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Electroencephalographic depression after abruptly increasing partial pressure of end-tidal carbon dioxide: a case series

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Abstract

Background Prolonged electroencephalographic depression during surgery is associated with poor outcomes for patients. However, the published literature on electroencephalographic depression caused by a sudden increase in the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) is lacking.

Case presentation We report four patients who were scheduled for laparoscopic liver surgery under general anesthesia. During the process of EEG monitoring with Sedline, four patients experienced electroencephalographic depression closely after a sudden increase in $P_{ET}CO_2$. The four patients showed that electroencephalographic depression mainly manifested as a slow in EEG frequency, a reduction in the amplitude and power of EEG, and a decrease in spectral edge frequency. Patient state index was elevated in three cases.

Conclusions To summarize, our patients showed EEG depression when $P_{ET}CO_2$ suddenly increased, which suggests that clinical doctors should be alert to electroencephalographic depression when the $P_{ET}CO_2$ abruptly increases. EEG monitoring devices should be applied in patients with possible hypercapnia. Anesthesiologists must comprehensively interpret the raw EEG, spectral edge frequency, and density spectral array data, in addition to patient sedation index values.

Keywords Partial pressure of end-tidal carbon dioxide, Electroencephalographic depression, Hypercapnia, EEG, Carbon dioxide narcosis

Introduction

Electroencephalographic suppression has been demonstrated to be associated with poor outcomes such as delirium and death after surgery [1, 2]. Perioperative electroencephalographic depression often represents a deeper state of anesthesia and can also be caused by pathological states, including severe hypercapnia, hypothermia, coma, hypoglycemia and encephalopathy. An observational study showed that acute severe hypercapnia inhibited amplitude-integrated electroencephalogram (aEEG) [3].

EEG monitoring has been shown to benefit in titrating anesthetics to avoid deep anesthesia and related adverse

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events, such as electroencephalographic suppression [4, 5]. During the process of EEG monitoring with Sedline, four patients experienced electroencephalographic depression closely after a sudden increase in $P_{ET}CO_2$ ($P_{ET}CO_2$ exceeded 45 mmHg within 1 min). The purpose of this case series is to remind clinicians to be alert to electroencephalographic depression when $P_{ET}CO_2$ abruptly increases and to emphasize the value of EEG monitoring in patients with possible hypercapnia. We must comprehensively interpret the raw EEG, spectral edge frequency, and density spectral array data, in addition to patient sedation index values. This study was approved by the Ethics Committee of West China Hospital Sichuan University (HX-2023-221), and informed consent was waived.

Case presentation

Patient 1

A 53-year-old man (160 cm, 60 kg) diagnosed with hepatic cholangiocarcinoma was scheduled for laparoscopic lobectomy under general anesthesia. His medical history was normal. During operation, the accumulation of water in the CO_2 absorption device resulted in a sudden increase in $P_{ET}CO_2$ and lasted approximately 12 min, with the maximum value of $P_{ET}CO_2$ reaching 70 mmHg.

Patient 2

A 44-year-old woman (165 cm, 62 kg) diagnosed with hepatic hemangioma was scheduled for laparoscopic resection of the complex hepatic hemangioma under general anesthesia. Her medical background was normal. The $P_{ET}CO_2$ suddenly increased to 64 mmHg and lasted approximately 2 min when the hepatic portal vein was unclamped.

Patient 3

A 52-year-old man (165 cm, 57 kg) who suffered from hepatocellular carcinoma was scheduled for laparoscopic resection of right complex liver cancer under general anesthesia. He had a history of hepatitis B virus infection, which led to cirrhosis (Child-Pugh A) and portal hypertension. Abnormal laboratory findings included an aspartate aminotransferase level of 109 IU/L, a glutamate aminotransferase level of 105 IU/L, and a platelet count of $82*10^9$/L. Other laboratory examinations were normal. During the hepatectomy surgical process, after the portal vein had been clamped for 15 min, the $P_{ET}CO_2$ started to increase from 45 to 56 mmHg within 1 min and fluctuated in this range for approximately 10 min.

