Neurocrit Care (2019) 31:297–303
https://doi.org/10.1007/s12028-019-00695-7

NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Multimodal Regional Brain Monitoring of Tissue Ischemia in Severe Cerebral Venous Sinus Thrombosis

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Abstract

Background: Comatose critically ill patients with severe diffuse cerebral venous thrombosis (CVT) are at high risk of secondary hypoxic/ischemic insults, which may considerably worsen neurological recovery. Multimodal brain monitoring (MBM) may therefore improve patient care in this setting, yet no data are available in the literature.

Methods: We report two patients with coma following severe diffuse CVT who underwent emergent invasive MBM with intracranial pressure (ICP), brain tissue oximetry ($PbtO_2$), and cerebral microdialysis (CMD). Therapy of CVT consisted of intravenous unfractionated heparin (UFH), followed by endovascular mechanical thrombectomy (EMT). EMT efficacy was assessed continuously at the bedside using MBM.

Results: Despite effective therapeutic UFH (aPTT two times baseline levels in the two subjects), average CMD levels of lactate and glucose in the 6 h prior to EMT displayed evidence of regional brain ischemia. The EMT procedure was associated with a rapid (within 6 h) improvement in both CMD lactate (6.42 ± 0.61 4.89 ± 0.55 mmol/L, $p = 0.02$) and glucose (0.49 ± 0.17 vs. 0.96 ± 0.32 mmol/L, $p = 0.0005$). EMT was also associated with a significant increase in $PbtO_2$ (22.9 ± 7.5 vs. 30.1 ± 3.6 mmHg, $p = 0.0003$) and a decrease in CMD glutamate (12.69 ± 1.06 vs. 5.73 ± 1.76 µmol/L, $p = 0.017$) and intracranial pressure (ICP) (13 ± 4 vs. 11 ± 4 mmHg ($p = 004$). Patients did not require surgical decompression, regained consciousness, and were discharged from the hospital with a good neurological outcome (modified Rankin score 3 and 4).

Conclusions: This study illustrates the potential utility of continuous bedside MBM in patients with coma after severe brain injury, irrespective of the primary acute cerebral condition. Despite adequate ICP and $PbtO_2$ control, the presence of CMD signs of regional brain cell ischemia triggered emergent EMT to treat CVT, which was associated with a significant and clinically relevant improvement of intracerebral physiology.

Keywords: Cerebral venous sinus thrombosis, Multimodal brain monitoring, Endovascular mechanical thrombectomy

Introduction

Severe diffuse cerebral venous thrombosis (CVT) represents a rare and challenging cause of stroke [1–3]. The pathophysiology of CVT implies (1) a rise in cerebral venous pressure that is secondary to diffuse cerebral sinus and cortical thrombosis, followed by blood–brain barrier disruption, vasogenic edema, and elevated intracranial pressure (ICP); (2) reduced cerebrospinal fluid (CSF) absorption from the subarachnoid spaces via the arachnoid villi structures because of venous thrombosis and subsequent intracranial hypertension [1, 2, 4]. These CVT mechanisms translate into clinical signs of intracranial hypertension [1, 2, 4] that may become refractory and eventually require surgical decompression or, more recently, endovascular therapy by way of in situ

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mechanical thrombectomy [3, 5–10]. Severe CVT is an infrequent cause of intensive care unit (ICU) admission and intracranial hypertension, and available data on brain monitoring are very limited. Few reports have shown the potential utility of noninvasive assessment of brain perfusion with transcranial Doppler in CVT patients [11, 12]. Invasive ICP monitoring is rarely used [13], and we only found one military case report describing the use of ICP and brain oximetry ($PbtO_2$) to guide decompressive craniectomy in the setting of severe CVT [14]. Based on recent consensus recommendations for the use of multimodal brain monitoring (MBM) in neurocritical care patients, MBM is increasingly utilized, especially in patients with severe acute post-traumatic and ischemic/hemorrhagic cerebral conditions [15]. Broadening the use of MBM to patients with other forms of severe brain injuries, in particularly those at high risk of elevated ICP and impaired cerebral perfusion such as severe CVT, may seem reasonable, but still deserves further exploration. We describe for the first time the two illustrative cases where MBM, combining ICP, $PbtO_2$, and cerebral microdialysis (CMD) monitoring, was used in patients with severe diffuse CVT. We hereby demonstrate the value of MBM both in triggering escalation therapy (endovascular in situ mechanical thrombectomy) and for the timely bedside follow-up of treatment efficacy. This case report study supports the concept of individualized neurocritical care targeted to improve intracerebral physiology under the guidance of invasive MBM.

