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Clinical Outcomes of Intraoperative Contrast-Enhanced Ultrasound Compared with Intraoperative Neurophysiological Monitoring During Circumferential Decompression for Myelopathy Associated with Thoracic-Ossification of the Posterior Longitudinal Ligament

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Background: Circumferential decompression (CD) is an essential treatment option for myelopathy associated with thoracic-ossification of the posterior longitudinal ligament (T-OPLL) when laminectomy cannot achieve sufficient ventral decompression. Although intraoperative neurophysiological monitoring (IONM) is widely used, the operation has a relatively high risk. This study is the first to describe the use of contrast-enhanced ultrasound (CEUS) to evaluate the spinal cord blood flow (SCBF) during thoracic spine surgery in humans. The objective of this study was to compare clinical outcomes between intraoperative CEUS and IONM during CD.

Material/Methods: Sixty-eight T-OPLL patients who received CD from 2007 to 2014 were reviewed. All patients underwent IONM. CEUS was used on the following 2 occasions on 18 patients to evaluate SCBF: the first measurement was performed after laminectomy and the second after ventral decompression. Outcomes were evaluated by the Hirabayashi recovery rate (HRR).

Results: The overall HRR of all patients was 56.7%. Regarding CEUS, the HRR was 20.0% in Group A (SCBF decreased) and 63.6% in Group B (SCBF increased), indicating a significantly poorer neurological outcome in Group A ($P < 0.01$). Regarding IONM, the HRR did not significantly differ between Groups C (no meaningful change in potential), D (potential changed up to alert criteria), and E (potential improved).

Conclusions: IONM is relatively effective in detecting impending spinal cord dysfunction. Intraoperative CEUS is a safe and reliable method for assessing SCBF changes, which may be used as a supplement to IONM, thus reducing the incidence of false-negative results.

MeSH Keywords: **Intraoperative Neurophysiological Monitoring • Microbubbles • Ossification of Posterior Longitudinal Ligament • Spinal Cord Ischemia • Thoracic Vertebrae • Ultrasonography**

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Background

The incidence of thoracic-ossification of the posterior longitudinal ligament (T-OPLL) is relatively low, although the disease progression in individual cases is rapid; thus, any delay in treatment may result in severe damage to the spinal cord. Conservative treatment for myelopathy due to T-OPLL is mostly ineffective; therefore, surgical treatment is the only effective option [1]. To date, there is no consensus regarding the optimal surgical technique for T-OPLL. Among the available surgical techniques, posterior decompression is the most basic. Intraoperative ultrasonography (IOUS) is conducted to examine any residual ventral spinal compression after posterior decompression is completed. Additional ventral decompression of the spine is needed when laminectomy does not achieve sufficient ventral decompression [2–4].

However, even if combined with multimodal intraoperative neurophysiological monitoring (IONM), circumferential decompression (CD) remains technically challenging, with a relatively high risk of postoperative neurological deterioration because of 3 reasons. First, the blood supply to the spinal cord has a substantial effect on spinal cord functions [5,6]. The thoracic spinal cord, especially the mid- and lower thoracic spinal cord, is the watershed of the spinal blood supply, making it vulnerable to ischemic damage that is sometimes very hard to detect [7]. Second, because the field of vision is poor and the working space is restricted for ventral decompression after laminectomy, the difficult operation may cause a new-onset spinal cord injury (SCI) to an already debilitated spinal cord. Third, IONM has some limitations and has a risk of false-negative outcomes [8,9]. Hence, an assessment of intraoperative changes of the spinal cord blood flow (SCBF) may help to detect impending spinal cord dysfunction and to predict neurological outcomes.

Many clinical studies have confirmed that microbubble contrast-enhanced ultrasound (CEUS) correlates well with blood perfusion in various organs, especially for end-capillary blood, and can provide clear images. The microbubbles are safe and have been clinically applied in humans [10–12]. There are also literature reports describing the use of this method to evaluate blood perfusion of spinal cord in animal models [5]. Therefore, we used intraoperative microbubble CEUS to observe SCBF changes during CD in this study, which is the first to describe the use of this CEUS-based imaging modality to evaluate spinal cord perfusion during thoracic spine surgery in humans. In this study, we enrolled 68 patients with myelopathy associated with T-OPLL who underwent CD. All patients underwent IONM, and intraoperative microbubble CEUS was used in 18 of these patients. The aim of this study was to compare clinical outcomes between CEUS and IONM during CD.

