Role of PiCCO monitoring for the integrated management of neurogenic pulmonary edema following traumatic brain injury: A case report and literature review

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Abstract. Neurogenic pulmonary edema (NPE) is occasionally observed in patients with traumatic brain injury (TBI); however, this condition is often underappreciated. NPE is frequently misdiagnosed due to its atypical clinical performance, thus delaying appropriate treatment. A comprehensive management protocol of NPE in patients with TBI has yet to be established. The current study reported the case of a 67-year-old man with severe TBI who was transferred to our intensive care unit (ICU). On day 7 after hospitalization, the patient suddenly suffered tachypnea, tachycardia, systemic hypertension and hypoxemia during lumbar cistern drainage. Intravenous diuretics, tranquilizer and glucocorticoid were administered due to suspected left heart failure attack. Chest radiography examination supported the diagnosis of pulmonary edema; however, hypotension and hypovolemia were subsequently observed. Pulse index continuous cardiac output (PiCCO) hemodynamic monitoring and bedside echocardiography were performed, which excluded the diagnosis of cardiac pulmonary edema, and thus the diagnosis of NPE was confirmed. Goal-directed therapy by dynamic PiCCO monitoring was then implemented. In addition, levosimendan, an inotropic agent, was introduced to improve cardiac output. The patient had complete recovered from pulmonary edema and regained consciousness on day 11 of hospitalization. The current case demonstrated that PiCCO monitoring may serve a central role in the integrated management of NPE in patients with TBI. Levosimendan may be a potential medicine in treating cardiac dysfunction, along with its benefit from improving neurological function in NPE patients.

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Introduction

Neurogenic pulmonary edema (NPE) is characterized by abruptly increased pulmonary interstitial and alveolar fluid following central nervous system (CNS) events, including traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) or spinal cord injury (1). It is a relatively rare clinical syndrome with high mortality, and is frequently misdiagnosed due to its unspecific clinical presentation. TBI contributes to the majority of injury-associated mortality and permanent disability cases worldwide (2), with the incidence of such cases reported to be ~20% in patients with TBI (3). However, the incidence of NPE has reportedly increased to 50% (4) in patients succumbing within 96 h after suffering TBI, rendering NPE a life threatening complication in these patients.

The clinical manifestations of NPE are almost identical to those of acute respiratory distress syndrome and cardiogenic pulmonary edema, posing a great challenge for timely differential diagnosis and correct treatment decision in TBI patients (1). Although the underlying pathogenesis of NPE is poorly understood, it has been suggested that, on the basis of increased intracranial pressure, factors including direct cardiac injury, systemic sympathetic discharge, pulmonary vascular permeability and pulmonary venule adrenergic hypersensitivity may serve an essential role in NPE development (1,5). These postulated mechanisms may alone or synergically drive the development of NPE, suggesting that the actual pathophysiological alteration may be complicated and that appropriate monitoring is required. Since neurohemodynamic interaction serves a central role in the development of NPE, theoretically, hemodynamic monitoring would contribute to the evaluation of the patient's condition (5). Detection of global end diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI) and extravascular lung water (EVLWI) through an advanced transpulmonary thermodilution device is known as the pulse index continuous cardiac output (PiCCO) (6). This method allows the differentiation between permeability and hydrostatic pulmonary edema, and the guidance of fluid management (6). PiCCO has also shown favorable agreement with pulmonary artery catheterization (PAC) in monitoring cardiac output (7), making it a promising strategy for handling the cardiac involvement in NPE. However, to the best of our

knowledge, only one previous study has utilized this novel method for guiding the management of NPE (6).

Specific treatments, such as α-adrenergic blocking agents for underlying neurological insult, have been occasionally administered in patients with NPE (8). However, an α-adrenergic blocking agent can not be used in the case of systemic hypotension, thus an alternative treatment is required. Levosimendan, a novel positive inotropic agent, has been recommended for the treatment of acute heart failure in the European Society of Cardiology guidelines (9). In addition, a previous study unveiled the vasorelaxation ability of levosimendan on pulmonary vessels (10), suggesting that it can be used to alleviate pulmonary edema by directly reducing the hydrostatic pressure. However, its role in the management of NPE has not been investigated.