Patients

Patient # 1

Patient # 1 was a 65-year-old male subject, known for chronic alcohol abuse, who was admitted to our academic hospital due to generalized seizures and coma (Glasgow Coma Score 5) requiring intubation and mechanical ventilation. The admission computed tomography (CT) scan revealed a right temporoparietal hematoma with moderate (< 5 mm) mass effect. CT imaging was compatible with a CVT, confirmed by magnetic resonance imaging angiography that demonstrated a diffuse thrombosis of the superior sagittal sinus, sinus rectus, bilateral transverse and sigmoid sinuses.

Patient # 2

Patient # 2 was a 48-year-old woman who was admitted to our academic hospital following sudden loss of consciousness and coma (Glasgow Coma Scale 7). On admission, the CT scan showed a right frontoparietal hematoma with a moderate (< 5 mm) mass effect (similar to patient # 1). The CT angiography revealed a diffuse CVT of the superior sagittal, right transverse and sigmoid sinuses.

Intracranial Monitoring

Both patients underwent emergent placement in the operating room of parenchymal MBM, via a triple-lumen bolt (right frontal lobe, visually normal brain around the intracerebral hematoma, ipsilateral to the lesion), including an ICP (Codman, Raynham, MA, USA) and $PbtO_2$ (Licox, Integra Neurosciences, Plainsboro, NJ, USA) probes in combination with a CMD catheter (CMA 70, CMA Microdialysis AB, Solna, Sweden). Probes were placed in the right prefrontal region, in an area of "visually normal" brain, away from cerebral hematoma (Fig. 1). In both patients, anticoagulation was started immediately after CVT diagnosis, without bolus; therefore, therapeutic levels were not reached before MBM placement. There was no bleeding complication after MBM placement.

CVT Therapy

CVT therapy consisted of therapeutic anticoagulation with unfractionated heparin, started immediately following the diagnosis, aiming at an activated partial thromboplastin time of ≈ 2 times the baseline value. Because of persistent CMD signs of regional ischemia (see below, *individualized MBM-guided management of severe CVT*), escalation therapy was decided with the use of endovascular mechanical thrombectomy (EMT), allowing multiple-thrombus extraction (Fig. 2) and successful CVT recanalization (Fig. 3). Subsequent control CT scans showed an attenuation of peri-hematoma edema.

Individualized MBM-Guided Management of Severe CVT

Escalation therapy with the use of EMT was triggered in both patients by CMD evidence of regional brain ischemia (elevated CMD lactate, in concomitance with low CMD glucose; Fig. 4), despite adequate control of ICP and $PbtO_2$.

Compared to baseline (average 6-h prior to EMT therapy), EMT (average 6-h post-intervention) was associated with a significant improvement in CMD levels of lactate (6.42 ± 0.61 vs. 4.89 ± 0.55 mmol/L; $p = 0.02$), glucose (0.49 ± 0.17 vs. 0.96 ± 0.32 mmol/L; $p = 0.0005$), and glutamate (12.69 ± 1.06 vs. 5.73 ± 1.76 µmol/L; $p = 0.017$; Fig. 4). EMT was also associated with a significant decrease in ICP (13 ± 4 vs. 11 ± 4 mmHg; $p = 0.004$) and an increase in $PbtO_2$ (22.9 ± 7.5 vs. 30.1 ± 3.6 mmHg, $p = 0.0003$).

