td>18/24</td>
<td>52</td>
<td>36 GDC, 4 Micrus, 1 Matrix, 1 Matrix/GDC</td>
</tr>
<tr>
<td>Pcomm</td>
<td>39</td>
<td>1/38</td>
<td>6/33</td>
<td>48</td>
<td>34 GDC, 4 Micrus, 1 Matrix/GDC</td>
</tr>
<tr>
<td>MCA</td>
<td>14</td>
<td>2/12</td>
<td>3/11</td>
<td>53</td>
<td>14 GDC</td>
</tr>
<tr>
<td>Bas tip</td>
<td>45</td>
<td>5/40</td>
<td>24/21</td>
<td>56</td>
<td>45 GDC</td>
</tr>
<tr>
<td>PCA</td>
<td>12</td>
<td>2/10</td>
<td>1/11</td>
<td>57</td>
<td>12 GDC</td>
</tr>
<tr>
<td>PCA</td>
<td>5</td>
<td>1/4</td>
<td>1/4</td>
<td>53</td>
<td>5 GDC</td>
</tr>
<tr>
<td>Ophth</td>
<td>5</td>
<td>3/2</td>
<td>1/4</td>
<td>46</td>
<td>4 GDC, 1 Micrus/GDC</td>
</tr>
<tr>
<td>Peri</td>
<td>2</td>
<td>0/2</td>
<td>2/0</td>
<td>54</td>
<td>2 GDC</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>17/147</td>
<td>56/108</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

Acomm indicates anterior communicating artery; Pcomm, posterior communicating artery; MCA, middle cerebral artery; Bas tip, basilar tip artery; PICA, posterior inferior cerebellar artery; PCA, posterior cerebral artery; Ophth, ophthalmic artery; Peri, pericallosal artery; GDC, Guglielmi detachable coils.

Figure 1. Arrows indicate neck refilling; arrowheads indicate coils. (A) DSA image of an occluded middle cerebral artery aneurysm; (B) DSA image of a basilar tip artery aneurysm with minor neck refilling; (C) DSA image of a basilar tip artery aneurysm with moderate neck refilling; (D) DSA image of a posterior communicating artery aneurysm with significant neck refilling.
Ultrasound Technique

TCCS was performed with a Toshiba Powervision SSA-380 ultrasound machine and a multifrequency transcranial probe (2 to 3 MHz). The technique has been described previously in detail.9,10,16,17 Both the temporal and occipital bone windows were used to insonate the intracranial vessels.5 The color-flow images were magnified for detailed evaluation of the aneurysms and the parent artery. Video images were recorded for review at a later date. Patients were imaged both before and after contrast enhancement. Two contrast agents were used and an infusion of Levovist (2.5 g; Schering AG) was administered at a concentration of 300 mg/mL and rate of 1 mL/min, by means of an antecubital venous injection.15 After a minimum period of 15 minutes for wash out, an IV bolus of 1 mL of SonoVue 25 mg (Bracco) was given.14 All of the DSA films were reviewed retrospectively in conjunction with a consultant neuroradiologist at each center. The aneurysms were classified as either completely occluded or with some residual flow (Figure 1). The degree of residual flow was subjectively classified as follows: (1) very minor neck remnant; (2) moderate residual flow requiring continuing or increased surveillance; and (3) extensive refilling requiring retreatment. Aneurysms with either moderate or extensive residual flow were considered to be clinically relevant.

The same ultrasonic criteria for assessing occlusion or residual flow were used and have been documented previously (Figure 2).15 Assessment was repeated in the event of contrast enhancement.

Statistical Analysis

Data were expressed as means. Logistic regression was used to compare the dependent variables and predictors.

Results

We obtained 208 studies from 166 patients (8 patients had 2 aneurysms, 3 patients had 3, and 28 patients had multiple studies). The mean time from embolization was 18 months (range, 3 months to 8 years).

We did not include 44 studies (21%) in the primary analysis (16 ophthalmic, 8 posterior inferior cerebellar, 8 pericallosal, 4 middle cerebral, 3 superior cerebellar, 3 posterior communicating, 1 anterior communicating, and 1 basilar tip artery aneurysm) because of a poor (n=34) or absent (n=10) acoustic window. The inability to image these aneurysms prevented any diagnosis using TCCS. Of the remaining 164 examinations, 141 had contrast enhancement with Levovist, and, of these, 68 had an additional enhanced study with SonoVue.

Detection Rates for Aneurysm Refilling

Table 2 shows the number of aneurysms correctly identified by TCCS with the degree of refilling before and after contrast enhancement. There was no difference in unenhanced TCCS detection of refilling with coil type ($P=0.13$), aneurysm rupture status ($P=0.33$), patient age ($P=0.98$), or gender ($P=0.89$). The same was true after Levovist ($P=0.05$, $P=0.49$, $P=0.47$, and $P=0.23$, respectively) and Sonovue enhancement ($P=0.06$, $P=0.30$, $P=80$, and $P=0.12$, respectively).