Material and Methods

Patients

This study was approved by the Ethics Committee of our hospital and was conducted according to the principles of the Declaration of Helsinki. All patients provided informed consent to undergo the procedures. The study included 68 patients with T-OPLL who received CD at our institution between April 2007 and April 2014. Myelopathy caused by T-OPLL was diagnosed after thorough history taking, neurological examinations, plain radiography, computed tomography, and magnetic resonance imaging (MRI). Radiographic examinations demonstrated multilevel T-OPLL in all patients.

Surgical procedures

The decompression levels were determined preoperatively according to preoperative symptoms, physical examination, and radiologic findings. It reported that the ossification-kyphosis angle in the sagittal view of MRI has a potential for indicating the effectiveness of posterior decompression. When the ossification-kyphosis angle was $>20^\circ$ [13], decompression strategy (laminectomy or CD) was selected based on IOUS findings. The presence of echo-free space between the OPLL and ventral side of the spinal cord indicated sufficient decompression by laminectomy. If there was no echo-free space and the ventral spinal cord was still impinged by OPLL, additional ventral decompression was needed.

On the basis of the IOUS findings, all patients underwent CD, and the CD level of each patient is summarized in Table 1. With the patient in prone position, a posterior midline incision was made to expose the posterior elements. Patients received posterior decompression with removal of ligamentum flavum ossification after the insertion of pedicle screws and fixation using a temporary rod. After posterior decompression, CEUS was performed for the first time. Then, the residual facets and pedicles were removed with a high-speed drill and curette. The posterior third of the vertebral cancellous bone was removed along the pedicles at a 60° angle to make a “cave” at the levels requiring ventral decompression. Finally, the “cave wall” (the posterior wall of the vertebral body and OPLL) was pressed to collapse, and OPLL was resected to achieve complete ventral decompression. After ventral decompression, the second measurement using CEUS was performed. Subsequently, the pedicle screws were connected, followed by bone grafting and fusion of the remaining facet joints and transverse processes [14].

Intraoperative microbubble CEUS

SonoVue (Bracco, Italy) was used as a contrast agent. Currently, the only contraindication of food and drug administration to

Table 1. Summary of operations of Groups A and B.

Case number	Sex	Age (years)	Diagnosis/levels	CD level	PD level	Ossification-kyphosis angle (°)	Blood loss (mL)	Operative time (min)
1	M	38	OPLL/T9-11; OLF/T3-5 T11-12	T9-11	T9-11	31.2	1000	120
2	M	41	OPLL/T3-5; OLF/T3-6	T3-5	T3-7	24.5	3600	425
3	F	48	OPLL/C7-T5; OLF/T5-8	T2-3	T1-5	22.1	1500	270
4	F	43	OPLL/C7-T6	T1-3	C6-T6	21.4	3500	350
5	F	51	OPLL/C7-T3	T1-2	C7-T3	26.6	1000	300
6	F	62	OPLL/T4-7; OLF/T9-12	T5-6	T4-8	25.5	2500	235
7	M	69	OPLL/T1-2	T1-2	T1-3	29.2	900	230
8	F	59	OPLL/T4-6; OLF/T3-4	T5-7	T3-7	24.1	2000	275
9	M	62	OPLL/T4-8	T5-6	T4-8	21.8	2000	210
10	M	52	OPLL/T10-11; OLF/T9-11	T10-11	T9-12	23.9	3000	250
11	M	47	OPLL/T9-11; OLF/T2-12	T6-8	T5-9	20.6	1800	290
12	F	51	OPLL/T2-4; OLF/T3-5	T2-3	T1-5	34.1	2000	380
13	M	46	OPLL/T9-10; OLF/T9-10	T9-10	T9-11	20.9	1700	275
14	F	42	OPLL/T1-7	T2-3	T1-7	23.4	200	110
15	F	64	OPLL/T6-8; OLF/T2-12	T6-7	T5-10	22.1	3500	300
16	F	44	OPLL/T5-10	T8-10	T5-12	21.2	2000	330
17	F	42	OPLL/T4-6; OL/2-8	T5-6	T2-8	21.4	2000	285
18	M	54	OPLL/T8-11	T8-9	T7-11	39.1	3900	325

M – male; F – female; OPLL – ossification of the posterior longitudinal ligament; OLF – ossification of ligament flavum; CD – circumferential decompression; PD – laminectomy.

intravenous microbubble contrast agents is a history of allergy to the agent, which was also used as our exclusion criterion. Given that microbubble contrast agents are not metabolized in the liver or renally excreted, there are no additional risks of adverse effects in patients with hepatic or renal insufficiency [12]. SonoVue consists of phospholipid-stabilized microbubbles, which are filled with sulfur hexafluoride (SF₆). Upon the addition of saline, a suspension of microbubbles (mean diameter, 2.5 μm; 2×10⁸ microbubbles/mL) stabilized by a lipid monolayer was produced. Given that microbubbles are smaller than red blood cells, they can enter the microcirculation.