Patient Outcome

Patient #1 had prolonged ICU stay, due to persisting coma, complicated by ventilator-induced pneumonia, eventually requiring a tracheotomy tube and neurological rehabilitation subsequently. He was discharged at day 28

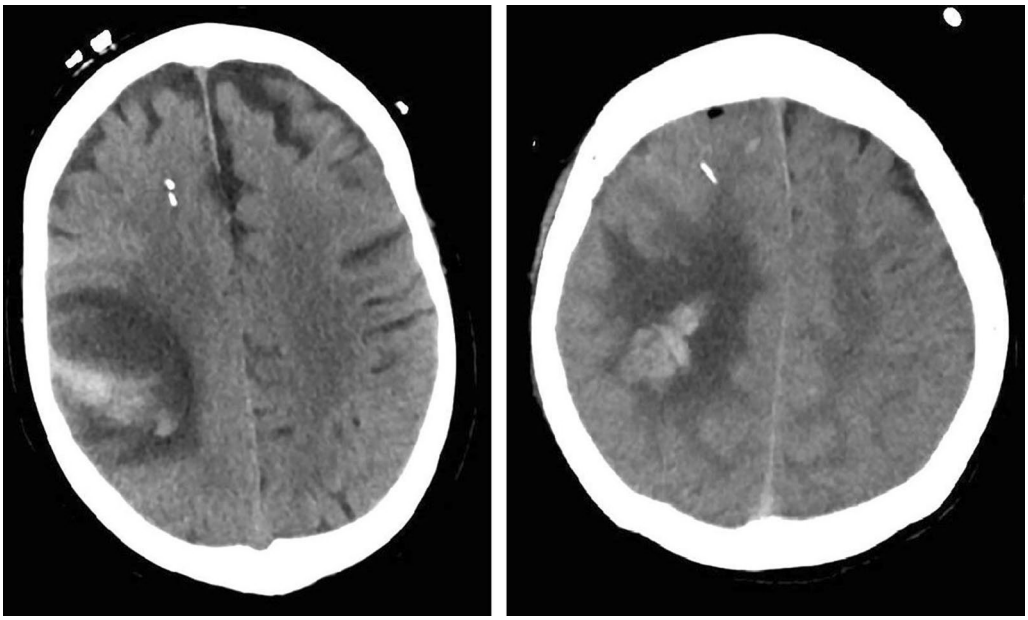

Fig. 1 Axial brain CT scan after ICP placement showing CVT-related parenchymal hematoma and the positioning of intracranial monitors in right frontal lobe, visually normal brain area, both in patient 1 (left) and patient 2 (right)

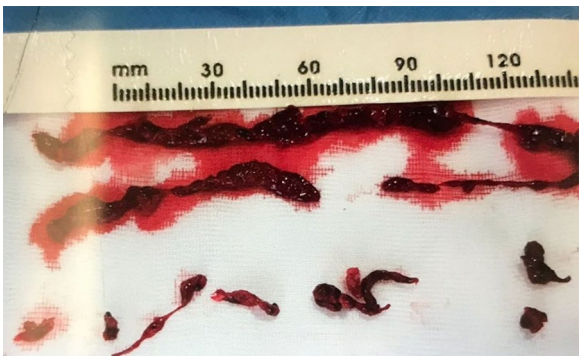

Fig. 2 Picture shows successful extraction of multiple large thrombi after endovascular mechanical thrombectomy (patient # 1)

with a normal state of consciousness and a residual left hemiparesis (modified Rankin Scale [mRS] 4).

Patient #2 was extubated at day 7 and discharged at day 15 from admission, with a normal state of consciousness and a residual left hemiparesis (mRS 3).

