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american physiological society
JOURNAL OF APPLIED PHYSIOLOGY

J Appl Physiol 133: 585–592, 2022.
First published July 7, 2022; doi:10.1152/japplphysiol.00199.2022

INNOVATIVE METHODOLOGY

Inducing oscillations in positive end-expiratory pressure improves assessment of cerebrovascular pressure reactivity in patients with traumatic brain injury

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Abstract

The cerebral pressure reactivity index (PRx), through intracranial pressure (ICP) measurements, informs clinicians about the cerebral autoregulation (CA) status in adult-sedated patients with traumatic brain injury (TBI). Using PRx in clinical practice is currently limited by variability over shorter monitoring periods. We applied an innovative method to reduce the PRx variability by ventilator-induced slow (1/min) positive end-expiratory pressure (PEEP) oscillations. We hypothesized that, as seen in a previous animal model, the PRx variability would be reduced by inducing slow arterial blood pressure (ABP) and ICP oscillations without other clinically relevant physiological changes. Patients with TBI were ventilated with a static PEEP for 30 min (PRx period) followed by a 30-min period of slow [1/min (0.0167 Hz)] +5 cmH_2O PEEP oscillations (induced (*i*PRx period). Ten patients with TBI were included. No clinical monitoring was discontinued and no additional interventions were required during the *i*PRx period. The PRx variability [measured as the standard deviation (SD) of PRx] decreased significantly during the *i*PRx period from 0.25 (0.22–0.30) to 0.14 (0.09–0.17) (P = 0.006). There was a power increase around the induced frequency (1/min) for both ABP and ICP (P = 0.002). In conclusion, 1/min PEEP-induced oscillations reduced the PRx variability in patients with TBI with ICP levels <22 mmHg. No other clinically relevant physiological changes were observed. Reduced PRx variability might improve CA-guided perfusion management by reducing the time to find "optimal" perfusion pressure targets. Larger studies with prolonged periods of PEEP-induced oscillations are required to take it to routine use.

NEW & NOTEWORTHY Cerebral autoregulation assessment requires sufficient slow arterial blood pressure (ABP) waves. However, spontaneous ABP waves may be insufficient for reliable cerebral autoregulation estimations. Therefore, we applied a ventilator "sigh-function" to generate positive end-expiratory pressure oscillations that induce slow ABP waves. This method demonstrated a reduced variability of the pressure reactivity index, commonly used as continuous cerebral autoregulation measure in a traumatic brain injury population.

cerebral autoregulation; monitoring; PEEP; PRx; TBI

INTRODUCTION

Cerebral autoregulation (CA) is the cerebral mechanism to adapt cerebrovascular resistance after slow changes in arterial blood pressure (ABP). As CA regulates cerebral blood flow, impairments in CA may result in cerebral hypo- or hyperperfusion. In patients with traumatic brain injury (TBI) with intracranial pressure (ICP) monitoring, CA is commonly calculated as the Pearson correlation between slow changes in ABP and ICP and referred to as the pressure reactivity index (PRx) (1, 2). A positive ABP-ICP correlation (positive PRx) indicates impaired CA, whereas a negative PRx indicates intact dynamic CA (2). CPPopt is the cerebral perfusion pressure (CPP) value at which the CA is best preserved. PRx monitoring

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Submitted 4 April 2022 / Revised 5 July 2022 / Accepted 5 July 2022

can delineate "optimal" CPP (CPPopt) for patients with TBI with curve fitting software at the bedside. A large retrospective observational study showed that deviation from automated CPPopt is associated with increased mortality when CPP is less than "optimal" and with a permanent neurological disability when CPP is greater than "optimal" (3).

Targeting a CPPopt value may, therefore, improve cerebral physiology and clinical outcome. Current strategies for PRx monitoring require prolonged recordings of continuous PRx measurements averaged over time for CA trends or over CPP intervals for CPPopt calculation. Such time-averaging is necessary to reduce variability in PRx due to incoherent, physiological variability of ABP and ICP slow waves. When spontaneous ABP fluctuations are used to calculate PRx, CPPopt cannot be calculated in up to 25% of the monitoring time (4). Inadequate power and reduced variability of spontaneous ABP slow waves have been proposed as a cause of failure to delineate CA and CPPopt (5, 6). In 2012, Brady et al. (13) reduced the variability of PRx, recorded from anesthetized piglets, by inducing 1/min (0.0167 Hz) ABP sinusoidal waves with oscillations of positive end-expiratory pressure (PEEP) during volume-controlled ventilation. So far, the use of PEEP oscillation for the purpose of monitoring PRx has not been applied to patients with TBI to demonstrate feasibility and safety in a clinical intensive care unit (ICU) setting. We sought to reduce the PRx variability using controlled PEEP oscillations offered by repetitively applying the ventilator "sigh function." We tested the feasibility of using this adaptation of the mechanical ventilation to reduce the variability in the PRx calculation. A previous study showed that applying repetitive ventilator sighs was feasible and safe in ICU patients with respiratory insufficiency (8).