Moreover, the microbubbles can be detected based on the pronounced difference in echogenicity between SF₆ and surrounding soft tissue. When injected intravenously, microbubbles pass through the anterior and posterior spinal arteries and reach the microcirculation of the spinal cord. Tissue perfusion can be evaluated in real time on the CEUS image, where microvessels in the regions of interest (ROIs) appear as white regions with a

stronger intensity (Figure 1). The exact number of microbubbles in the ROI was difficult to estimate; thus, the concentration of contrast agent was instead assessed in terms of light intensity. Each frame of the video recorded during surgery was converted to a greyscale digital image and stored with a resolution of 8 bits per sampled pixel, which allowed 256 different intensities to be distinguished, from 0 (black) to 255 (white). For each patient, we measured the average gray value at different times to build a time-intensity curve.

Previous studies demonstrated that the maximum blood concentration of SF₆ microbubbles was reached quickly and then rapidly declined, and the route of SF₆ elimination was via the lungs in the exhaled air. We found that each curve had 3 phases. The first phase of the curve is flat, which corresponds to the period before the microbubbles arrive; in the second phase, the intensity of the reflected signal increases quickly and corresponds to the infusion; and in the third phase, as the microbubbles are eliminated, and once the injection stops,

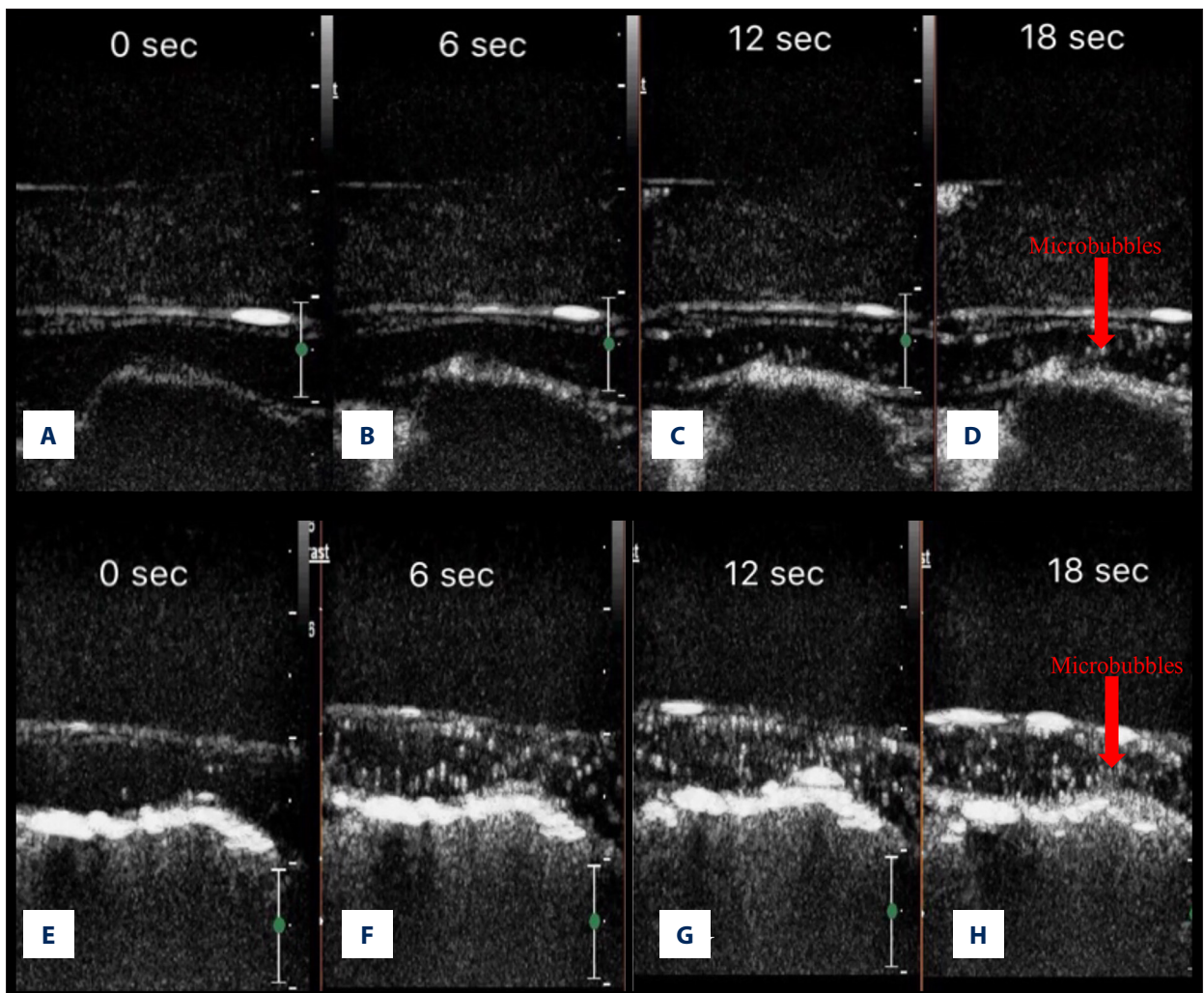


Figure 1. (A–H) Time evolution of blood perfusion evaluated using microbubble contrast-enhanced ultrasound. From left to right: Images taken at 0, 6, 12, and 18 seconds after the appearance of microbubbles. Tissue perfusion can be evaluated in real time on the contrast-enhanced ultrasound image, where microvessels in the regions of interest (ROIs) appear as white regions with a stronger intensity. The upper and lower images were taken before and after decompression, respectively.

the concentration of microbubbles begins to decrease, which leads to a progressive decrease of the curve. Thus, it is possible to assess the SCBF in a given ROI according to the intensity of the reflected signal. We used the software Origin (version 9.0; OriginLab Inc, Northampton, MA, USA) to generate a time-intensity curve and calculate the area under this curve. This value was correlated with the blood flow in the ROI, which reflected the total volume of the spinal cord blood perfusion at the decompression position (Figure 2) [6].