In the current study, a TBI case with NPE diagnosed when performing lumbar cistern drainage was reported. PiCCO monitoring was applied, and showed a favorable ability to interpret the pathophysiological progression and provide compelling assistance for the diagnosis and treatment of this complication. To the best of our knowledge, the present study was the first to report the use of levosimendan to improve cardiac output, and demonstrated a potential neuroprotective effect in the treatment of NPE.

Case report

The present case was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China). Written informed consent was obtained from the patient for the publication of this manuscript.

A 67-year-old male patient was transferred to the General Intensive Care Unit (ICU) of the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) in November 2014, 4 days after falling from a height of 2 meters. The patient was diagnosed with multiple injuries with severe TBI, spleen contusion, clavicle and multiple rib fractures at a local hospital. Upon initial admission, emergency decompressive craniectomy and hematoma removal were performed initially when progressive intracranial hypertension was suspected. A second craniotomy was performed due to increased volume of drain output on the same day. Other treatments including respiration support, antibiotics and fluid administration were also administrated. The patient had no medical history other than administration of amlodipine due to hypertension for 5 years.

During the admission in our ICU, the patient was unconscious with Glasgow Coma Scale (GCS) score (11) of 3 (E1VTM1), with possible scores ranging from 3-15; GCS scores of 3-8, 9-12 and 13-15 indicate severe, moderate and mild brain injury respectively. The patient's body temperature, pulse rate, blood pressure and respiratory rate were 38˚C, 88 beat per minute (bpm), 124/67 mmHg and 18 count per minute (cpm), respectively. Physical examination revealed wheezing rales of bilateral lungs upon auscultation. A head computed tomography (CT) scan showed bilateral frontal lobe and right temporal lobe contusion and laceration, subdural hematoma and SAH with post decompressive craniectomy presentation (Fig. 1). In addition, a chest X-ray scan indicated board bilateral infiltrates, consolidation and pleural effusion
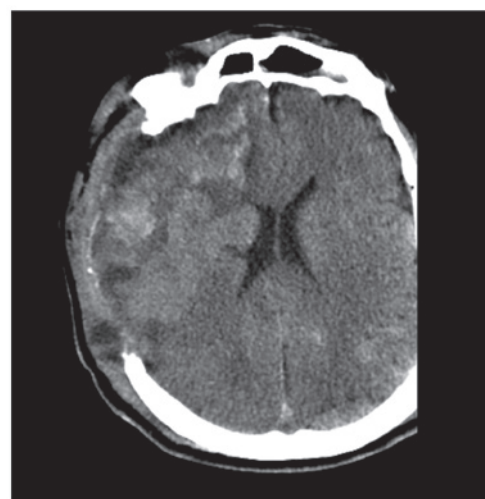

Figure 1. Head computed tomography on admission revealed bilateral frontal lobe and right temporal lobe contusion and laceration, subdural hematoma and subarachnoid hemorrhage.

(Fig. 2A). Subsequently, pulmonary infection was confirmed based on the findings of further laboratory tests, including elevated percentage of neutrophils (91.2%; normal range, 50-70%) in complete blood counting, C-reactive protein (patient level, 92.6 mg/l; normal range, 0-8 mg/l) and serum procalcitonin (PCT; patient level, 4.2 ng/ml; normal range, 0-0.05 ng/ml). Subsequently, cefoperazone/sulbactam (Pfizer, Inc., New York, NY, USA) was intravenously administered every 8 hours from days 1-3 as treatment for the pulmonary infection, and 20% mannitol (100 ml; Baxter Healthcare Co., Ltd., Shanghai, China) was intravenously infused every 8 h from days 1-11 post-admission, in order to reduce intracranial pressure. The patient remained hemodynamically stable and moderate improvement of the neurological status (GCS score, 5; E2VTM2) was observed over the next few days.