In this clinical study, we hypothesized a reduced variability of PRx in adult-sedated patients with TBI with volume-controlled ventilation and significant transmission of PEEP oscillations to ABP and ICP signals and no other relevant physiological changes.

METHODS

Ethical Considerations and Patient Selection

A single-center, observational prospective study was performed between May 2020 and November 2021. Our local ethical committee approved monitoring and data collection (METC 16-4-243). Written proxy informed consent was obtained for each subject. Adult ($\geq$ 18 yr old) patients with TBI with ICP monitoring were screened for inclusion within 48 h after ICU admission. Exclusion criteria were moribund (neurological) status, primary decompressive craniectomy, significant thoracic trauma, ICP $>$ 22 mmHg, and PEEP $>$ 12 cmH_2O. The management of our patients is in line with the recently published tier-based TBI consensus treatment protocol (9). Parenchymal ICP probes (NEUROVENT-TEMP, RAUMEDIC, Helmbrechts, Germany) were used in all patients. The patients were not participating in the COGiTATE intervention study (4).

Ventilation Strategy

For this study, the ventilation mode was changed from Bilevel Positive Airway Pressure (BiPAP) to Intermittent Positive Pressure Ventilation (IPPV) using settings that maintained similar minute ventilation (MV), PEEP, and FI_{O_2} values (Evita XL or Infinity V500 ventilator, Dräger, Lubeck, Germany). IPPV was applied to guarantee unchanged MV (and Pa_{CO_2} levels) during PEEP oscillation application. Baseline PEEP levels were at least 5 cmH_2O with 100% endotracheal tube compensation and AutoFlow option turned on. Nursing interventions (like turning or suctioning) were kept to a minimum during the observation periods. A baseline period of 30 min (named PRx period) was followed by a cyclic PEEP oscillation period (named induced *i*PRx period) of 30 min. As a safety precaution, the sigh function had to be switched off (and discontinuation of the study) when peripheral oxygen saturation (Sp_{O_2}%) decreased below 92% for 1 min or ICP $>$ 25 mmHg or CPP $<$ 50 mmHg or CPP $>$ 100 mmHg for more than 5 consecutive minutes.

Sigh Settings on the Ventilator to Generate Cyclic PEEP Oscillations

The ventilator has the option to apply sighs of different repeatability, duration and intensity, offered by the following settings: number of sigh cycles, interval repeat time (s), and PEEP-sigh levels (cmH_2O). When the number of cycles exceeds the interval period, the expiration pressure sensor sets the new PEEP level. Consequently, the machine pressure changes and the expiration valve opens to end up with the new set PEEP value for the duration of the interval period (personal communication by Dräger Company).

As in Brady et al. (13), we intended to retrieve slow oscillations of 0.0167 Hz (1/min) with limited intensity ($+5$ cmH_2O). This oscillation frequency falls within the PRx calculation frequency range (0.003–0.05 Hz) and was shown to be an optimal frequency for measuring PRx in a piglet model (10). Therefore, the settings were set per patient (without any spontaneous breathing effort due to deep sedation) as follows: the number of sigh cycles as the ventilator breathing frequency per minute divided by two, the interval repeat time as 30 s, and the sigh level on 5 cmH_2O (on top of the applied baseline PEEP level).