Discussion

The main finding of the present case report study is that MBM and especially CMD allow early detection of regional brain cell ischemia in severe CVT. In our two cases, implementation of MBM to patient care prompted early timely EMT. Importantly, despite adequate control of ICP and PbO2, CMD values remained abnormal and were restored following successful venous recanalization, implying a close relationship between CMD biomarkers and cerebral venous patency. To the best of our knowledge, this is the first study specifically addressing real-time correlation of brain cell hypoxia/ischemia and venous patency in CVT. EMT has been proposed when anticoagulation is contraindicated, in patients with deteriorating neurological status, or with an extension of cerebral thrombosis [1–3, 16]. In a recent systematic review [3], including 235 patients treated with EMT, complete resolution of CVT was obtained in 69% of patients [3]. However, little is known about the effect of EMT on intracranial hypertension associated with CVT. Decompressive craniectomy is usually performed in cases of refractory intracranial hypertension [1, 4]. In the largest single-center study [4], comprising 587 patients, good outcomes were expected for young patients (< 40 years old) operated early. In our cases, the initial CT scan did not show considerable mass effect, and MBM was initially placed (Fig. 5).

Two different pathophysiological mechanisms have been proposed for CVT formation [1, 2, 4]. The first one considers that the thrombosis of cerebral veins increases venous pressure and disrupts the blood–brain barrier, resulting in vasogenic edema. Cerebral blood flow and cerebral perfusion pressure drop, which leads to Na^+/K^+ pump failure [17–23]. This results in cytotoxic edema, and the association of cytotoxic and vasogenic edema rapidly leads to intracranial hypertension. The other mechanism postulates that thrombosis of major venous