On day 7 of hospitalization, a lumbar puncture revealed substantially elevated intracranial pressure (ICP; >300 mmH$_2$O; normal range, 70-200 mmH$_2$O), although relevant therapies including decompressive craniectomy and osmotherapy were adequately provided. Therefore, the patient was subjected to lumbar cistern drainage. The condition of the patient was generally stable prior to the surgery, with a pulse rate, blood pressure, and respiratory rate of 94 bpm, 123/78 mmHg and 22 cpm, respectively. His arterial blood peripheral oxygen saturation (SpO$_2$) was maintained at 100% under ventilation support of 40% fraction of inspired oxygen (FiO$_2$) and 5 cmH$_2$O positive end-expiratory pressure (PEEP). However, at the end of the procedure, the patient suffered sudden profuse sweating, tachypnea (25-35 cpm), tachycardia (140-90 bpm), systemic hypertension (160-200/90-120 mmHg) and decreasing SpO$_2$ (85-95%). Pink frothy sputum was observed upon airway aspiration, while board bilateral crackles and rales were detected upon auscultation. The diagnosis of acute left heart failure and cardiogenic pulmonary edema was initially suspected, and thus 5 mg midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China), 40 mg furosemide (Kingyork, Tianjin, China), 40 mg methylprednisolone (Pfizer, Inc.) and 10 mg morphine (Northeast Pharmaceutical Group Co., Ltd., Shenyang, China) were intravenously injected
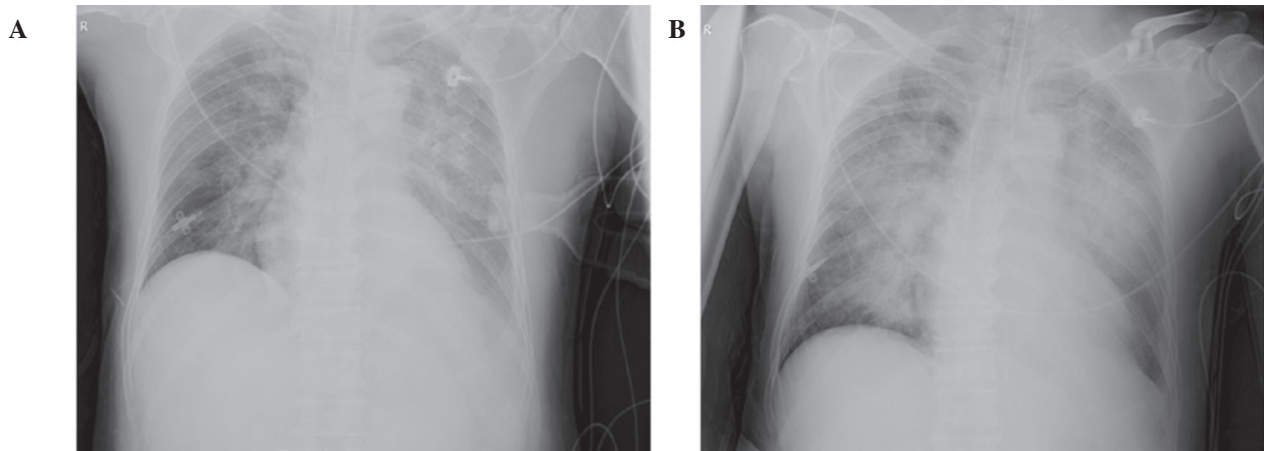
Figure 2. Chest radiography showed (A) board bilateral infiltrates, consolidation and pleural effusion on admission, and (B) typical signs of pulmonary edema with Kerley B lines and 'bat-wing' pattern on hospitalization day 7 (neurogenic pulmonary edema onset).

following the lumbar drainage procedure, and adjustment of ventilation parameters was performed (IPPV mode; FiO_2, 100%; PEEP, 15 cmH_2O; pressure support, 30 cmH_2O; tidal volume, 600-700 ml; respiratory rate, 20 cpm). After 30 min, the vital signs gradually became relatively stable, with a pulse rate of 102 bpm, blood pressure of 120/68 mmHg, respiratory rate of 30 cpm and SpO_2 of 95-98%; thus, the patient was transferred back to the general ICU.