An ultrasonic apparatus (Aloka Co., Japan) with a 2–5-MHz probe for morphology and a 3–9-MHz probe for observing blood flow were used. The probe was manually positioned to obtain an oblique longitudinal sagittal slice. In the appropriate position, the spinal cord was precisely horizontal on the image, and the central canal of the spinal cord was visible along

the full segment of the spinal cord. Each patient underwent the following 2 CEUSs during the operation: the first was after posterior laminectomy and the second after complete ventral decompression. Two milliliters of SonoVue were injected into the median vein of the elbow. The SCBF of the CD segment was observed along the long axis using the immersion method, and a video recording of microbubble perfusion over the course of 1 minute after injection was stored [15].

Ultrasound is relatively subjective and depends on the experience of the operator. To reduce error, the operation is completed by senior ultrasonologists according to the standard process. The probe was manually positioned to obtain an oblique longitudinal sagittal slice. The appropriate position was determined by the pedicle screw that was inserted. Then, the spinal cord was precisely horizontal on the image, and the central

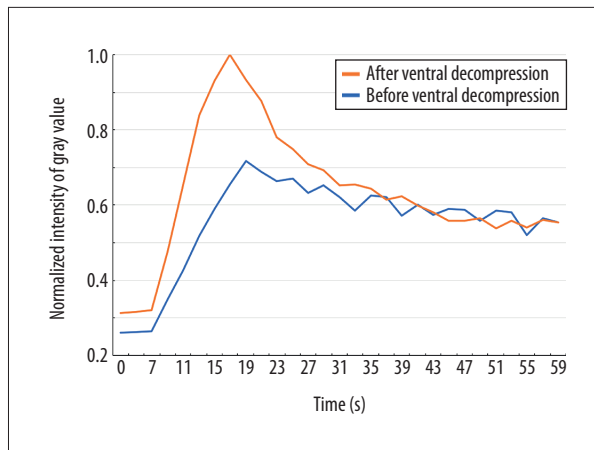


Figure 2. The time-intensity curves of patient no. 18. Each curve has 3 phases. The first phase of the curve is flat, which corresponds to the period before the microbubbles arrive; in the second phase, the intensity of the reflected signal increases quickly and corresponds to the infusion; and in the third phase, as the microbubbles are eliminated, once the injection stops, the concentration of microbubbles begin to decrease, which leads to a progressive decrease of the curve. The area under this curve correlates with blood flow in the regions of interest, which reflects the total volume of spinal cord blood perfusion at the decompression position. The area is significantly larger after ventral decompression than before ventral decompression, which reflects increased spinal cord blood flow after ventral decompression.

canal of the spinal cord was visible along the full segment of the spinal cord.