Data Collection

The following patient characteristics were collected: sex, age, pupil reactivity, the best Glasgow coma scale motor score before ICU admission, presence of major extracranial injuries (11), the Marshall computed tomography admission score (12), the time between the estimated time of injury and start (*i*)PRx period and the 6-month Glasgow Outcome Scale Extended (GOSE). We collected signals at a sample rate of 250 Hz including ABP (mmHg), ICP (mmHg), heart rate (HR, /min); electrocardiography (ECG, μV), end-tidal carbon dioxide (Et_{CO_2}, kPa), heart rate (HR; /min), and peripheral oxygen saturation (Sp_{O_2}, %). The data were collected using intensive care monitoring (ICM+) software (Cambridge Enterprise, University of Cambridge, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). Before the PRx- and after the *i*PRx period, the ventilator settings (PEEP, cmH_2O), tidal volume per body weight (VT, mL/kg), dynamic lung compliance (Cdyn, mL/cmH_2O), MV (L/min), fraction of inspiratory oxygen (FI_{O_2}, %), and arterial blood gas (ABG,

Table 1. *Baseline patients' characteristics and outcome results (n = 10)*

Number of Patient with TBI	Sex, Male	Age, yr	Fixed and Dilated Pupils at Admission	GCS-Motor pre-ICU Admission	Extracranial Trauma Presence*	Marshall CT-Score on Admission Scan†	The Period Between Estimated Time of Injury and Start PRx Period (h)	GOSE
1	Yes	38	No	5	No	Diffuse injury (II)	41	NA§
2	Yes	68	No	6	No	Diffuse injury (II)	26	Dead
3	Yes	27	No	NA	Yes	Diffuse injury (I)	14	8
4	Yes	32	One	1	Yes	Nonevacuated mass lesion (VI)	44	Dead
5	Yes	32	No	6	No	Nonevacuated mass lesion (VI)	81‡	Dead
6	Yes	20	No	1	Yes	Diffuse injury (II)	48	Dead
7	Yes	19	No	6	Yes	Diffuse injury (I)	6	8
8	Yes	18	No	4	No	Nonevacuated mass lesion (VI)	28	4
9	Yes	68	No	3	No	Evacuated mass lesion (V)	14	Dead
10	Yes	32	No	5	Yes	Nonevacuated mass lesion (VI)	23	5

The baseline and patient characteristics of the included n = 10 patients with TBI. *Extracranial trauma was defined as requiring hospital admission on its own right (11); †Marshall CT-score classification score (12); ‡a patient with secondary deterioration of consciousness. The patient was enrolled within 48 h after the start of ICP monitoring; §lost to follow up. CT, computed tomography; GCS-motor, Glasgow coma scale motor score; GOSE, Glasgow outcome scale extended; ICP, intracranial pressure; NA, not available; TBI, traumatic brain injury.

including arterial oxygen saturation (Sa_{O_2}, %), pH, carbon dioxide tension (Pa_{CO_2}, kPa), and oxygen tension (Pa_{CO_2}, kPa) were noted.

Pressure Reactivity Index Data Collection

PRx was real time calculated by the ICM+ software as the moving (80% overlap) Pearson correlation between 10-s mean values of ABP and ICP over a 300-s window (30 data points) to capture slow cyclic waves between 0.003 (300 s) and 0.05 (20 s) Hz (2). PRx values were sampled every minute and exported for further retrospective analysis. The first 4 min were removed for both the baseline (PRx) and study (*i*PRx) periods to correct the 80% overlap due to moving average application. The mean PRx and associated standard deviation (SD) over the remaining 26-min periods were calculated for each patient and used for further statistical analysis.

Data Analysis

Raw ABP, ICP, ECG, and Et_{CO_2} signals were exported from the bedside ICM+ software. The signals were visually inspected and artifacts were removed. Missing ABP values from data gaps shorter than one heartbeat were removed. ABP, HR, ICP, CPP, and Et_{CO_2} were averaged for each 30-min study period. For the *i*PRx period, we calculated the average difference in MAP between the peak and nadir of the PEEP oscillation. First, we averaged the ABP values over 10 s to calculate the MAP. We then calculated the peak (maximum) and nadir (minimum) of the MAP using the MATLAB function *findpeaks*. The minimal peak distance was set at 30 s (to capture each peak and nadir) and the minimal amplitude of the peak height at 1 mmHg (to exclude detection of small peaks). The obtained difference between maximum and minimum value per minute