In the ICU, the symptoms of tachypnea (32 cpm) and tachycardia (122 bpm) remained, but hypotension (85/45 mmHg) was newly developed. Symptoms of hypovolemia, including cold limbs, cyanosis of the lips and oliguria, were subsequently observed, and thus norepinephrine (Grand Pharmaceutical Co. Ltd., Wuhan, China) was administered intravenously at 0.05 μg/kg/min with an increment of 0.05 μg/kg/min when the blood pressure was below 90/60 mmHg for a total of 13 h. Arterial blood gas measurement showed a pH of 7.299, CO_2 partial pressure of 46.2 mmHg (normal range, 36-44), O_2 partial pressure of 98.5 mmHg (normal range, 75-95), blood base excess of -3.7 mmol/l and oxygen saturation of 98.5%, while receiving 100% of FiO_2. Elevated levels of serum markers were also detected, including brain natriuretic peptide (BNP) of 3,438.60 pg/ml (normal range, 2-4 pg/ml), myocardial enzyme (troponin I) of 0.935 ng/ml (normal range, <0.1 ng/ml) and C-reactive protein (CRP) of 221.9 mg/l. On the same day, chest X-ray imaging showed typical signs of pulmonary edema (Fig. 2B).

In order to further clarify the pathogenesis of pulmonary edema, PiCCO monitoring by transpulmonary thermodilution technique was performed (day 7). The initial PiCCO measurements revealed elevated GEDVI of 860 ml/m^2 (normal range, 680-800 ml/m^2), EVLWI of 12 ml/kg (normal range, 3-7 ml/kg), and mild reduced cardiac index (CI) of 2.84 l/min/m^2 (normal range, 3.0-5.0 l/min/m^2) combined with normal pulmonary vascular permeability index (PVPI) of 1.4 (normal range, 1-3). Thus, the diagnosis of hydrostatic-type pulmonary edema was established. Bedside two-dimensional echocardiography excluded marked left ventricular dysfunction [left ventricle ejection fraction (EF), 50%; normal range, 50-70%] or left abnormal ventricular wall motion, thus eliminating the possibility of cardiogenic pulmonary edema.

A diagnosis of NPE was finally established based on the aforementioned findings.

Goal-directed therapy guided with PiCCO was selected for the subsequent treatment of NPE. Fluid administration was restricted and a low dose of furosemide at 0.5 μg/kg/min was administered intravenously for 10 h to achieve negative fluid balance until the EVLWI and GEDVI values reduced to the normal level. Methylprednisolone (40 mg, once daily, intravenously) was used to further relieve edema (day 7-8). A reduction in heart rate (70-80 bpm) and respiratory rate (12-16 cpm) along with an elevation of the mean arterial pressure (83-101 mmHg) was observed, and thus a reduction of FiO_2 to 40% and of norepinephrine infusion to the initial dosage (0.05 μg/kg/min) was performed, without affecting the blood oxygen saturation. On day 8, PiCCO demonstrated normalized EVLWI at 7 ml/kg and GEDVI at 723 ml/m^2. However, a reduced CI (2.08 l/min/m^2) was still observed, whereas the stroke volume variation (SVV) was within the normal range, indicating inadequate cardiac reserve. On day 8, levosimendan, an inotropic agent, was also administered intravenously for 24 h to improve the cardiac output, with a maintenance dose of 0.14 μg/kg/min (Qilu Pharmaceutical Co., Ltd., Jinan, China) subsequent to termination of norepinephrine administration, due to the patient's blood pressure stabilizing. An elevated CI of 2.79-4.06 l/min/m^2 was then determined by PiCCO monitoring during levosimendan administration, and was returned to similar levels thereafter. Repeated bedside echocardiography examinations also confirmed the improvement of left ventricular systolic function (EF, 65%). PiCCO monitoring continued for a total of 6 days after admission, and the patient remained hemodynamically stable (Fig. 3).