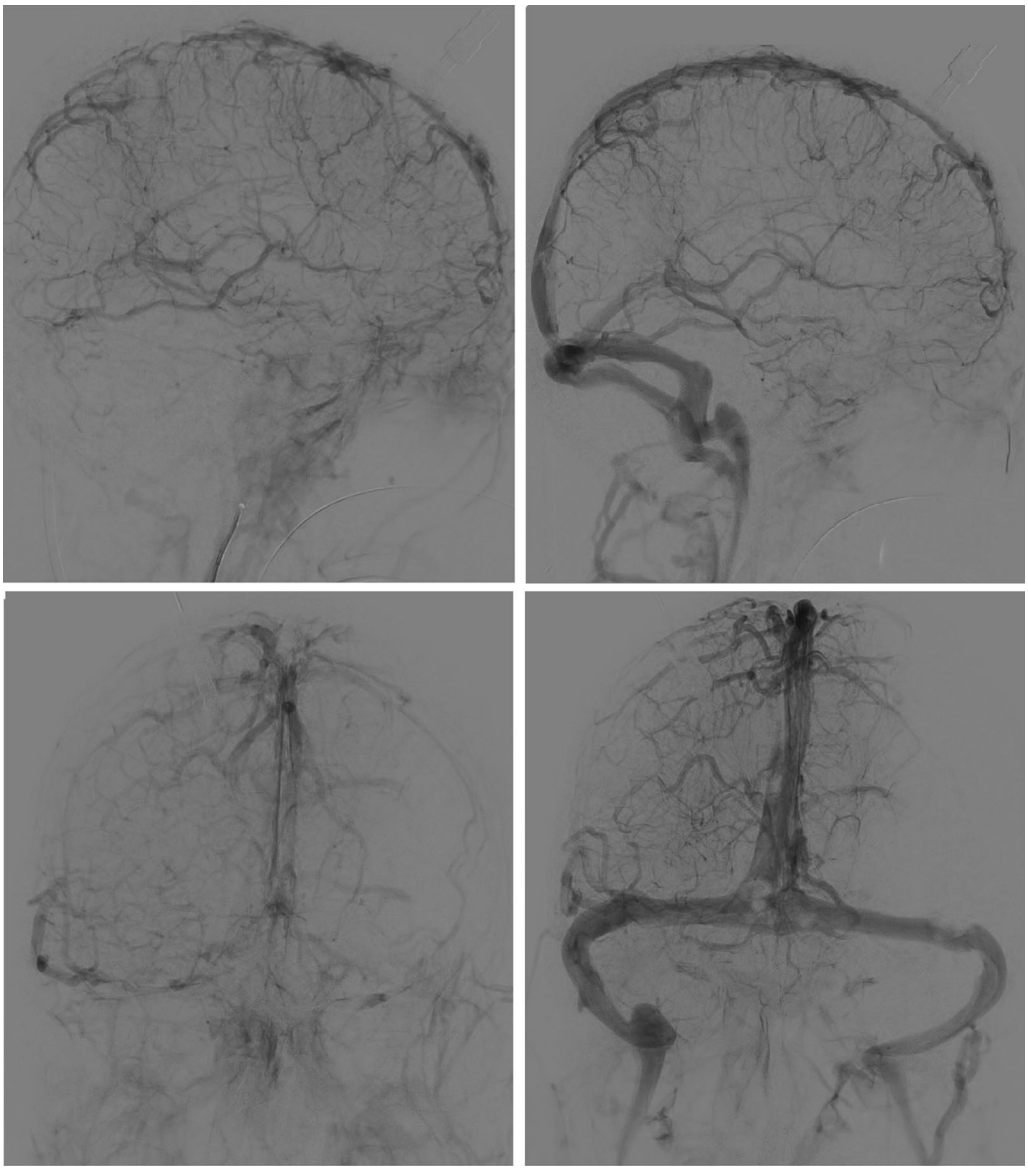

Fig. 3 Digital subtraction angiography in lateral (upper panel) and antero-posterior view (lower panel) before (left) and after (right) endovascular mechanical thrombectomy showing recanalization of the occluded sinuses (patient # 1)

sinuses may lead to diminished reabsorption of CSF through the arachnoid villi structures, leading to intracranial hypertension [1]. The observed MBM changes, and especially the immediate decrease in ICP and increase in PbO_2 observed in our cases, could represent arguments in favor of the first pathophysiological mechanism. Further studies are mandatory in order to confirm the correlation of EMT and decreased ICP. It is difficult to conclude that CMD and $PbtO_2$ improvements are directly or indirectly related to the decrease in ICP upon EMT, i.e., solely due to ICP improvement; however, we observed proportionally greater improvements in CMD values (particularly, lactate and glucose, both indicating cerebral ischemia) compared to ICP, thereby suggesting a