Regarding CEUS, the cases were divided into the following 2 groups: in Group A, SCBF decreased after ventral decompression, and in Group B, SCBF improved after ventral decompression.

IONM

Spinal cord activity was recorded under multimodal IONM during the whole operation, including somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs). The alert criteria used for SSEPs were a 50% loss of amplitude and/or 10% increase in latency in the cortical and sub-cortical recording channels once the technical factors such as hypotension, hypothermia, hypovolemia, nerve compression from limb positioning, electrode displacement, and excessive depth of anesthesia were eliminated. For MEPs, the alert criterion used was a loss of or a significant reduction in amplitude (>80% loss) in previously stable lower-limb MEP in one or more muscles once technical and anesthetic factors had been ruled out. We regarded the amplitude of MEP decreases sharply by >50% in

a short period as a warning line. In addition, the mean arterial pressure (MAP) was maintained at >85 mmHg during the entire operation. In the event of a neuromonitoring change detected by the monitoring team, interventions were made by surgeons in response to the alerts.

True-positive is a monitoring change indicative of an “evolving” injury as indicated by one of the following conditions: (a) despite all interventional measures, an alert was irreversible and a new postoperative neurologic deterioration occurred; and (b) an alert that responded favorably to the intervention (recovered to or close to the stable baseline value) and had no new postoperative deficit.

Regarding IONM, the patients were divided into the following 3 groups: Group C had no meaningful change in potential, Group D had potential changed up to the alert criteria, and Group E had potential improved.

Neurological evaluation

Neurological outcomes were assessed using the modified Japanese Orthopedic Association (JOA) score for thoracic myelopathy, with a total score of 11 points [16]. The JOA classification was conducted by professional surgeons with >12 years of experience who were not involved in the surgical procedures. The Hirabayashi recovery rate (HRR) was calculated using the following formula, with 75–100%, 50–74%, 49–25%, and <25% indicating excellent recovery, good recovery, fair recovery, and unchanged or deteriorated, respectively: $HRR = (JOA \text{ score at follow-up} - \text{preoperative JOA score}) / (11 - \text{preoperative JOA score}) \times 100\%$ [17].

Statistical methods

IBM SPSS (version 20; SPSS Inc, Chicago, IL, USA) was used for the statistical analyses. General data were described as mean±standard deviation. Statistical comparisons were performed using the Mann-Whitney U-test and Kruskal-Wallis H-test. A P value of <0.01 was considered statistically significant.

Results

Demographics and surgical characteristics

Demographics and surgical characteristics are summarized in Tables 1 and 2. The age, sex, intraoperative blood loss, levels of CD, levels of laminectomy (PD), and operative time are summarized in Table 2. There was no significant difference among the different groups.

Table 2. Summary of operations of patients of different groups.

	Regarding CEUS			Regarding IONM				Patients with CEUS (n=18)	Patients with INOM but without CEUS (n=50)	P value
	Group A (n=4)	Group B (n=14)	P value	Group C (n=44)	Group D (n=16)	Group E (n=8)	P value			
Age (years)	49.0	51.4	0.721	52.4	53.6	53.0	0.566	50.8	53.8	0.205
Sex (M: F)	1: 3	7: 7	0.382	16: 28	3: 13	3: 5	0.402	8: 10	14: 36	0.201
Levels of CD	2.5	2.3	0.574	2.5	2.0	2.0	0.572	2.3	2.0	0.157
Levels of PD	6.0	4.9	0.382	4.8	4.5	4.4	0.803	5.2	4.5	0.252
Blood loss (mL)	2625.0	1971.4	0.233	2038.8	2118.8	2175.0	0.629	275.6	269.0	0.329
Operative time (min)	290.0	271.4	0.798	265.8	300.4	238.8	0.017	2116.7	2053.4	0.522
Presence of CSF	1	5	0.593	10	6	3	0.426	6	13	0.552

CEUS – contrast-enhanced ultrasound; IONM – intraoperative neurophysiological monitoring; M – male; F – female; CD – circumferential decompression; PD – laminectomy; CSF – cerebrospinal fluid leakage.

CEUS data

The effect of the operation on SCBF was evaluated in terms of the changes in perfusion volume. Perfusion was assessed using CEUS before and after ventral decompression. After ventral decompression, SCBF increased in 14 patients but decreased in 4 (Table 3, Figure 2). Only one IONM alarm was reported in the 4 decreased patients.