On day 8 of hospitalization, a repeat chest X-ray scan revealed the complete disappearance of pulmonary edema signs (Fig. 4A). The patient regained consciousness with intermittent confusion on the day 11 of hospitalization (GCS score, 10; E3VTM6). Subsequently, the patient recovered rapidly and mechanical ventilation was ceased on the day 13 after admission. On day 16, a chest X-ray scan revealed evident improvement of lung infiltrates (Fig. 4B), along with marked reduction of serum inflammatory and cardiac biomarkers (CRP, 41.9 mg/l; PCT, 1.67 ng/ml; BNP, 778.8 pg/ml), and thus
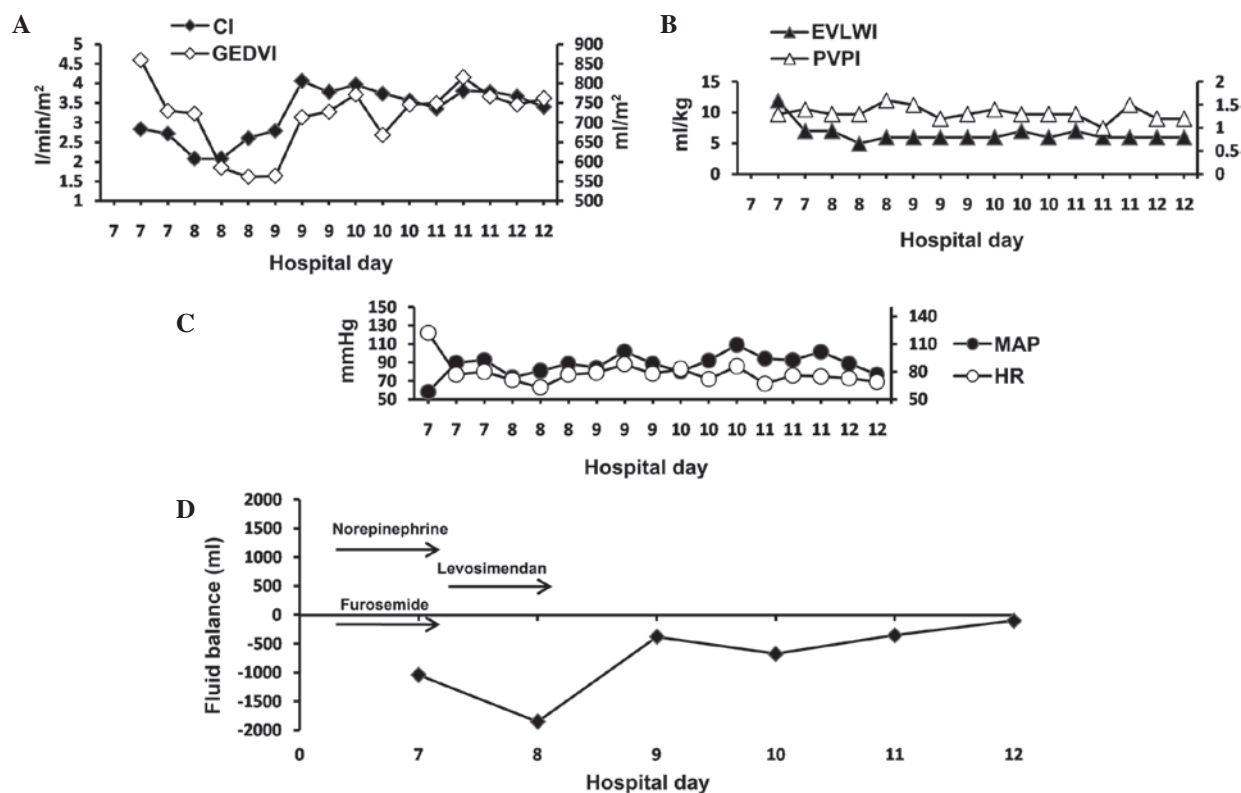
Figure 3. Changes of (A) CI and GEDVI, (B) EVLWI and PVPI, (C) MAP and HR and (D) fluid balance and major intravenous medication were reported over time during PICCO monitoring (from day 7-12 following hospital admission). PiCCO, pulse index continuous cardiac output; CI, cardiac index; GEDVI, global end diastolic volume index; EVLWI, extravascular lung water index; PVPI, pulmonary vascular permeability index; MAP, mean arterial pressure; HR, heart rate.
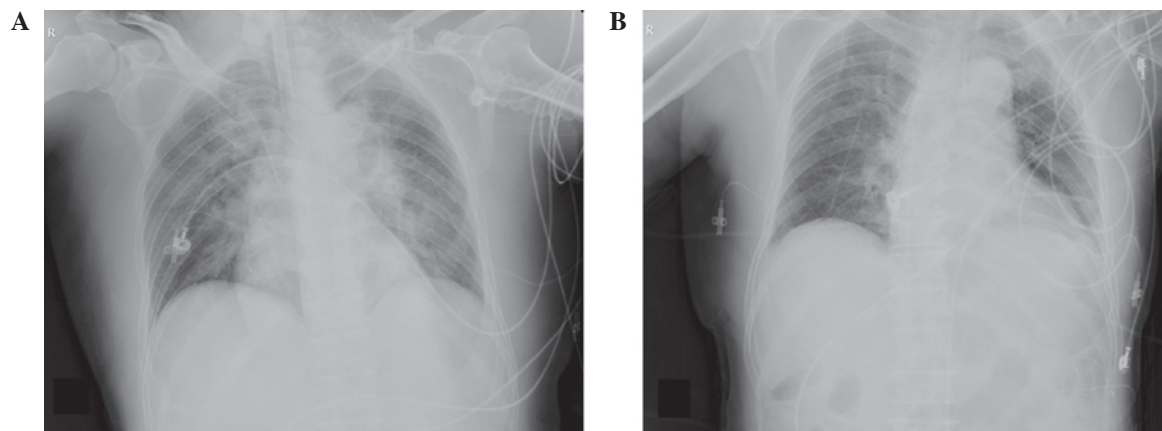