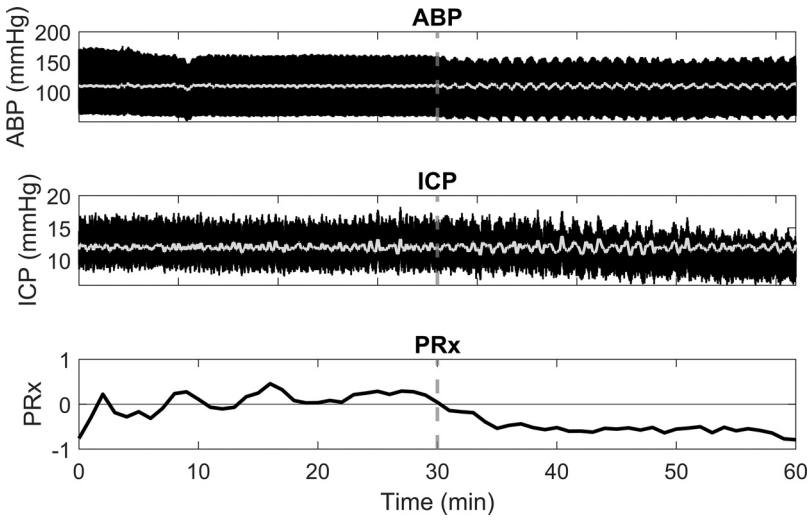

Figure 1. Data recording (n = 1 patient) showing reduced variability of the pressure reactivity index. Example of a data recording from a patient with TBI with stable and negative PRx during the induced cyclic PEEP oscillations PRx period (*i*PRx). The *top* two rows show high-frequency ABP (mmHg) and ICP (mmHg) signals. On top of the high-frequency ABP and ICP signals, slow waves are shown (gray lines). The *bottom* row shows the updated PRx signal during both periods (PRx and *i*PRx). The dotted gray vertical line represents the end of the PRx period and the start of the *i*PRx period. The ABP and ICP signals are stable during the PRx period, whereas both signals show slow waves with a frequency of 1/min (0.0167 Hz) during the *i*PRx period. The mean PRx signal fluctuates around zero during the PRx period (SD of PRx 0.20), whereas during the *i*PRx period, PRx is more stable and decreases to a value of −0.58 (SD of PRx 0.10). ABP, arterial blood pressure; ICP, intracranial pressure; PEEP, positive end-expiratory pressure; PRx, pressure reactivity index; SD, standard deviation; TBI, traumatic brain injury.

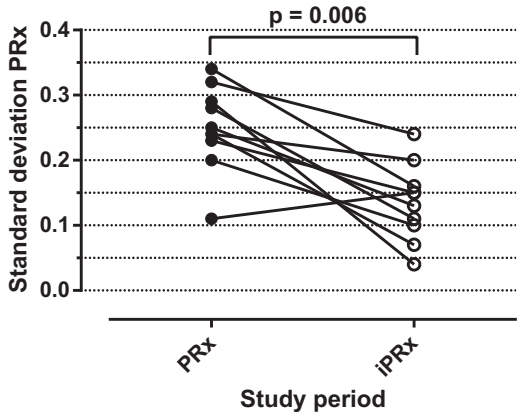

Figure 2. Standard deviation of the pressure reactivity index (n = 10). The variability of the PRx during PRx period (n = 10) and the *i*PRx period (n = 10). The SD for each individual patient with TBI and both study periods is shown. The SD of PRx significantly decreased during the induced PRx (*i*PRx) period with induced cyclic PEEP oscillations, except for one patient. For the cohort, the SD of PRx decreased for the *i*PRx period compared with the PRx period [0.14 (0.09–0.17) vs. 0.25 (0.22–0.30), P = 0.006, Wilcoxon-signed rank test]. *i*PRx, induced pressure reactivity index; PEEP, positive end-expiratory pressure; PRx, pressure reactivity index; SD, standard deviation; TBI, traumatic brain injury.

was averaged for the *i*PRx period. Frequency analysis was applied for studying the transmission of PEEP oscillations to the ABP and ICP signals. The power spectrum density (PSD) was computed over detrended data using Welch's method (333-s rectangular window, 50% overlap) for the frequency range of 0.003–0.05 Hz. We calculated the following for both PRx and *i*PRx periods: *1*) the peak frequency, which is the frequency with the maximum PSD value in the PRx frequency range (0.003–0.05 Hz); *2*) the power calculated for the frequency range around the induced frequency (0.015–0.018 Hz); *3*) the power calculated for the PRx frequency range (0.003–0.05 Hz), and *4*) the relative power (%) defined as the power in the induced frequency range (0.015–0.018 Hz) compared with the power of the PRx frequency range (0.003–0.05 Hz). The data processing and analysis were performed in MATLAB software (v. 2019a, The MathWorks, Natick, MA).

