Transcranial targeting low frequency ultrasound thrombolysis system: evaluation of the probe fixation devices for blood flow monitoring

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Abstract

Background: We developed the transcranial targeting low frequency ultrasound thrombolysis system (TCTLoFUT) which will be used for an acute ischemic stroke (AIS). TCT-LoFUT can emit the T beam (500 kHz continuous waveform, 0.72 W/cm²) for thrombolysis to a target thrombus with the D beam (2 MHz pulsed waveform, 0.72 W/cm²) for diagnostic TC-CFI. We report the in vitro thrombolytic efficacy by TCTLoFUT and estimate the blood flow monitoring in human with a newly developed head-fixture for TCT-LoFUT using a same aspect of commercial probe.

Methods: A) Sonothrombolysis experiment: The 1.25 ml of blood was extracted by the healthy volunteer. The blood in a syringe for 40 min and created a fresh thrombus with a centrifuge (4500 rotation / 5 min). The alteplase concentration in a syringe solution was made to be 358 IU/ml. The intermittent T/D beams were applied under the 60 min of protocol which was described in our studies. The rt-PA independent group (rt-PA, n=39) and the rt-PA + TCT-LoFUT group (rt-PA+US, n=13) were compared. The sound intensity in a syringe was 0.05 W /cm². B) Blood-flow monitoring evaluation: We evaluated the blood flow monitoring by middle cerebral artery (MCA) detection in 10 healthy volunteers for 30 min. We used the 2.5 MHz TCCFI probe with the fixture which was developed for same aspect of the TCT-LoFUT.

Results: A) Sonothrombolysis experiment: The recanalization rate of 60 min after were 64.1% in rt-PA group and 92.3% in rt-PA+US group. Average recanalization time was shortened from 27.2 min in rt-PA group to 21.4 min in rt-PA+US group (p < 0.01). B) Blood-flow monitoring evaluation: The MCA could be detected using the fixture for TCT-LoFUT.

Conclusions: TCT-LoFUT has a function of the blood-flow monitoring simultaneously with a thrombolysis accelerating effect which will be used for AIS patients.

Keywords: Sonothrombolysis, Low frequency, Color flow imaging, Fixation.
Introduction

We have developed a transcranial targeting low-frequency ultrasound thrombolysis system (TCT-LoFUT) with recombinant tissue plasminogen activator (rt-PA) for use in the treatment of acute ischemic stroke (AIS) [1]. The TCT-LoFUT probe has a laminated ultrasound (US) phased array structure in a single sector scan probe that can emit 490-kHz continuous waveform (CW) US as a T-beam for mid-frequency sonothrombolysis to a target thrombus under navigation by 2.5-MHz pulsed waveform US as a D-beam for diagnostic transcranial color flow imaging (TC-CFI) (Figure 1). We have already confirmed the efficacy of sonothrombolysis using this method in monkey and human clot in vitro studies with rt-PA [2, 3] and the biological safety of the approach in macaque monkey brain [4].

To achieve stable sonothrombolysis with blood flow monitoring, an adequate probe fixation device is indispensable. Since 2000, several authors have reported various head frame probe holders for transcranial Doppler (TCD) [5, 6, 7], transcranial color duplex sonography (TCDS) [8] and TC-CFI [9] for stable blood flow monitoring. TC-CFI is more useful for intracranial vessel orientation with navigation under color flow imaging, particularly in Japanese populations, which show a low detection rate for intracranial vessels. We also developed a head frame holder for the TCT-LoFUT probe at first, but motion of the examinee’s head disturbed stable blood flow monitoring [10]. We manufactured and developed two types of the probe-fixation device, and evaluated middle cerebral artery (MCA) or posterior cerebral artery (PCA) blood flow monitoring with the same aspect and property with a commercial probe, and identified problems with clinical use.

Methods

Subjects

Basic freehand evaluation with a commercial sector scan probe was performed for 16 healthy volunteers (12 males, 4 females; mean age ± standard deviation, 26.3±7.0 years) without hypertension, diabetes mellitus, and dyslipidemia, history of cerebrovascular disease or smoking. MCA blood flow monitoring in AIS was evaluated in 10 patients (9 males, 1 female; mean age, 64.4±15.6 years) with the P-type device. Moreover, using the P-type device, another 7 AIS patients with suspected paradoxical emboli in the MCA or PCA (all male; mean age, 53.9±11.5 years) were examined for right-left shunt (RLS) using the Valsalva maneuver.

After P-type device evaluation, blood flow monitoring in AIS was evaluated in another 6 patients (all male; mean age, 57.2±14.4 years) with the developed BJ-type device. All examinations were performed at the Jikei University Hospital. This study was conducted under the consent and approval of the Ethics Committee of the Jikei University School of Medicine. All volunteers and patients provided informed consent prior to enrollment.