Figure 4. (A) Chest radiography on hospitalization day 8 (1 day after NPE) demonstrated no evident sign of pulmonary edema and absorbed infiltrates when compared with previous X ray images. (B) Follow-up chest radiography on hospitalization day 16 showed largely absorbed infiltrates when compared with previous chest X ray images. NPE, neurogenic pulmonary edema.

the antibiotic therapy was stopped. On day 22 after admission, a repeat head CT scan revealed significantly absorbed hematoma and reduced brain swelling (Fig. 5). The patient recovered uneventfully and was transferred to a rehabilitation center at 27 days after admission.

In the rehabilitation center, the patient predominantly received exercise rehabilitation. One month later, the patient regained almost complete consciousness, and ws able to walk short distances. The patient was discharged from the rehabilitation center in December 2014, requiring no additional tests or treatment. At follow-up in June 2015, the patient had recovered other than occasional confusion, and required no medication other than hypertensive drugs.

Discussion

Secondary pathophysiological changes following TBI, including alteration of cerebral blood flow, impairment of cerebrovascular autoregulation and edema formation, contribute to the elevation of ICP (12). Elevated ICP is believed to form the basis of NPE, and results in neurological compression, ischemia and disruption of the 'trigger zone', known as the
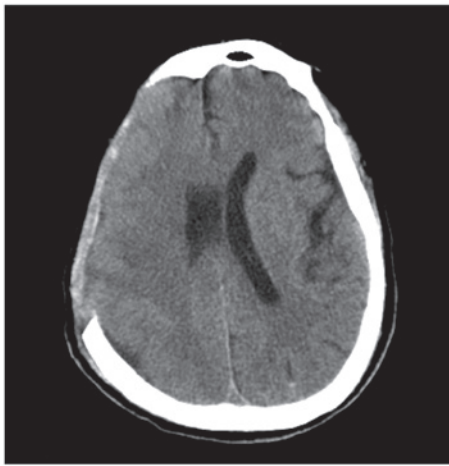
Figure 5. Follow-up head computed tomography revealed that the intracranial hematoma and subarachnoid hemorrhage were significantly absorbed and reduced brain swelling on hospitalization day 22.