Statistical Analysis

To evaluate reduced PRx variability, we compared the SD of PRx between the PRx and the *i*PRx periods. The transmission of PEEP oscillations to the ABP and ICP signals was studied using PSD calculations. We also compared relevant discrete and continuous physiological variables between the PRx and *i*PRx periods to evaluate potential effects on systemic and brain physiology in our patients with TBI.

Gaussian distribution was not assumed for the sample size in this study. Data are therefore reported as median and the first and third quartile (Q1–Q3). The Wilcoxon-signed rank test was used to compare distributions of variables during the PRx- and *i*PRx period, taking into account the repetitive (paired) measures and nonparametric assumptions. However, no statistics were applied to the mean absolute PRx, as we had no predefined hypothesis about the absolute PRx values itself during the *i*PRx period besides observation. An α of 0.05 was set for statistical significance. The statistical analyses were conducted in GraphPad (GraphPad Prism v. 6.0 for Windows, GraphPad Software, La Jolla, CA, www.graphpad.com).

RESULTS

In the study period, 16 patients with TBI were screened. Two patients underwent an urgent primary decompressive craniectomy, one patient was considered neurologically moribund, one patient had ICP levels > 22 mmHg before the start of the measurement, and no researcher was available for one scheduled measurement. In addition, the first patient was excluded due to an incorrect set number of cycles on the ventilator. The remaining 10 patients were included for data analysis. We included only male patients with 6-month mortality of 50%. Patient demographics can be found in Table 1.

Pressure Reactivity Index Variability

An example of a patient recording is given in Fig. 1. During the pressure reactivity index (PRx) period, the ABP and ICP signals showed very limited slow wave activity, resulting in PRx values fluctuating around zero (i.e., signifying apparent no correlation between the two signals). The slow wave activity however became clearly apparent in the ABP and ICP signals as soon as the cyclic PEEP oscillations started. This in turn led to stable, consistently negative, PRx values indicating intact CA. For the cohort, the SD of PRx decreased significantly during the *i*PRx period compared with the PRx period [0.14 (0.09–0.17) vs. 0.25 (0.22–0.30), P = 0.006]. The cohort change in SD between PRx and *i*PRx is summarized in Fig. 2. In addition, we observed that PRx values became decisively more negative in seven patients, consistent with a presumed intact CA. However, importantly, in one patient, PRx numbers increased to a value above 0.25 and in another patient, the PRx remained positive, signifying impaired CA after PEEP oscillations in two patients (Fig. 3).

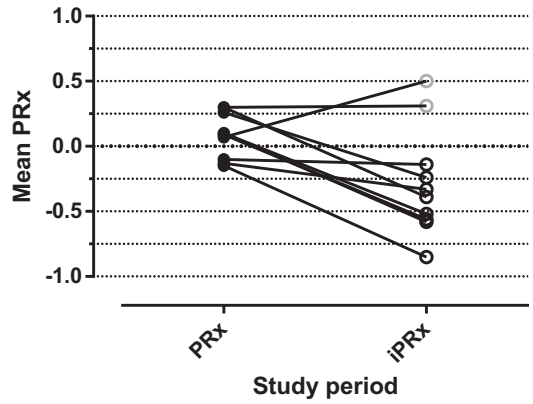

Figure 3. Mean differences in the pressure reactivity index (n = 10). The mean PRx for the PRx period (n = 10) and the *i*PRx period (n = 10). The mean values for each patient with TBI during both study periods are shown. Eight patients show a decrease in mean PRx (all below 0), consistent with intact CA and two patients ended up with positive values (above 0.25 level, consistent with impaired CA, gray dots) during the cyclic-induced PEEP oscillations. CA, cerebral autoregulation; (*i*)PRx, (induced) pressure reactivity index; PEEP, positive end-expiratory pressure; TBI, traumatic brain injury.