Study methodology

We evaluated the function of the probe-fixation devices using the same aspect of a commercial 2.5-MHz sector scan probe (S50) with EUB 8500 (Hitachi Medical Corporation, Tokyo, Japan) via the temporal window (TW), as the TCT-LoFUT is not currently approved for clinical use. Figure 2 compares the color flow imaging (CFI) function between the commercial and TCT-LoFUT probes. These pictures suggest that the potentiality of CFI function in the TCT-LoFUT probe is equivalent to a commercial probe.

![Figure 1. Structure of the TCT-LoFUT probe, which has a laminated array structure in the same manner as a commercial probe. (a) Commercial probe (Hitachi S50); (b) TCT-LoFUT probe.](image-url)
Figure 2. Comparison of color flow imaging (CFI) with 2.5 MHz pulsed waveform between the commercial and TCT-LoFUT probes. (a, b) Flow phantom CFI with a commercial probe (a) and TCT-LoFUT probe (b); (c, d) TC-CFI of the MCA in a 30-year-old female volunteer using a commercial probe (c) and the TCT-LoFUT probe (d).

All blood flow detection was performed by two expert examiners, a neurologist and a sonographer with certification from the Japan Academy of Neurosonology. We first evaluated 16 volunteers to detect bilateral MCA blood flow images via the TW by free hand. Next, we evaluated the high-intensity transient signal (HITS)/micro-embolic signal (MES) at MCA in 9 patients with AIS for 30 min of TC-CFI using P-type fixation via the TW. We also evaluated RLS in 7 patients with suspected paradoxical emboli using P-type device. The manufactured P-type fixation keeps the TCT-LoFUT probe in a holder arm and the opposite side arm pad attached to the head for fixation (Figure 3a). The side of each arm is interchangeable. The evaluation points were fixation time, re-fixation and pain from fixation. Finally, we evaluated HITS/MES at the MCA in 6 patients with AIS for 30 min of TC-CFI using BJ-type fixation via the TW. Figure 3b shows BJ-type fixation, which was developed from a commercial surgical fixture arm (PointsetterTM; Mitaka-Kohki, Tokyo, Japan). This method uses hydraulic and pneumatics pressure in a ball joint arm that can tightly fix and easily release the probe attachment to the TW with a single-touch button. The degree of freedom is changed more easily than with the P-type for movement of the probe holder arm. The probe holder arm can extend to

Figure 3. Photograph of the probe fixation devices. (a) Pillow type; (b) Ball joint type.
other types of probe use. The evaluation points were TW permeability, fixation time, number of times for re-fixation, number of times for sample volume re-set up, pain by fixation and body motion.

Results

MCA detection in volunteers
MCA detection ratio on 32 sides using the free hand technique was 90.6%. Detection on both sides was impossible in a 53-year-old woman. A 29-year-old man reported poor health during an inspection, and only one side was detectable.

HITS/MES detection with the P-type fixation device
HITS/MES could be detected in only 1 of 10 cases (10.0%). Two patients needed over 5 min for fixation time and re-fixation. No patients complained of fixation pain (Table 1).

RLS detection with the P-type fixation device
RLS was detected in 2 of 7 cases (28.6%). One patient needed over 5 min for fixation time and re-fixation. No patients complained of fixation pain (Table 2).

HITS/MES detection with the BJ-type fixation device
No patient could be detected any HITS/MES. TW permeability was slightly poor in 4 patients. Fixation time was within 5 min in all patients (mean, 155±121 s), faster than for the P-type device. No patients complained of pain, but 4 patients could not keep quiet for 30 min and we had to fix the head and set the sample volume again (Table 3).

Discussion

The development of US probe fixation devices is one of the most important issues for accurate transcranial ultrasound. In 1993, Michel et al. reported a multipurpose probe fixation device for newborns via the anterior fontanel [11]. The following year, Woodtli et al. (1994) reported a head and TCD probe-holding technique for monitoring the vertebrobasilar circulation in adult [12]. Three years later, two authors reported probe fixation devices for MCA blood flow monitoring [13, 14].

Since 2000, several authors reported head frame holders for probe fixation. Alexandrov et al. (2000) in a pioneer sonothrombolysis clinical study with rt-PA, reported recanalization blood flow monitoring in MCA using the fixation head frame for power M-mode Doppler (PMD) [5]. Hong et al. (2010) followed MCA and basilar artery vasomotor reactivity tests using a modified head frame for PMD [7]. Mackinnon et al. (2003) reported a unique trial [6]. They developed a long-term ambulatory monitoring head frame with a battery-powered Doppler unit that can servocontrol a 2-MHz transducer probe and store Doppler signal on flash disc drives.

On the other hand, the proposed criteria for judging probe-holding systems include ease of application, stability during patient movement, cost, comfort and durability, and compatibility with multiple probes [8, 14]. We have developed two types of fixation device aimed at recanalization blood flow monitoring in sonothrombolysis. No fixation pain was seen with either device. We could detect RLS in 2 of 7 patients using a P-type device with the Valsalva maneuver. The BJ-type device made up for the shorter set-up time by offering higher functionality.