A1 and A5 groups of neurons, nuclei of the solitary tract, the area postrema, the medial reticulated nucleus and the dorsal motor vagus nucleus in the medulla oblongata (1,5). There are generally two types of NPE: The 'early' form develops within minutes to hours following the injury, whereas the 'late' form develops 12-24 h after the injury (1,5). In the case reported in the present study, the patient developed NPE during lumbar cistern drainage when significant increasing of ICP was detected. The possible explanation for this late outbreak of NPE (10 days after the initial TBI) may be that, after surviving the edema peak (usually 3-7 days post-TBI), the balance among cerebral blood flow, cerebral perfusion pressure and metabolism was restored; however, lumbar cistern drainage due to elevated ICP may cause the sudden alteration to ICP, possibly disturbing the newly established balance, inducing another brain injury and resulting in the outbreak of NPE.

Although the exact pathophysiological process remains unclear, sympathetic surge or 'catecholamine storm' is considered to be the primary mechanism of NPE (1,5). Evidence from animal models revealed that elevated heart rate, and systemic and pulmonary hypertension upon CNS injury indicated a rapid activation of the sympathetic nervous system (13,14). In patients with a clinical diagnosis of NPE, levels of serum catecholamine were consistently raised soon after the outbreak of the syndrome and paralleled with the alleviation of the condition (6,8). The proposed pathogenesis of NPE induced by sympathetic surge includes hemodynamic disturbance, elevated pulmonary endothelial permeability, (so called 'blast theory') and direct cardiac injury (1,5). These mechanisms alone or in combination, as observed in cases of NPE with Takotsubo's cardiomyopathy (15-17), give rise to the hydrostatic or permeable types of pulmonary edema, thus posing a substantial challenge for the timely recognition and management of this syndrome. In a previous case of postoperative NPE, Merenkov et al (18) reported that on-site bedside lung ultrasound was able to identify pulmonary edema, exclude cardiac involvement and guide serial fluid management. However, lung sonography testing cannot quantitatively measure the EVLWI, which is considered as the most sensitive and accurate parameter for accessing pulmonary edema (19-21). EVLWI was also shown to be closely

co-associated with the ICP level in NPE (22), rendering it a reliable parameter for the precise fluid and ICP management. The newly developed PiCCO monitoring system, based on the thermodilution technique, is extensively used for the assessment of EVLWI and the estimation of intrathoracic volumes (GEDV and ITBV). PiCCO has also been proven to show favorable accordance for measuring cardiac output with the traditional 'gold standard' measurement by PAC in various groups of patients (7,23,24), and to be less invasive. Mutoh et al (6) demonstrated that, with combination of PVPI, GEDV and cardiac output monitoring, PiCCO was able to differentiate between the hydrostatic and permeable types of pulmonary edema in three NPE cases with aneurismal SAH. In the present study, the patient initially presented with systemic hypertension, increased heart rate and tachypnea during lumbar cistern drainage, indicating a burst of sympathetic activation. Following treatment with intravenous diuretics and morphine and adjusting ventilation parameters under consideration of acute heart failure, the patient developed hypotension and symptoms of hypovolemia, including cold limbs, cyanosis of lips and oliguria. At that time, PiCCO monitoring was decided to assist in reaching the appropriate diagnosing and in further management. The elevated GEDVI and EVLWI, normal PVPI, exclusion of major cardiac systolic dysfunction or abnormal wall motion with bedside echocardiography, the absence of excessive fluid administration and no history of heart disease suggested a non-cardiac origin of hydrostatic pulmonary edema. NPE was the most likely etiology in the current patient. However, myocardial injury represented by mild decreased CI and elevated cardiac enzyme (troponin I) and BNP levels, was likely to contribute to systemic hypotension and aggravation of hydrostatic edema. In a previous small sample study, all the NPE cases resulting from TBI were found to present cardiac dysfunction (25). The reversible myocardial dysfunction may be caused by direct catecholamine cardiotoxicity or indirect abruptly elevated afterload. Biomarkers such as BNP alone for cardiac pulmonary edema identification and prognosis prediction can be interfered by various factors, including hypovolemia (26) and abnormal BNP released from the injured CNS lesion (27). However, BNP levels appeared to be associated with the disease status evolution in the present study patient, possibly due to a certain degree of cardiac involvement.