Unenhanced TCCS

Influence of Aneurysm Location

The influence of aneurysm position on correctly identified refilling status using TCCS is seen in Table 3. Refilling of aneurysms in the posterior cerebral and middle cerebral territories appeared to be more reliably identified ($P=0.01$ and 0.05, respectively).
Influence of Aneurysm Size
There was no significant difference in size between aneurysms that were included in the analysis and those that were not (mean size, 8 mm for both groups; \( P = 0.3 \)). Of the 164 studies, aneurysm size made no difference to the TCCS identification of refilling status (\( P = 0.49 \)).

Contrast-Enhanced TCCS
After contrast enhancement, the TCCD detection of refilling improved particularly in aneurysms with a minor neck remnant (Table 2). Levovist showed an increase in the detection of refilling status compared with the unenhanced images, particularly in the posterior communicating and basilar tip aneurysms, although neither reached significance (\( P = 0.46 \) and 0.08, respectively). No significant differences were seen with SonoVue enhancement.

Clinically Relevant Aneurysms
The ability of TCCS to correctly identify the refilling status was higher in clinically relevant aneurysms, both before and after contrast enhancement (Table 2).

All 208 Studies
If the 44 studies initially excluded from the analysis are assumed to have false-negative findings on TCCS, the sensitivity is reduced, but specificity is essentially unchanged. TCCS findings of occluded aneurysms based on DSA demonstrated a sensitivity of 50% and specificity of 79%. For aneurysms with neck recurrence, the sensitivity and specificity of TCCS for minor refilling was 15% and 90%, moderate refilling was 23% and 96%, and extensive refilling was 16% and 100%, respectively.

Discussion
DSA is currently used as the prime imaging modality for the surveillance of aneurysms postembolization. MRA has shown a high sensitivity to residual flow, although artifacts can lead to technical problems and inconclusive results.\(^{18–20}\) Both of these modalities are expensive and time consuming. Surveillance of aneurysm coils with ultrasound has the advantage of relative ease of use, accessibility in the outpatient environment, and low cost.

Despite the use of contrast agents for enhancement of the intracranial vasculature,\(^{14}\) we were still unable to provide an adequate examination in 21% of cases, in line with previous publications.\(^{21}\) Limitations of the acoustic window prohibited the imaging of the majority of aneurysms located outside of the Circle of Willis, particularly for the ophthalmic, posterior inferior cerebellar, and pericallosal territories. It could be argued that the cohort of 44 studies should be included in the primary analysis. However, because it was not possible to even image these aneurysms (a known limitation of ultrasound), we were not able to form any diagnosis on these studies, either positive or negative. In our experience, TCCS is not yet suitable as a screening method for surveillance in these locations, despite the introduction of contrast agents.

The percentage of aneurysms identified with the correct degree of refilling by TCCS was highest in the posterior and middle cerebral artery territories. The orientation of these aneurysms to the patent vessel may allow for better visual-

<table>
<thead>
<tr>
<th>Variable</th>
<th>DSA</th>
<th>Unenhanced TCCS</th>
<th>Unenhanced TCCS Clinically Relevant</th>
<th>TCCS With Levovist</th>
<th>TCCS With Levovist Clinically Relevant</th>
<th>TCCS With SonoVue</th>
<th>TCCS With SonoVue Clinically Relevant</th>
</tr>
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<tbody>
<tr>
<td>Acomm</td>
<td>42</td>
<td>26 (62%)</td>
<td>33 (79%)</td>
<td>29 (69%)</td>
<td>38 (93%)</td>
<td>39 (87%)</td>
<td>36 (86%)</td>
</tr>
<tr>
<td>Pcomm</td>
<td>39</td>
<td>20 (51%)</td>
<td>28 (72%)</td>
<td>24 (62%)</td>
<td>34 (87%)</td>
<td>21 (54%)</td>
<td>31 (79%)</td>
</tr>
<tr>
<td>MCA</td>
<td>14</td>
<td>11 (79%)</td>
<td>13 (93%)</td>
<td>11 (79%)</td>
<td>13 (93%)</td>
<td>11 (79%)</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Bas tip</td>
<td>45</td>
<td>21 (47%)</td>
<td>33 (73%)</td>
<td>27 (60%)</td>
<td>39 (87%)</td>
<td>22 (49%)</td>
<td>34 (76%)</td>
</tr>
<tr>
<td>PICA</td>
<td>11</td>
<td>8 (72%)</td>
<td>10 (90%)</td>
<td>8 (72%)</td>
<td>11 (100%)</td>
<td>8 (72%)</td>
<td>10 (90%)</td>
</tr>
<tr>
<td>PCA</td>
<td>6</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Ophth</td>
<td>5</td>
<td>2 (40%)</td>
<td>4 (80%)</td>
<td>3 (60%)</td>
<td>5 (100%)</td>
<td>2 (40%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Peri</td>
<td>2</td>
<td>0</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
<td>0</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

Acomm indicates anterior communicating artery; Pcomm, posterior communicating artery; MCA, middle cerebral artery; Bas tip, basilar tip artery; PICA, posterior inferior cerebellar artery; PCA, posterior cerebral artery; Ophth, ophthalmic artery; Peri, pericallosal artery.
ization of the neck and, thus, refilling status. However the numbers involved could have influenced the disparity in detection rates. Only 5 aneurysms were located on the posterior cerebral artery compared with 43 and 42 in the anterior communicating and posterior communicating sites, respectively.