IONM data

Combined SEP and MEP was monitored in 68 operations. Alerts occurred in 16 patients. Forty-four patients showed no meaningful change in potential, and 8 showed a significant improvement in potential. There were 12 true-positives, 2 false-negatives, 50 true-negatives, and 4 false-positives; thus, sensitivity was 85.7% and specificity was 92.6%. One of the 2 false-negative cases underwent CEUS, which showed that SCBF decreased.

IONM alerts occurred in 16 cases: 4 of them were false-positive, 7 of them were not relieved after intervention with new motor deficits, and 5 of them were relieved after intervention without new motor deficits (rescue case). Alerts occurred in 7 cases during anterior decompression of spinal cord, 2 of which were rescued after intervention; 2 cases occurred during laminectomy, one of which was rescued after intervention; 2 cases occurred before suture, one of which was rescued after intervention; 1 case occurred during the exposure of the posterior elements, the intervention was effective.

Neurological outcome

The patients were followed up for a period of 22–56 months (36.6±10.2 months). The average JOA score of all patients improved from 4.3±1.90 points before surgery to 8.1±2.38 points at the final follow-up (P<0.01). The overall HRR was 56.7%. No aggravation of spinal dysfunction was noted at the final follow-up.

The HRR was 20.0% in Group A (SCBF decreased) and 63.6% in Group B (SCBF increased). The Mann-Whitney U-test revealed that the HRR was significantly higher in Group B than in Group A (P<0.01) (Table 4). The HRR was 54.4% in Group C (no meaningful change in potential), 54.7% in Group D (potential changed up to alert criteria), and 70.8% in Group E (potential improved). The Kruskal-Wallis H-test revealed that the HRR was not significantly different among the 3 groups (Table 4). In Group A, 2 patients received aggressive neuroprotective therapies after the operation because of postoperative neurological deterioration, whereas the other 2 patients did not. The mean HRR of the former 2 patients and the latter 2 patients were 36.4% and 6.7%, respectively.

Other complications

Cerebrospinal fluid leakage (CSF) was the most common postoperative complication (n=19), including 3 cases of severe leakage requiring cerebrospinal membrane repair. The presence of CSF is summarized in Table 2, and there was no significant difference among the different groups. Postoperative pleural effusion was noted in 2 cases. There were no other complications, including death, bilateral lower-limb paralysis, and wound infection.

Table 3. Intraoperative monitoring results and patients' outcomes of Groups A and B.

Case number	CEUS code	SSEP code	MEP code	Complications	Preoperative JOA score	Final JOA score
1	0	2	2	CSF	4	10
2	0	2	2	CSF	5	11
3	0	2	2	CSF	1	3
4	1	2	2	PND	5	7
5	0	2	2	No	4	8
6	0	1	2	No	5	9
7	0	2	2	CSF	1	8
8	1	2	2	CSF	2	2
9	0	0	2	CSF	3	9
10	1	2	2	No	5	6
11	0	2	2	No	4	9
12	0	1	1	CSF	7	9
13	0	2	0	CSF	6	9
14	0	2	2	No	4	8
15	0	1	2	CSF	6	9
16	0	2	2	CSF	6	10
17	1	1	2	PND, PE	6	8
18	0	2	2	No	5	9

CEUS (contrast-enhanced ultrasound) code: 0=spinal cord blood flow increased; 1=spinal cord blood flow decreased; SSEP (somatosensory-evoked potentials) and MEP (motor-evoked potentials) code: 0=potential improved, 1=potential changed up to alert criteria, 2=no meaningful change in potential; JOA score – modified Japanese Orthopedic Association score; PE – pleural effusion; PND – postoperative neurological deterioration.

Table 4. Neurological outcomes of different groups.

	Regarding CEUS			Regarding IONM			
	Group A (n=4)	Group B (n=14)	P value	Group C (n=44)	Group D (n=16)	Group E (n=8)	P value
Preoperative JOA score	4.5	4.4	0.798	4.2	4.6	4.5	0.768
Final JOA score	5.8	8.6	0.008	7.9	8.1	9.1	0.428
HRR (%)	20.0	63.6	0.003	54.4	54.7	70.8	0.322

CEUS – contrast-enhanced ultrasound; IONM – intraoperative neurophysiological monitoring; JOA score – modified Japanese Orthopedic Association score; HRR – Hirabayashi recovery rate=(JOA score at follow-up–preoperative JOA score)/(1-preoperative JOA score)×100%.