Patient 4

A 52-year-old man (165 cm, 62 kg) diagnosed with hepatocellular carcinoma was scheduled for laparoscopic central hepatectomy under general anesthesia. He was previously diagnosed with hepatitis B virus infection and received routine antiviral treatment. Abnormal laboratory findings included an aspartate aminotransferase level of 117 IU/L, a glutamate aminotransferase level of 161 IU/L, and a platelet count of $87*10^9$/L. Other physical and laboratory examinations were normal. There was a sudden increase in $P_{ET}CO_2$ during the opening of the hepatic portal vein. The maximum value of $P_{ET}CO_2$ was 58 mmHg, and the duration of increased $P_{ET}CO_2$ was approximately 2 min.

The anesthesia protocols used were similar for all four patients. The perioperative monitoring included SEDLine frontal EEG (Masimo Inc., Irvine, CA, USA), invasive arterial blood pressure, electrocardiogram (ECG), pulse oxygen saturation (SpO_2), $P_{ET}CO_2$, body temperature, and train of four ratios (TOF) for neuromuscular blockage monitoring. Anesthesia was induced by intravenous injection of a 2 mg bolus of midazolam and propofol target control infusion (TCI) at a plasma target concentration of 3 μg/ml; 0.4 μg/kg sufentanil and 0.2 mg/kg cisatracurium were intravenously injected when the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) score was 1. Tracheal intubation was performed when TOFcnt ≤ 2. Anesthesia was maintained with desflurane and remifentanil, and the dosage was adjusted to maintain the PSI in the range of 25–50. The perioperative target blood pressure was maintained not beyond ±20% of the baseline. Cisatracurium (0.05 mg/kg) was added when the TOFcnt was ≥2. All patients received a lung-protective ventilation strategy, and the target $P_{ET}CO_2$ was between 35 and 45 mmHg. When the $P_{ET}CO_2$ increased suddenly, the respiratory parameters were immediately adjusted to increase the minute volume of ventilation.

After the $P_{ET}CO_2$ abruptly increased, density spectral array (DSA) monitoring revealed that the bilateral spectral edge frequency (SEF) decreased in all four patients (Fig. 1A), and burst suppression (BS) even emerged in patient 1 (black vertical bars with blue bottom in Fig. 1A). BS analysis of patient 1 showed that the BS ratio was 16.25%, duration of suppression was 117s, and peak-to-peak voltage of the bursts was 27.72(2.42) μV. The maximum reduction of SEF were from 8.8 to 2.7 Hz (69.3%), 18.5 to 8.4 Hz (54.6%), 12.6 to 5.2 Hz (58.6%) and 11.5 to 8.5 Hz (26.2%), respectively in four patients (Fig. 1B). During this period, the change in the SEF was opposite to that in the $P_{ET}CO_2$; that is, the SEF decreased as the $P_{ET}CO_2$ increased and returned to its original state as the $P_{ET}CO_2$ returned to normal. The duration of the SEF decrease was roughly consistent with the duration of the $P_{ET}CO_2$ increase, with a 1-minute delay (Fig. 1B). Interestingly, the patient sedation index (PSI) increased in 3 out of 4 patients (patients 1, 3, and 4), which is very different from over sedation (Fig. 1B). The PSI of patient 2