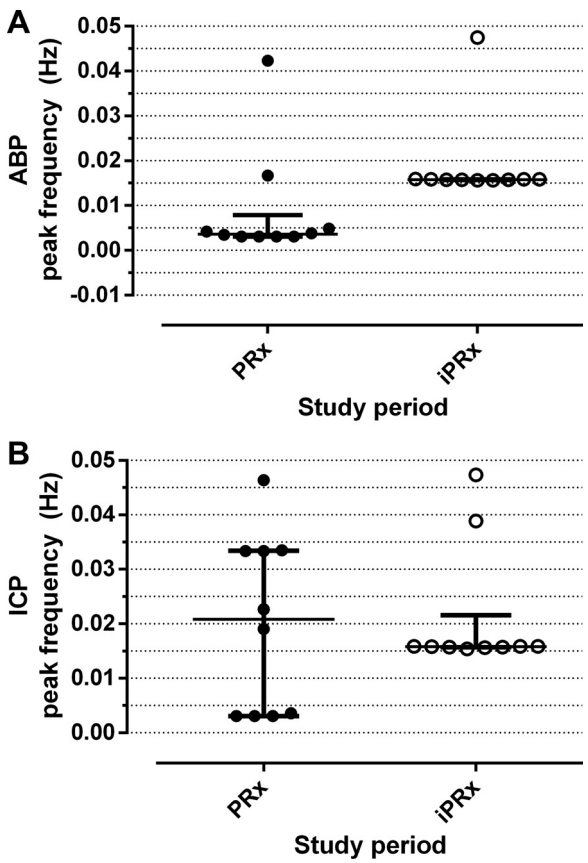

Figure 4. Peak frequency in the arterial blood pressure (ABP) and intracranial pressure (ICP) signals (n = 10). The peak frequency calculated within the frequency range of 0.003–0.05 Hz for the PRx period (n = 10) and the *i*PRx period (n = 10). *A*: the ABP peak frequencies of the ABP signal are shown. The peak frequency transferred to the induced frequency (0.0167 Hz) in nine patients with TBI. *B*: peak frequencies of the ICP signal for the PRx period (n = 10) and the *i*PRx period (n = 10). During the *i*PRx period, the peak frequency of the ICP signal is 0.0167 Hz in eight patients. ABP, arterial blood pressure; (*i*)PRx, (induced) pressure reactivity index; ICP, intracranial pressure; TBI, traumatic brain injury.

Frequency Analysis: Transmission of PEEP Oscillations

Cyclic PEEP oscillations resulted in slow induced cyclic ABP waves in all patients. The peak frequency in the ABP signal transferred to the induced frequency of 0.0167 Hz in nine patients, as shown in Fig. 4*A*. In the ICP signal, the peak frequency transferred in eight patients to 0.0167 Hz frequency, as shown in Fig. 4*B*.

The ABP power within the PRx frequency range significantly increased during cyclic PEEP oscillations [PRx period 1.3 (0.43–2.6) vs. *i*PRx period 7.7 (3.0–9.4) mmHg^2, P = 0.002]. Also, the relative ABP power in this frequency range increased [PRx period 6.4 (4.5–8.3) vs. *i*PRx period 58% (41–78), P = 0.004]. The power of ICP increased in the PRx frequency range [PRx period 0.23 (0.12–0.52) vs. *i*PRx period 0.43 mmHg^2 (0.33–0.62), P = 0.027]. Similarly, the relative power of ICP also increased significantly [PRx period 5.9 (1.8–7.8) vs. *i*PRx period 31% (17–59), P = 0.002] (Table 2).

Physiological Changes after PEEP Cyclic Oscillations

No patients showed clinical deterioration that required discontinuation of the sigh function. In other words, no patients exceeded the predefined safety thresholds. No additional medication and/or change in the ventilator setting was needed during the *i*PRx period. The physiological changes are summarized in Tables 3 and 4. ABP decreased by a clinically insignificant amount during the *i*PRx period [PRx period 80 (75–82) vs. *i*PRx period 78 mmHg (74–81), P = 0.055]. In addition, the difference in peak-nadir MAP during the *i*PRx period was 6.9 (4.4–7.8) mmHg. No changes were observed in median ICP and CPP signals.

An effect of cyclic PEEP oscillations on the respiratory variables was observed. The dynamic lung compliance increased [PRx period 51 (41–61) vs. *i*PRx period 57 mL/cmH$_2$O (46–66), P = 0.002]. Simultaneously, the Pa_{O_2} increased [PRx period 11.6 (10.4–14.6) vs. *i*PRx period 12.4 kPa (9.7–18.8), P = 0.039]. The Pa_{CO_2} and the Et_{CO_2} remained unchanged (Tables 3 and 4).