Although contrast enhancement did not improve the detection of occluded aneurysms, it did increase the detection of residual flow. The flow within an embolized aneurysm is complex. Contrast enhancement, in conjunction with power Doppler, allows the imaging of low-flow signals and decreases the dependence of the angle of insonation. This can assist in the detection of low-velocity flow around and within the coil nidus. Indeed, we found the greatest increase in detection with contrast was in aneurysms with minor refilling. Interestingly, in 1 case we noted low flow within the aneurysm, which was not seen on the DSA. This could reflect early refilling or persistent low-velocity flow within the coils, the clinical relevance of which is uncertain.

Ultrasonic contrast agents are suspensions of microbubbles typically 2 to 7 μm in diameter; their aim is to increase the strength of the back-scattered beam without causing excessive “blooming,” a source of shadowing and misinterpretation. We used contrast enhancement where possible in all of the studies, regardless of the initial signal strength. An increase in false positives with contrast suggests that some studies may have over estimated the flow in the aneurysm neck as a factor of excess back scattering, implying that contrast should be used selectively, where the quality of the unenhanced vasculature is suboptimal.

Levodist administered by infusion extends the signal enhancement to 10 minutes. Therefore, we allowed a minimum of 15 minutes after the end of each infusion before giving a bolus of SonoVue, so as to avoid contamination between contrast agents. In addition, we assessed the Doppler signal for residual microbubbles before administering SonoVue to reduce this risk. The operator was not blinded to the type of contrast examination, so direct comparison between contrast performances may not be entirely valid. However, we found that both contrast agents improved detection. Because the method of contrast introductions were different (Levodist was administered as an infusion, whereas SonoVue was administered as a bolus, because, at the time of recruitment, SonoVue was not available for intravenous infusion) and the population numbers were not the same, direct comparison between the 2 contrast agents was not possible.

We considered aneurysms with moderate or extensive refilling to be clinically relevant, requiring increased surveillance or retreatment. All of the studies were retrospectively reviewed with the consultant neuroradiologist who had performed the DSA. However, there was inevitably a subjective view at each center as to the degree of refilling requiring retreatment. In our previous study, TCCS identified all of the aneurysms classed as having clinically relevant residual flow. The lower detection rate in this study may be attributable in part to the variations between the centers or differences in coiling methodology. The DSA assessments at each center could be seen as a strength of the study (as a multicenter assessment of the technique); however, it could also be viewed as a limitation. The use of standardization in neuroradiological assessment would have reduced a potential subjective bias in the classifications.

One operator performed all of the ultrasound examinations. A criticism of TCCS imaging of the intracranial vasculature is the degree of operator expertise required. Although it is accepted that TCCS requires experience, particularly when using contrast agents, White et al conducted a study comparing the performance of experienced and inexperienced operators. They found very little difference in the detection of aneurysms between the 2 groups (sensitivity 5%, specificity 2%).

The limited spatial resolution of TCCS prevents the detection of reliable and reproducible intracranial abnormalities smaller than 4 mm. However, we did not find any significant difference with respect to size in the detection of refilling by TCCS nor in the aneurysms included/excluded. The mean aneurysm size was 8 mm, slightly smaller than in our earlier study. Many aneurysms that are treated by endovascular means are of the order of 3 to 5 mm, and accurate imaging of these small aneurysms is important for ongoing surveillance. However, our findings did suggest that aneurysm size is not a major factor in the TCCS detection of refilling of coiled aneurysms. Indeed, it could be argued that once an aneurysm has been treated with coils, the initial size of the aneurysm is not relevant in an ultrasound surveillance examination.

In this study, the sensitivity of TCCS to identify aneurysm neck recurrence ranged from 32% to 94% with a specificity of 77% to 100%. These values are exclusive of the 44 patients whose TCCS images were of inadequate image quality because of a poor acoustic window. In comparison, the figures for MRA are of the order of 83% to 97% sensitivity with 100% specificity and that of plain radiographs are 78% and 96%, respectively. It is, therefore, clear that TCCS cannot be the primary choice for surveillance. However, the definite advantages of ultrasound (ease of use, cost, and availability) suggest that selective use of this technique could be part of the surveillance protocol, especially where MRA is either unavailable or there is a patient intolerance to the procedure. We feel that a TCCS examination could be obtained at the time of the initial surveillance DSA. If the findings are comparable, additional follow-up could then be undertaken by TCCS with the addition of alternative imaging methods only if there is a change in aneurysm status.

Conclusion
We suggest that ultrasound could be considered as a selective method to monitor coiled IAs and assist in the long-term surveillance. This may be particularly so for aneurysms located in the Circle of Willis, specifically the posterior cerebral and middle cerebral arteries, where the aneurysm has been clearly imaged and the findings confirmed with an initial surveillance DSA. The long-term outcome of aneurysms with a very minor neck recurrence is unknown. Surveillance of these aneurysms and those more difficult to assess is still required.
Acknowledgments

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References


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