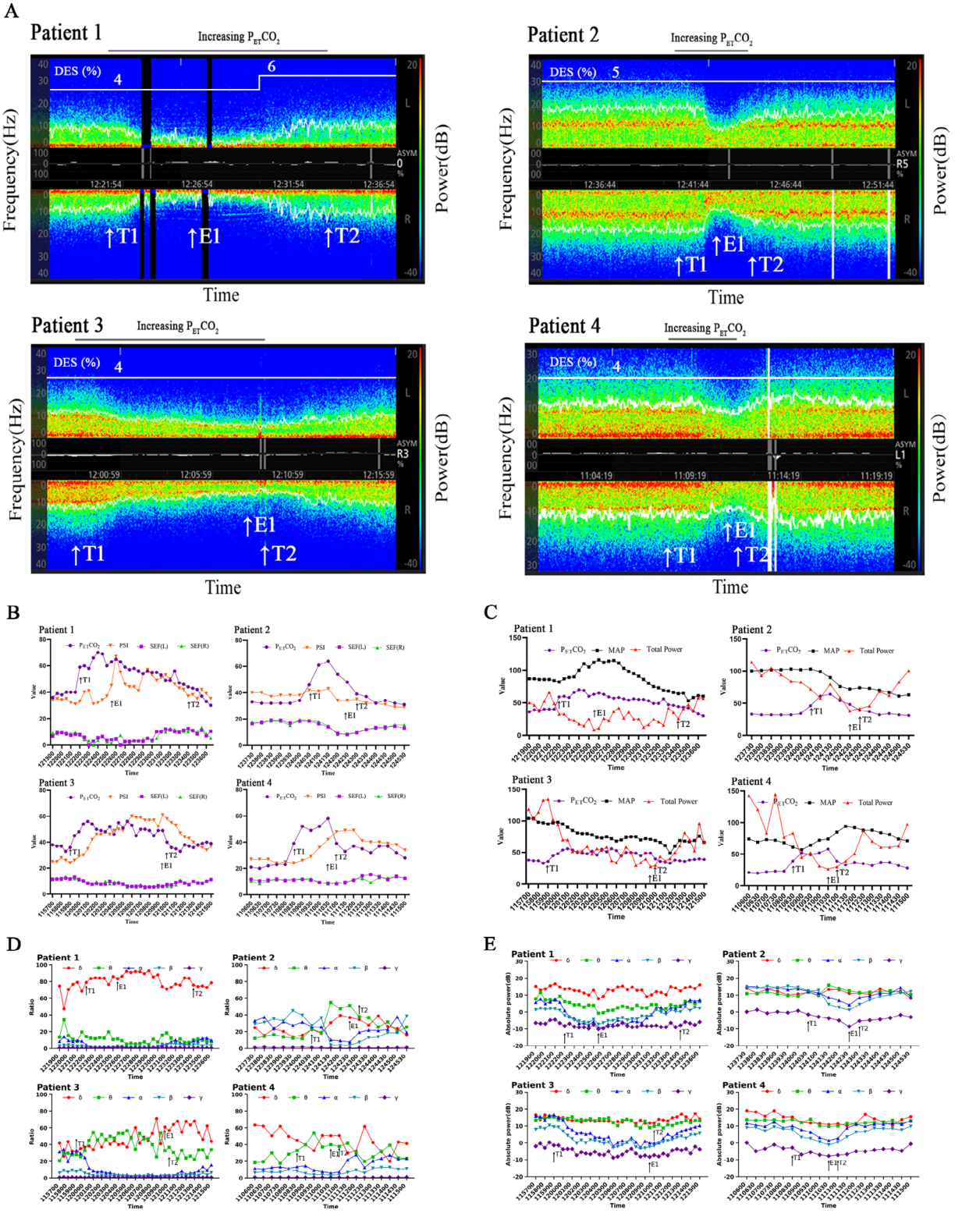

Fig. 1 Changes in the DSA, PSI, SEF, and EEG power during the $P_{ET}CO_2$ increase. (**A**) Changes in the DSA during the increase in $P_{ET}CO_2$. (**B**) Changes in PSI and SEF during the increase in $P_{ET}CO_2$. (**C**) Changes in EEG power and MAP during the increase in $P_{ET}CO_2$. (**D**) Changes in power ratio of each EEG frequency range during the increase in $P_{ET}CO_2$. (**E**) Changes in absolute power of EEG frequency range during the increase in $P_{ET}CO_2$. T1: The time of initial increase in $P_{ET}CO_2$; T2: The time of $P_{ET}CO_2$ return to a normal level; E1: The time of lowest EEG total power. Abbreviations: DSA = density spectral array; PSI = patient sedation index; SEF = spectral edge frequency; MAP = mean arterial pressure

remained unchanged as the $P_{ET}CO_2$ increased. The phase space plot of CO_2 vs. SEF is shown in Fig. 2. The overall clockwise trend when CO_2 was beyond 40mmHg indicated that the elevated CO_2 took precedence over the decrease of SEF in patients 2, 3, and 4. However, it was difficult to determine the direction of patient 1 probably because SEF remained at a low level and even EEG burst suppression occurred when CO_2 was markedly elevated.

After analyzing the EEG total power of the four patients, we found that the EEG total power decreased with the rise of $P_{ET}CO_2$ level, and the total power recovered when the $P_{ET}CO_2$ returned to a normal level (Fig. 1C). We also extracted the raw EEG of this period and compared them with those obtained within 10 min before the event, which showed that the EEG frequency slowed down while the amplitude decreased during this period (Fig. 3).