Discussion

IONM outcomes

In this study, combined SEP and MEP were monitored in 68 operations. The sensitivity was 85.7% and the specificity was

92.6%. The results suggested that multimodal IONM is relatively effective in detecting impending spinal cord dysfunction.

However, there were 2 patients with false-negatives that underwent postoperative neurological deterioration. The reasons may be that as follows: First, SSEP, which cannot directly monitor

the motor conduction pathway, is a method used to monitor the sensory pathway [18], and SSEP is not sensitive to spinal cord ischemia [19]. Second, MEP cannot detect segmental spinal cord injury when the muscles recorded are different from the innervated muscles arising from the spinal anterior horn cell exposed to the risk of injury [20]. In our study, one of the false-negative cases was suspected segmental spinal cord injury because motor deficits were observed in a limited number of muscles and were mostly transient, and all paralysis recovered within 2 months after surgery. Third, there is no perfect alert criterion [9,21]. When the alarm criteria are set relatively high, although specificity is increased, some SCI will be neglected, and, at present, there is no alarm standard based on the characteristics of thoracic surgery. Although false-negative IONM is rare, the outcome is disastrous for patients. One of the 2 false-negatives underwent CEUS, which showed that SCBF decreased. This indicated that CEUS can be used as a supplement to IONM, thus reducing the incidence of false-negative cases.

D-wave monitoring is considered the criterion standard to judge the integrity of the corticospinal tract; it has high specificity and is not easily affected by anesthesia factors. The combined recording of D-waves and muscle MEPs reduces the number of false-positive cases [22]. However, it is relatively difficult to record D-wave below the middle of the thoracic spinal cord, and it needs the help of the surgeon to place it in the corresponding spinal cord, which increases the risk of iatrogenic injury and limits the application of D-wave in thoracic surgery. In addition, the specificity in this study is 92.6%, which is acceptable. Thus, at present, we do not use D-wave monitoring.

Most alerts (75.0%) occurred during decompression for OPLL. For these patients, interventions after the monitoring alarm were mostly ineffective. However, the rest of the alerts occurred during non-decompression progress and intervention after the monitoring alarm were mostly effective for these patients. Although the intervention effect in the decompression process of thoracic surgery is generally poor, appropriate intervention immediately after the IONM alert may prevent neurological deterioration.

The HRR of Groups C and D were 54.4% and 54.7%, respectively, and there was no significant difference between the 2 groups. The reason may be that the IONM cannot directly reflect the changes of the anatomic structure of the spine, and the alert criterion uses neurological deterioration immediately after the operation as the observation index. This makes the relationship between alert and prognosis of neurological function unclear. Although the HRR did not significantly differ between Groups C, D, and E, Group E showed greater improvements (70.8%) than Groups C and D. Due to the small sample size of our study, it may have been underpowered; thus, studies with larger sample sizes are needed.

CEUS outcomes

After ventral decompression, SCBF increased in 14 patients with high HRR compared to patients with low HRR. Spinal cord neurons are very sensitive to ischemic hypoxia, with short-term ischemia and hypoxia potentially causing nerve damage [23]. Chronic direct compression of the spinal cord by T-OPLL and spinal cord ischemia are important causes of nerve damage. It has been suggested that the blood supply to the spinal cord has a substantial effect on spinal cord functions [5,6]. Therefore, we recommend complete resection of the OPLL compressing the spinal cord, which would provide the maximum degree of decompression of the spinal cord and, presumably, the best recovery of neurological function.

However, in this study, we found that 4 patients with decreased SCBF after decompression showed worse HRR than those with increased SCBF. Although many scholars found that ischemia-reperfusion injury, a type of dysfunction, can occur upon reperfusion following a certain period of ischemia, they believe that delayed SCI after spinal surgery is also associated with reperfusion of blood flow after spinal cord compression [24]. It is suggested that the reduction of SCBF after decompression is more likely to lead to delayed SCI after surgery in this study, where there is some divergence regarding the underlying principles of ischemia-reperfusion injury. Moreover, many studies have found that the spinal cord can have improved tolerance of ischemia-reperfusion injury after ischemic preconditioning [25]. Donato et al. found that remote ischemic preconditioning can be performed in a clinical setting through intermittent ischemia of an upper or lower limb, and clinical trials using this procedure in the context of predictable ischemia-reperfusion have produced promising results [26]. Hu et al. suggested that neurologic recovery in the remote ischemic preconditioning group was better than that in the non-remote ischemic preconditioning group [27]. OPLL-induced stenosis of the thoracic spinal canal, which eventually results in spinal cord ischemia, is a chronic process similar to the process of ischemic preconditioning and therefore may confer the blood vessels in the vicinity of the affected segment a certain degree of tolerance or adaptability to the ischemic state, which decreases the risk of reperfusion injury. Thus, further exacerbation of ischemia may play a more important role in postoperative neurological deterioration.