However, both devices showed some problems in clinical use. First, detection rates of HITS/MES were low with both devices. Next, Mackinnon et al. (2004) pointed out that the embolus detection is a very time-consuming factor even by experts [6]. Nevertheless, skill is required to understand the structure of device and to fix the head, particularly with the P-type device. Third, although ease of application and compatibility with multiple probes is suitable with the BJ-type device, development of a probe fixation device from commercial surgical arms is very expensive. Fourth, the BJ-type device must be connected to

Table 1. Blood flow monitoring with the P type fixation device.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Target Vessel</th>
<th>HITS/MES</th>
<th>Fixation time</th>
<th>Re-fixation</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>F</td>
<td>lt MCA</td>
<td>(-)</td>
<td>&gt;5 min</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>rt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>M</td>
<td>lt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>M</td>
<td>rt MCA(M2)</td>
<td>(-)</td>
<td>&gt;5 min</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>M</td>
<td>lt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>lt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>M</td>
<td>rt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>M</td>
<td>rt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>M</td>
<td>lt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>lt MCA</td>
<td>(+)</td>
<td>&gt;5 min</td>
<td>(+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

HITS = High intensity transient signal; MES = Micro embolic signal; MCA = Middle cerebral artery
Table 2. Blood flow monitoring in RLS suspected patient with the P type fixation device.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Target Vessel</th>
<th>RLS</th>
<th>Fixation time</th>
<th>Re-fixation</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>M</td>
<td>bilateral MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>M</td>
<td>rt MCA</td>
<td>(+)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>lt MCA and PCA</td>
<td>(-)</td>
<td>&gt;5 min</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>rt MCA</td>
<td>(+)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>bilateral MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>M</td>
<td>rt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>rt MCA</td>
<td>(-)</td>
<td>&lt;5 min</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

RLS = Right left shunt; MCA = Middle cerebral artery; PCA = Posterior cerebral artery

Table 3. MCA blood flow monitoring with the BJ type fixation device.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age(y)</th>
<th>Sex</th>
<th>HITS/MES</th>
<th>TW permeability</th>
<th>TW fixation Time (sec)</th>
<th>Re-fixation time</th>
<th>Re-set SV (time)</th>
<th>Body Motion</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>(-)</td>
<td>F</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>rare</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>(-)</td>
<td>F</td>
<td>105</td>
<td>0</td>
<td>1</td>
<td>often</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>M</td>
<td>(-)</td>
<td>SP</td>
<td>300</td>
<td>1</td>
<td>0</td>
<td>intense</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>(-)</td>
<td>SP</td>
<td>240</td>
<td>0</td>
<td>1</td>
<td>often</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>(-)</td>
<td>SP</td>
<td>240</td>
<td>3</td>
<td>5</td>
<td>intense</td>
<td>(-)</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>(-)</td>
<td>SP</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>rare</td>
<td>(-)</td>
</tr>
</tbody>
</table>

MCA = Middle cerebral artery; TW = Temporal window; F = fair; SP = Slightly poor; SV = Sample volume

Shiogai et al. (2012) recently reported brain tissue perfusion monitoring with TCDS via both the TW and fonsal window using the Sonopod head frame holder, which is compatible with multiple probes [8]. They also pointed out shifts in the fixed probe due to patient movements during monitoring, but re-adjustment of the probe in the Sonopod was easy. Their setup time for monitoring was usually around 5-10 min. Watt et al. (2012) published preliminary MCA blood flow monitoring data using a probe fixation device in 9 controls and 2 patients with unilateral AIS. Their device was designed to stabilize two 2-MHz TCD probes to sample bilateral MCA blood flow, but the aspects and properties of their fixation device was not described [15]. Ohyama et al. (2013) are currently developing a fixation device to be compatible with multiple probes [9]. That fixation device is a helmet-type device that can achieve long-term blood flow monitoring with stable probe fixation.

To use the TCT-LoFUT at the bedside, improvements in probe-fixation devices must be achieved not only for blood flow monitoring, but also for performing effective thrombolysis acceleration with rt-PA by 490-kHz CW-US with a newly developed safe method of transcranial ultrasonication [16].

Conclusions

The probe-fixation device for TCT-LoFUT must be further improved to actualize the stable ultrasound supply for sonothrombolysis with monitoring by TC-CFI function.
A probe-fixation device must be designed to minimize changes in the three-dimensional parameters specifying the stability of probe fixation.

Abbreviations

AIS: Acute ischemic stroke; CFI: Color flow imaging; CW: Continuous waveform; HITS: High-intensity transient signa; MES: Micro-embolic signal; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; PMD: Power M-mode Doppler; RLS: Right-left shunt; rt-PA: recombinant tissue plasminogen activator; TCD: Transcranial Doppler; TCDS: Transcranial color duplex sonography; TC-CFI: Transcranial color flow imaging; TCT-LoFUT: Transcranial targeting low-frequency ultrasound thrombolysis system; TW: Temporal window; US: Ultrasound

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Competing interests

The authors declare no conflict of interests associated with this manuscript.

References