The absolute power in each frequency range was reduced except in patient 4. Perhaps, the absolute power of patient 4 did not change due to the short duration of EEG depression (Fig. 1E). By further analyzing the power ratio and absolute power of each EEG frequency range during this period, the power ratio of δ band (0.1-<4 Hz) increased, while α band (8–13 Hz) and β band (14–30 Hz) decreased with the rise of $P_{ET}CO_2$. The ratio of the θ band (4-<8 Hz) increased in patients 2, 3, and 4, but decreased in patient 1. The ratio of the γ band (>30 Hz) did not change significantly in any of the four patients [6] (Fig. 1D).

The vital signs were stable before the $P_{ET}CO_2$ changed, and there was no bolus injection of any medications before the occurrence of EEG depression. The mean arterial pressure (MAP) remained above 50 mmHg during the $P_{ET}CO_2$ increase (Fig. 1C). The end-tidal desflurane

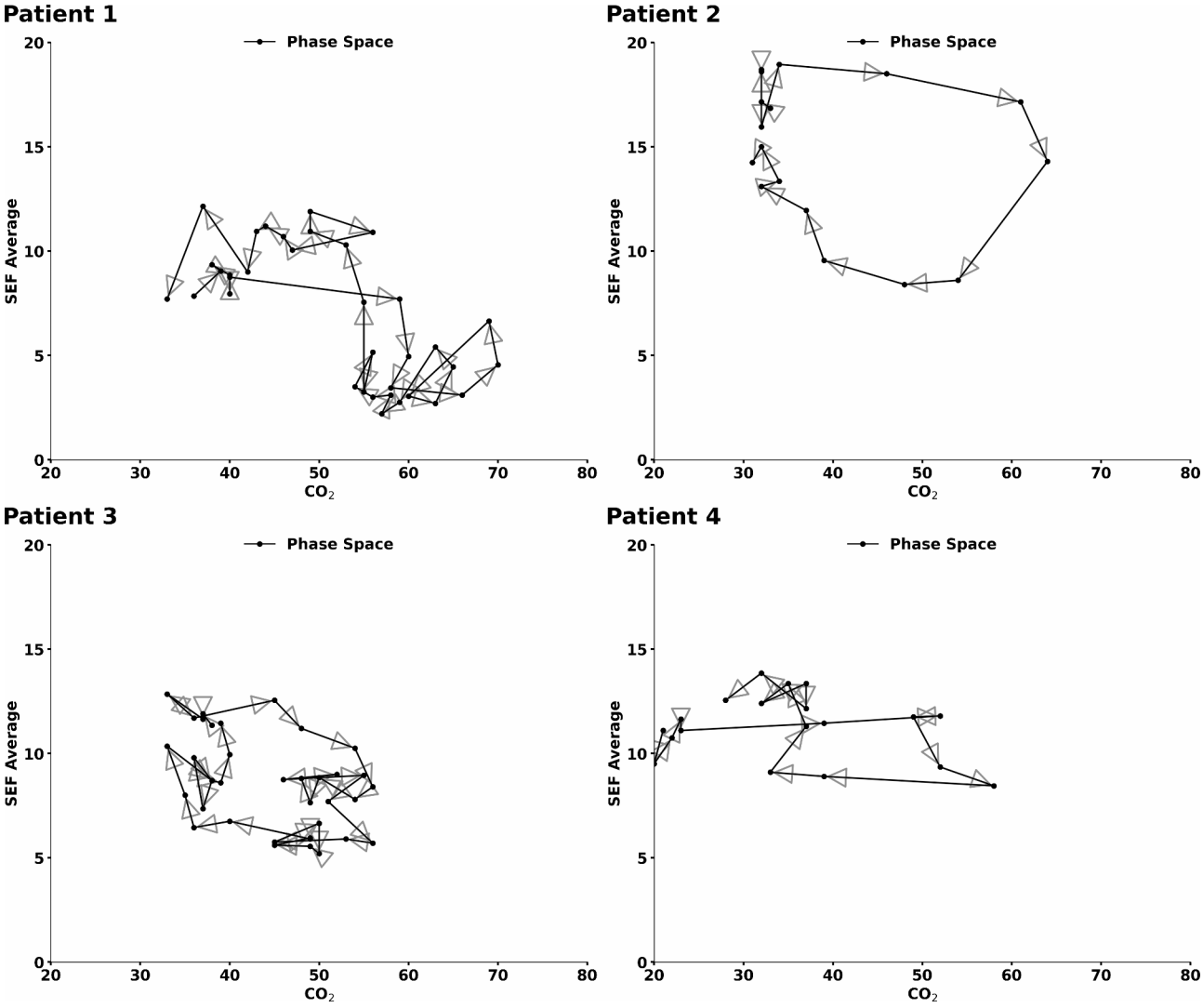

Fig. 2 The phase space plot of CO_2 vs. SEF. T1: The time of initial increase in $P_{ET}CO_2$; T2: The time of $P_{ET}CO_2$ return to a normal level; E1: The time of lowest EEG total power