DISCUSSION

In this clinical study, we demonstrated the effect of slow PEEP-induced cyclic ABP waves on cerebral autoregulation (PRx) estimations in patients with TBI. The main observations are that with cyclic PEEP oscillations *1*) PRx showed a reduced variability, as the SD of the PRx significantly decreased, and an improved demarcation between intact and impaired CA was observed, *2*) a clear transfer from PEEP oscillations to the ABP and ICP signal was seen, and *3*) only limited interaction with other physiological variables of which improved dynamic lung compliance and Pa_{O_2} might be attributed to the cyclic alveolar recruitment maneuver. Based on our data, some observations deserve further discussion.

Change in Pressure Reactivity Index

With the improved transmission of waves during the *i*PRx period, we found a clear indication of positive PRx in two

Table 2. *Frequency analysis for both study periods (n = 10)*

Median (Q1–Q3)	PRx Period	*i*PRx Period	*P* Value*
ABP–power (mmHg^2) (0.015–0.018 Hz)	0.053 (0.020–0.16)	4.9 (0.88–7.0)	0.002
ABP–power (mmHg^2) (0.003–0.05 Hz)	1.3 (0.43–2.6)	7.7 (3.0–9.4)	0.002
ABP – relative power† (%)	6.4 (4.5–8.3)	58 (41–78)	0.004
ICP–power (mmHg^2) (0.015–0.018 Hz)	0.01 (0.0025–0.031)	0.13 (0.10–0.22)	0.002
ICP–power (mmHg^2) (0.003–0.05 Hz)	0.23 (0.12–0.52)	0.43 (0.33–0.62)	0.027
ICP–relative power† (%)	5.9 (1.8–7.8)	31 (17–59)	0.002

*Wilcoxon-signed rank test was used for statistical comparison. †The relative power is computed as the power in the frequency range (0.015–0.018 Hz) compared with the PRx frequency range (0.003–0.05 Hz). ABP, arterial blood pressure; ICP, intracranial pressure; (*i*) PRx, (induced) pressure reactivity index; Q1–Q3, first and third quartile.

Table 3. *Hemodynamic and cerebral parameters during both study periods (n = 10)*

Median (Q1–Q3)	PRx Period	*i*PRx Period	*P* Value*
Mean ABP, mmHg	80 (75–82)	78 (74–81)	0.055
Heart rate, min^{-1}	79 (58–94)	82 (58–95)	0.193
Mean ICP, mmHg	12 (8–18)	12 (9–16)	0.625
CPP, mmHg	69 (64–70)	66 (63–69)	0.375
Et_{CO_2}, kPa	4.3 (3.6–4.7)	4.3 (3.7–4.7)	0.426

*Wilcoxon-signed rank test was used for statistical comparison. ABP, arterial blood pressure; CPP, cerebral perfusion pressure; Et_{CO_2}, end-tidal carbon dioxide tension; ICP, intracranial pressure; (*i*)PRx = (induced) pressure reactivity index; Q1–Q3, first and third quartile.

patients (suggestive of impaired CA) and clear negative PRx in eight patients with TBI (suggestive of intact CA) (Fig. 2). Although only studied in a limited number of patients, our results seem to suggest much improved discrimination of intact from impaired CA with reduced PRx variability at the bedside in a short period (30-min recordings). It is important to note that in general, due to the nature of the PRx calculations, values around 0 may indicate partially functioning pressure reactivity, but at the same time, they could also mean there is insufficient power of waves being transferred between ABP and ICP, thus violating the assumptions and invalidating any interpretations of the PRx. Therefore, a shift in PRx values toward clearly positive and clearly negative, as observed during the *i*PRx period, is highly meaningful.

However, it must also be acknowledged here that these estimates of CA functioning could not be verified against a gold standard. Our findings parallel the experimental results of Brady et al. in a piglet model in 2012. The authors studied slow PEEP-induced ABP waves with programming an additional sine wave component in the ventilator in two experimental conditions. In the first condition, the 10 sedated piglets showed a significant reduced variability of PRx with cyclic PEEP oscillations and a consistent negative PRx. Intact CA is expected in healthy piglets without brain damage and stable hemodynamic and respiratory conditions. Although the metrics to define PRx variability were slightly different, both studies showed a large reduction in PRx variability (44% in patients with TBI and 35% improvement in the piglets, respectively) (13). During the second experimental condition, the piglets were hemorrhaged with deep hypotension showing a sudden and consistent increase in PRx at the lower limit of autoregulation (LLA). The LLA was measured with continuous invasive cortical Doppler flux monitoring. With the cyclic PEEP oscillations turned on, the PRx above LLA was −0.42 (−0.67 to −0.29) and below LLA was 0.32 (0.22–0.43, $P < 0.0004$) (13). We monitored our patients with TBI during hemodynamic stable periods (with unknown LLA), but due to extensive neurological injury, some patients showed PRx values consistent with impaired CA during the cyclic PEEP oscillation period (Fig. 3). Therefore, despite the absence of a gold standard, the animal results of Brady et al. and our clinical results suggest that we have not changed the cerebral physiology, but improved the reliability of the methodology given the reduction in PRx variability.