Reason of decreased SCBF

Even if sufficient ventral decompression was achieved, SCBF was decreased in 4 patients, perhaps due to the following reasons. The thoracic spinal cord, especially the mid- and lower thoracic spinal cord, is the watershed of the spinal blood supply, making it vulnerable to ischemic damage [7]. Moreover, the field of vision is poor, and the working space is restricted

for ventral decompression after laminectomy. The complex operative procedure of ventral decompression may result in a new-onset SCI to an already debilitated spinal cord, which is a major reason for the decrease in SCBF after decompression. A new SCI occurs in the following 2 phases: the primary injury happens unexpectedly and is followed by a secondary injury, in which ischemia plays a crucial role [5,6]. After SCI, bleeding occurs in the spinal cord parenchyma and increases significantly throughout the first hour, which results in decreased SCBF.

Perspectives of intraoperative CEUS

The importance of saving nervous system function cannot be overemphasized and time is of importance. It is reported that a therapeutic window in secondary injury mechanisms could be manipulated by appropriate exogenous interventions. At the “rescue-able” time window, neuroprotective therapies are aimed at reducing the secondary injury pathology and should accordingly improve the neurological outcomes [28,29]. The presence of a new postoperative neurological deterioration after anesthesia recovery indicates a new meaningful intraoperative SCI (MISCI), and neuroprotective therapies should be used as soon as possible. IONM is effective in detecting impending spinal cord dysfunction in CD, but it seldom accurately detects an MISCI. Neuroprotective therapies, such as methylprednisolone pulse therapy and neurotrophic drugs, have a strict indication because they have adverse effects and increase financial burden. Thus, failure to detect MISCI early and accurately results in missing optimal treatment opportunities.

CEUS can detect the decrease in SCBF, indicating a new MISCI if the effect of whole-body perfusion could be excluded. It was reported that maintaining the MAP at >85 mmHg is beneficial for ensuring a stable SCBF [30,31]. To exclude the effect of whole-body perfusion, we maintained intraoperative MAP at >85 mmHg by ensuring adequate monitoring and interventions, such as increase in fluid infusion and vasopressor support during critical periods of easy bleeding. We found that patients in Group A (SCBF decreased) had a decrease in SCBF, suggesting that the new MISCI might have occurred. Thus, CEUS may help to seize the opportunity of “rescue-able” time windows. In Group A, 2 patients received aggressive neuroprotective therapies after the operation because of postoperative neurological deterioration. The other 2 patients did not have the alert criteria according to IONM or had immediate postoperative neurological deterioration, but their long-term prognosis was not good. The former had a better HRR than the latter, suggesting that early diagnosis and therapy may help to improve the neurological outcomes of patients in whom MISCI might have occurred.

Limitations of this study

This study has several limitations. First, the rarity of T-OPLL may have restricted the sample size, which limits the potential validity of the results. This is the first study that utilized this CEUS-based imaging modality to evaluate spinal cord perfusion during thoracic spine surgery in humans. Given the uniqueness of the innovative method used in the study and the potential implications for making challenging spinal cord surgery safer, additional multicenter prospective studies are needed to clarify the optimal treatment for patients with T-OPLL. Second, there is a supposed residual SCBF cut-off value that is unable to modify potentials, thereby resulting in false-negative cases. It is similar to setting the alert criteria for IONM. Thus, studies with a larger sample size and meta analyses are needed. Although the criterion used in this study was just a decrease in SCBF for CEUS, establishing a reliable warning criterion of CEUS by performing additional prospective studies is necessary to obtain reliable sensitivity and specificity values. Third, CEUS requires adequate operator expertise, and thus is highly operator dependent.

Conclusions

CD is a necessary and effective treatment option for myelopathy associated with T-OPLL, although it remains technically challenging, with a relatively high risk of postoperative neurological deterioration. IONM is relatively effective in detecting impending spinal cord dysfunction. Intraoperative CEUS is a safe and reliable method for assessing SCBF changes, and may be used as a supplement to IONM, thus reducing the incidence of false-negative cases. Moreover, intraoperative CEUS may help to predict the neurological outcomes and seize the opportunity of “rescue-able” time windows to provide timely neuroprotective therapies.

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Conflict of interest

None.

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