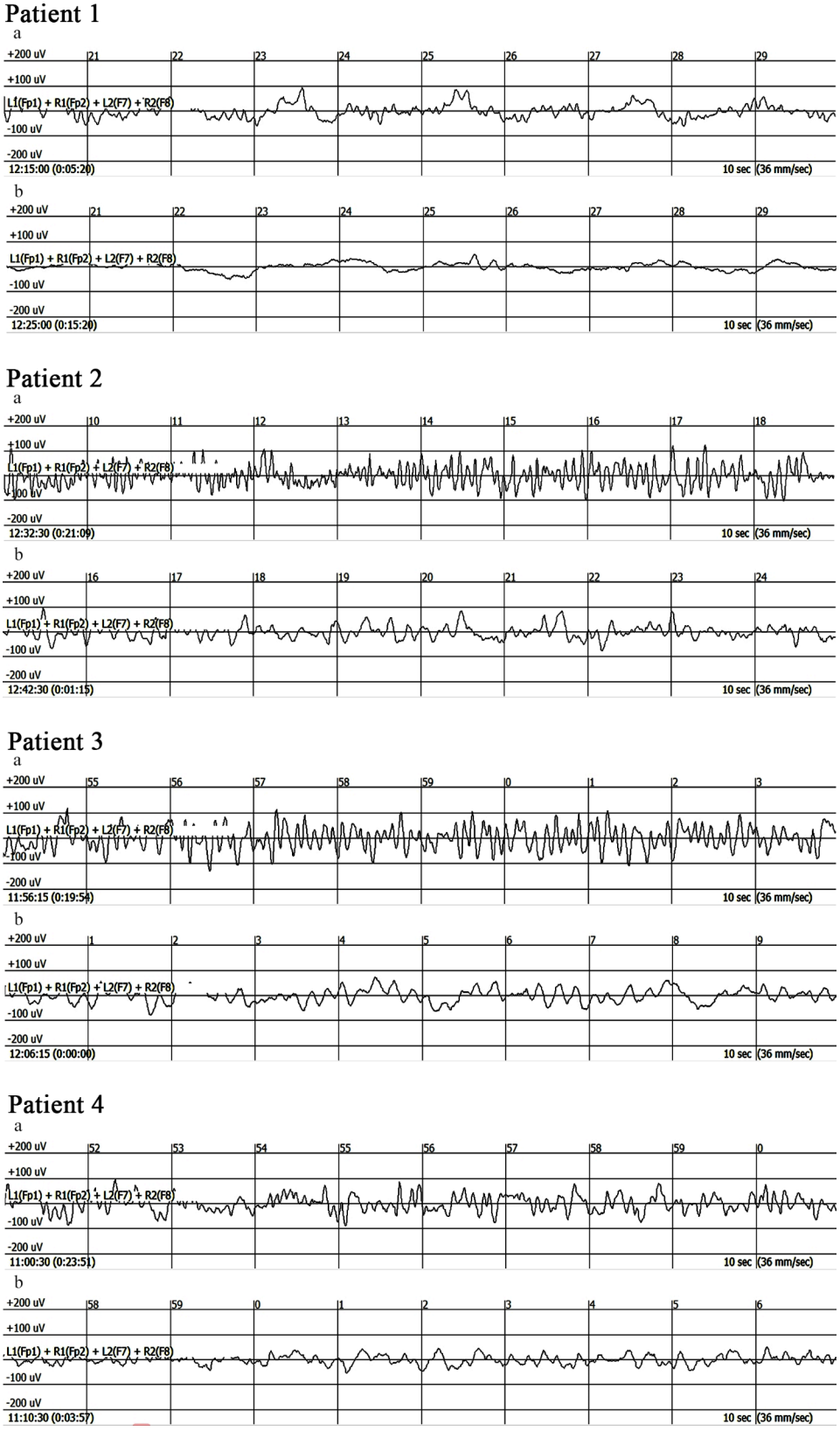

Fig. 3 The comparison of depressed EEG (Fig. 3b) and EEG before 10 min of depression (Fig. 3a). EEG (Fig. 3b) frequency slowed down while the amplitude decreased. **a**: EEG 10 min before E1; **b**: EEG of E1. E1: The time of lowest EEG total power

concentration and remifentanil dosage are summarized in Table 1. Four patients were treated actively when $P_{ET}CO_2$ elevation was found. Therefore, it returned to the normal level in a short time, so the duration of electroencephalographic depression lasted for a very short time. No postoperative delirium (assessed by the Confusion Assessment Method) occurred during the follow-up, and the length of hospital stay was similar to that of the same type of surgical patients.

Discussion and conclusions

The four cases showed that electroencephalographic depression after a sudden increase in $P_{ET}CO_2$ mainly manifested as a slow in EEG frequency, a decrease in the amplitude and power of EEG, a decrease in SEF, and an increase in the proportion of low EEG frequency. PSI changed inconsistently in the four patients.

Electroencephalographic depression is caused by excessive anesthesia depth, severe hypothermia, hypoxia, coma and some special brain diseases, such as neonatal encephalopathy and generalized convulsive seizures (GCS) [7]. However, moderate hypercapnia, as a risk factor leading to electroencephalographic depression, probably has been ignored. Severe hypercapnia can lead to hypercapnic encephalopathy, a decrease in consciousness and CO_2 narcosis. The inhibitory effects of hypercapnia on EEG activity and the central nervous system (CNS) have been investigated in previous studies [3, 8]. Hypercapnia is observed in patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA). It may also occur during the perioperative period, such as during hypoventilation, malignant hyperthermia, pneumoperitoneum, failure of the CO_2 absorber, and the use of a permissive hypercapnia strategy. In our cases, the increase in $P_{ET}CO_2$ almost always occurred during the opening of the portal vein during the hepatectomy process, suggesting that we should closely monitor $P_{ET}CO_2$ to avoid sharp fluctuations in $P_{ET}CO_2$ during this period.