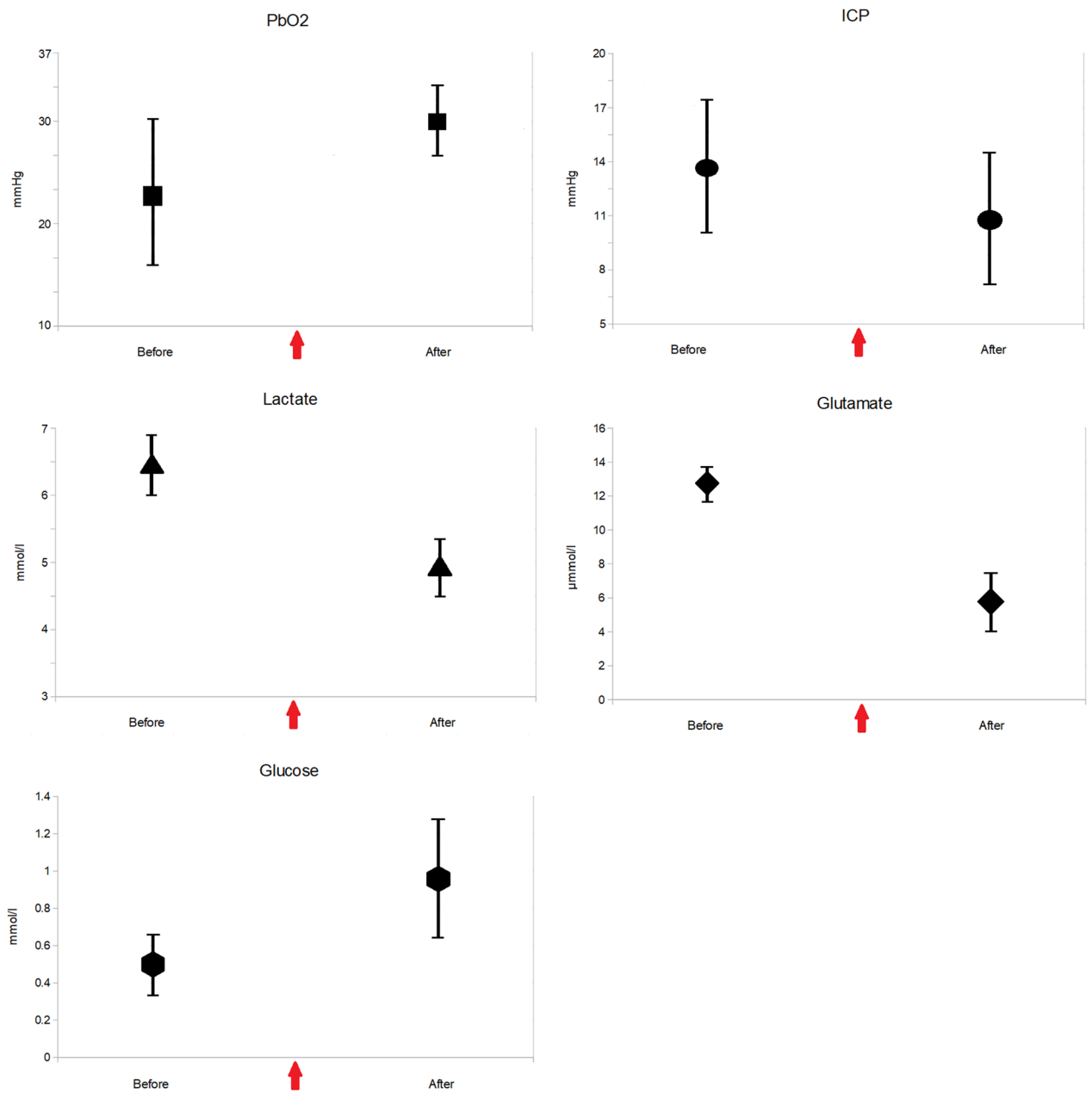

Fig. 4 Graphs showing mean (± standard deviation) values of ICP, $PbtO_2$, and CMD lactate, glucose, and glutamate in the two severe CVT patients. EMT procedure is marked with a red arrow in the timeline. Bars represent the mean ± standard deviation, 6 h before and 6 h after EMT (all $p < 0.05$ for comparisons between pre- and post-EMT)

direct effect of EMT on brain tissue and cell oxygenation. In the two patients presented, MBM allowed individualized neurocritical care targeted to improve intracerebral physiology, and eventually patient outcome.

Conclusion

We report two comatose critically ill patients with malignant cerebral venous sinus thrombosis, in whom continuous bedside multimodal monitoring,