To date, ventilation with PEEP and ICP reduction has been proven to be the most effective modality in handling NPE (28,29). However, a specific treatment protocol has not been developed. Regarding the heterogeneous hemodynamic presentation of NPE due to the predominance of specific underlying pathophysiological changes (1,5), an individualized treatment decision, including fluid management, the use of inotropic and vasoactive agents, is urgently required (1,28-30). These treatments constantly interfere with each other in managing TBI patients with NPE. For instance, elevated PEEP for the lung recruitment maneuver may limit venous return, further reduce cardiac stroke volume and increase the ICP (31). In addition, fluid resuscitation to help improve cardiac and brain perfusion may increase the interstitial edema and thus impair pulmonary function (32). In the current study, rapid reduction of EVLWI and normalized GEDVI along with improved clinical situation, such as relief of respiratory failure and hemodynamic instability, was obtained under guidance with the PiCCO system (Fig. 3), without causing deterioration

of cardiac or neurological function; this implies that intense and effective hemodynamic monitoring is the key to the optimal management.

Only a limited number of studies have described the specific treatment, such as the use of an α-adrenergic blocking agent, for underlying adrenergic surge in patients with NPE. The successful treatment with intravenous injection of phentolamine (8) was reported in a previous case of NPE caused by an intracranial hemorrhage from a ruptured arteriovenous malformation, in which increased serum catecholamine levels were documented. However, postoperative hypotension in the present patient excluded the usage of an α-adrenergic blocking agent. An inotropic agent was thus considered for correcting the relatively low CI, as detected by PiCCO. Levosimendan, a calcium sensitizer, is known to effectively improve cardiac function without increasing myocardial oxygen consumption (33). Possibly owing to this unique characteristic, several clinical trials or meta-analyses have implied favorable benefits, including improved cardiac function and reduction of mortality or length of hospital stay, upon levosimendan treatment when compared with dobutamine treatment in critically ill patients or those with a cardiology setting (34-37). The neuroprotective effect of levosimendan has been recently demonstrated in a TBI *in vitro* model (38), and in a cerebral reperfusion and spinal cord injury *in vivo* model (39,40). The exact mechanism is unclear, and is possibly attribute to the opening of ATP-sensitive K^+ channels (mitoKATP channels) and to the suppression of nitric oxide synthase expression, cell death and inflammatory response upon the application of levosimendan (40-42). Thus, treatment with levosimendan rather than dobutamine was selected in the current study, attempting to correct cardiac dysfunction without increasing oxygen consumption and preventing further brain injury. The current patient demonstrated completely reversed CI following levosimendan administration. To the best of our knowledge, this is the first report presenting the application of levosimendan in treating the cardiac dysfunction in NPE. The improved GCS score was largely attributing to lumbar cistern drainage therapy, while levosimendan treatment may partially help accelerate the recovery of brain function with its neuroprotective ability. Future clinical trials are needed to confirm the potential role of levosimendan in managing NEP patients with TBI.

In conclusion, the present study reported a case of NPE that was successfully diagnosed and treated with dynamic monitoring of PiCCO. The study demonstrated that successful identification and control of NPE was rapidly obtained through comprehensive monitoring of serial serum biomarker tests, bedside echocardiography and, most importantly, hemodynamic monitoring. Fluid management remains the key element in treating NPE. The application of the new medication, levosimendan, has extended our experience in handling the cardiac involvement under CNS insult. Further clinical trials are required to provide solid evidence on the potential of this neuroprotective inotropic agent.

Acknowledgements

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