According to the literature, the electroencephalographic suppression caused by hypercapnia is characterized by a decrease in the total power of the EEG and the proportion of the α band and β band, while the proportion of the δ band increases [9, 10]. Our findings confirmed this finding. However, there is no consensus on the change in the θ band. Feng Xu and colleagues [11] reported that under hypercapnic conditions in humans, the θ band did not significantly change. In our case series, the proportion of the θ band increased in patients 2, 3 and 4, but decreased in patient 1. We speculate that the proportion of the θ band may change with the degree of EEG depression, but further studies are needed to confirm this. Each anesthetic induced different burst suppression forms. Bursts induced by volatile anesthetics usually showed higher burst amplitudes and power than propofol. In addition, while bursts induced by isoflurane had the steepest burst slopes, bursts induced by propofol had significantly higher relative power in the α band [12, 13]. Furthermore, at the same extent of anesthesia depth (BIS level), propofol induced BS had a longer duration compared with sevoflurane [14].

The mechanism of electroencephalographic depression caused by hypercapnia remains unclear. One possible mechanism is a decrease in neuronal excitability caused by a decrease in intracranial pH resulting from respiratory acidosis [15]. Brain tissue acidosis might increase extracellular adenosine and decrease glutaminergic transmitter release, leading to a decrease in synaptic transmission and a reduction in neuronal excitability. Another possible mechanism might be related to the increase in cerebral blood flow (CBF) during hypercapnia, which might increase intracranial pressure and subsequently generate brain edema, affecting neuroactivity.