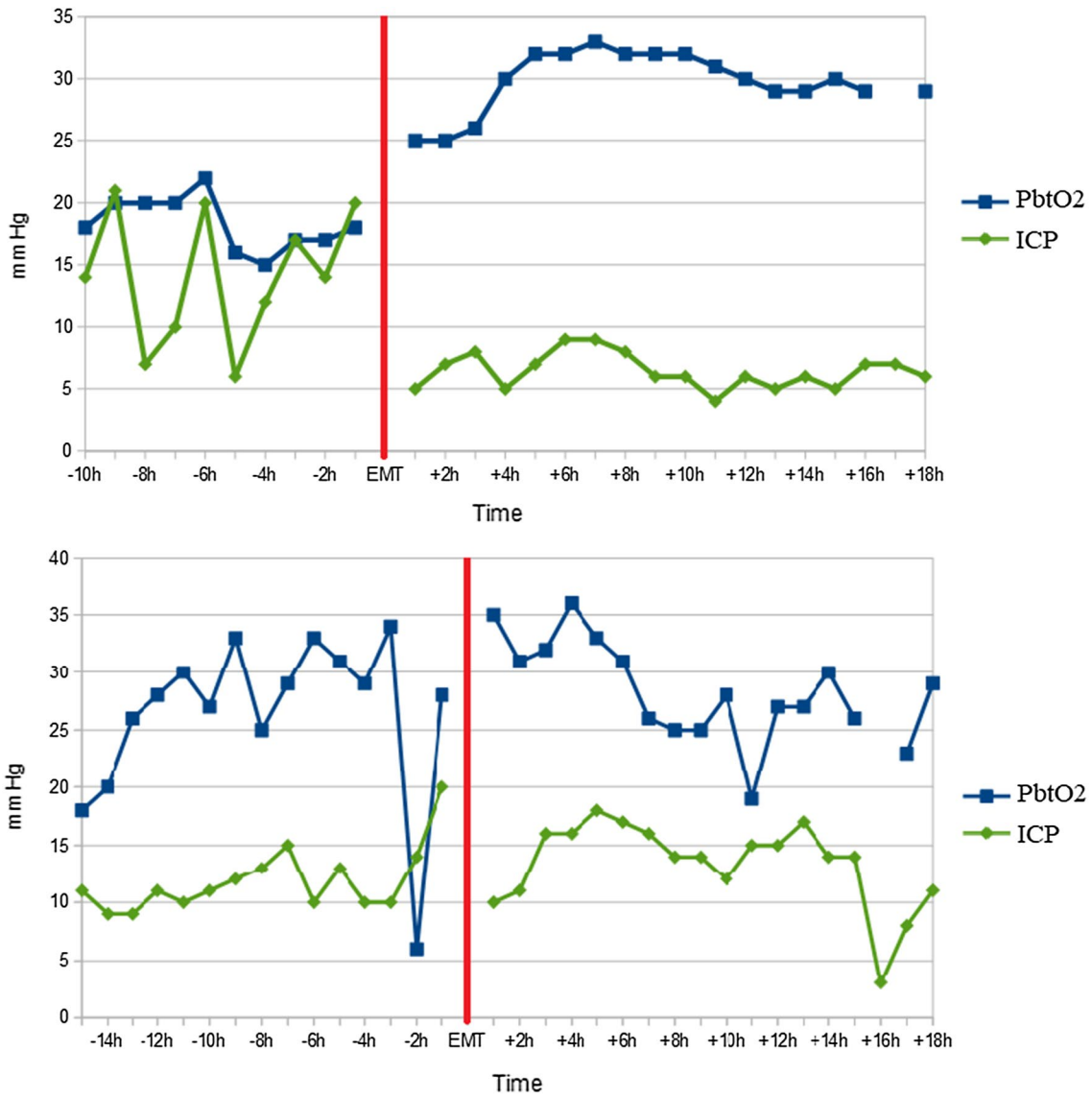

Fig. 5 Time-course PbO2 and ICP graph showing values from patient #1 (upper panel) and patient #2 (lower panel)

including brain tissue PO_2 and CMD, triggered emergent endovascular mechanical thrombectomy, which was associated with significant and clinically relevant improvement in intracerebral physiology. To the best of our knowledge, this is the first case report study illustrating the potential utility of multimodal brain physiology monitoring for the management of severe cerebral venous sinus thrombosis.

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Author contributions
AS collected and analyzed the data and wrote the manuscript. MR collected and analyzed the data. GS collected the data and reviewed the manuscript. ML analyzed the data and reviewed the manuscript. RTD analyzed the data and reviewed the manuscript. MO collected and analyzed the data and wrote the manuscript.

Source of support
Mauro Oddo is supported by research grants from the Swiss National Science Foundation.

Conflict of Interest
Alexandre Simonin, Marco Rusca, Guillaume Saliou, Marc Levivier, Roy Thomas Daniel, and Mauro Oddo declare that they have no conflict of interest.

Ethical approval
We confirm adherence to Swiss Ethics guidelines (swissethics) for this work.

Publisher's Note

Published online: 25 February 2019

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