Both the SEF and the PSI can predict the depth of sedation. SEF represents the proportion of 95% EEG power under that frequency. A decrease in the SEF indicates an increase in low-frequency EEG power and deep general anesthesia [16]. Although a review paper pointed out that SEF can be affected by age and some drugs (e.g. remifentanil) [17], our patients were adults between the age of 44 ~ 53. There were no adjustments in remifentanil concentration before the occurrence of EEG depression in our cases. The PSI, a derived feature of raw EEG, significantly covaries with changes in the sedative state under general anesthesia and can be used to predict the level of consciousness. Typically, the SEF and PSI change in the same direction under general anesthesia, but we found that the SEF and PSI change inconsistently with increasing $P_{ET}CO_2$. The possible reason for the PSI paradox is that PSI is susceptible to interference from other signals. Therefore, these sedation indicators may not be accurate for measuring EEG changes during CO_2 accumulation. When evaluating anesthesia levels based on EEG monitoring equipment, if we rely only on the PSI value to measure the sedation depth, the increase in $P_{ET}CO_2$ may misguide us to administer additional anesthetics.

Table 1 The basic parameters 5 min before electroencephalographic depression

	Patient 1	Patient 2	Patient 3	Patient 4
MAP (mmHg)	90	95	98	70
HR (beats/min)	120	68	102	83
SpO_2 (%)	100	100	100	100
Temperature (℃)	35.9	37.0	36.4	35.9
TOFcnt	1	0	0	1
End-tidal DES (%)	3.55	4.30	5.05	4.34
REM (μg. kg^{-1}. min^{-1})	0.2	0.15	0.1	0.1

Abbreviations: MAP = mean arterial pressure; HR = heart rate; SpO_2 = pulse oxygen saturation; TOFcnt = number of trains of four stimulations; End-tidal DES = end-tidal desflurane; REM = remifentanil

This finding suggested that we need to determine the characteristics of EEG changes in CO_2 accumulation. On the other hand, it provides inspiration for us to learn raw EEG, combining PSI and SEF as well as DSA for the measurement of anesthesia depth.

To summarize, our patients showed EEG depression when $P_{ET}CO_2$ suddenly increased. It is mainly manifested as a decrease in SEFs and EEG power, but PSI may increase, resulting in the illusion of light anesthesia at this time. First, we suggest that clinical doctors should be alert to electroencephalographic depression when the $P_{ET}CO_2$ abruptly increases. Second, EEG monitoring devices should be applied in patients with possible hypercapnia. Finally, we must comprehensively interpret the raw EEG, SEF, and DSA data, in addition to PSI values.

This case series has several limitations. First, when $P_{ET}CO_2$ increased, blood gas analysis was not performed at the same time. Although there is good consistency between $P_{ET}CO_2$ and $PaCO_2$, we cannot correctly determine the $PaCO_2$ at present. Second, this is a minor case series, much further data from a controlled setting is needed to confirm these effects. Future prospective studies are needed to confirm the relationship between CO_2 and brain EEG activity.

Abbreviations

EEG	electroencephalogram
ECG	electrocardiogram
TCI	target control infusion
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale
BS	burst suppression
MAP	mean arterial pressure
HR	heart rate
SpO_2	pulse oxygen saturation
TOFcnt	number of trains of four stimulations
End-tidal DES	end-tidal desflurane
REM	remifentanil
$P_{ET}CO_2$	partial pressure of end-tidal carbon dioxide
DSA	density spectral array
PSI	patient sedation index
SEF	spectral edge frequency
GCS	generalized convulsive seizures
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
OSA	obstructive sleep apnea
CBF	cerebral blood flow

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Author contributions
Shikuo Li: Drafting/revision of the manuscript for content, including medical writing for con-tent; major role in the acquisition of data; study concept or design; analysis or interpretation of data.Yuyi Zhao: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpreta-tion of data.Qifeng Wang: Major role in the acquisition of data, including medical writing for content.Xuehan Li: Major role in the acquisition of data, including medical writing for content.Yunxia Zuo: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpreta-tion of data.Chao Chen: Major role in EEG analysisEqual Author Contribution： Shikuo Li and Yuyi Zhao.

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Data availability
The anesthesia records and laboratory data used in the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of West China Hospital Sichuan University (HX-2023-221), and informed consent was waived.

Consent for publication
Written informed consent for publication of this paper was obtained from the patients.

Competing interests
The authors declare no competing interests.

Disclosures
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