Transmission Cyclic PEEP Oscillations

Slow PEEP oscillations were transmitted to the ABP signal (Fig. 4*A*), except for one patient. We speculate that this patient had autonomic dysfunction causing an intrinsic dominant oscillation in the ABP (0.045 Hz) signal. We observed a significant increase in absolute and relative ABP power. Comparing the interquartile ranges, the variability seems largely similar between the periods. This suggests a comparable intervention in our patients. In 8 out of 10 patients, the ICP peak frequency transferred to the PEEP-induced frequency (Fig. 4*B*). The transmission of intrathoracic pressure changes to the ICP signal not only depends on extracranial factors but also on complex intracranial factors like brain compliance, CA, and cerebral venous drainage (14, 15).

Interaction with Other Physiological Variables

The absolute ICP, CPP, and Pa_{CO_2} values were not influenced by the cyclic PEEP oscillations. The Pa_{O_2} and the dynamic lung compliance increased after the *i*PRx period. An intermittent increase in PEEP level probably causes increased alveolar pressure, which could result in higher alveolar recruitment in our respiratory stable patients. We only applied low sigh PEEP levels of +5 cmH_2O in all our patients with TBI as applied in Brady et al. (13). Higher PEEP levels might cause lung hyperextension and, together with lower MV and (cervical) venous drainage obstruction, lead to unwanted ICP increases.

Table 4. *Ventilation parameters during both periods (n = 10)*

Median (Q1–Q3)	Pre PRx Period	Post *i*PRx Period	*P* Value*
Arterial blood gas analysis			
pH	7.44 (7.40–7.45)†	7.43 (7.40–7.45)	0.656
Pa_{O_2}, kPa	11.6 (10.4–14.6)†	12.4 (9.7–18.8)	0.039
Pa_{CO_2}, kPa	4.6 (4.2–4.8)†	4.6 (4.3–4.9)	0.668
Sa_{O_2}, %	95 (94–96)	95 (94–96)	0.500
Ventilation parameters			
PEEP, cmH_2O	8 (5–8)	8 (5–8)	NA
Tidal volume per body weight, mL/kg	6.1 (5.8–6.8)	6.0 (5.7–6.7)	0.141
Minute volume, L/min	8.8 (7.9–9.0)	8.7 (7.5–9.1)	0.461
Dynamic lung compliance, mL/cmH_2O	51 (41–61)	57 (46–66)	0.002
Pa_{O_2}/FI_{O_2}, mmHg/%	330 (255–435)†	360 (285–458)	0.281

*Wilcoxon-signed rank test was used for statistical comparison. †One missing component. (*i*)PRx, (induced) pressure reactivity index; Pa_{O_2}, partial pressure of oxygen; Pa_{O_2}/FI_{O_2}, partial pressure of oxygen/ fraction of inspired oxygen ratio; Pa_{CO_2}, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; Q1–Q3, first and third quartile; Sa_{O_2}, arterial oxygen saturation.

Clinical Applicability

We consider our observations relevant for CA monitoring and related therapies in ventilated ICU patients. Previous studies investigated various methods to induce ABP waves, for example, thigh cuff inflation and deflation and cyclic leg raising (16, 17). However, these methods are limited to patients with TBI, because they might cause large and unwanted drops in ABP and/or affect the Pa_{CO_2} levels. Another method applied in the ICU is deep and slow breathing, which has successfully been done in awake (18) and comatose patients for CA assessment. The breathing frequency was decreased to 0.1 Hz (6/min) for a short (<10 min) duration in subarachnoid hemorrhage and patients with TBI (19, 20). However, lowering the breathing frequency is undesirable for long periods, as it results in large tidal volumes when aiming for sufficient MV to control Pa_{CO_2} levels.

Continuous CA assessment is preferred, as reduction in PRx variability may be an appropriate method to improve the availability (yield) of CPPopt calculations to guide cerebral perfusion management (5). Liu et al. attempted to reduce PRx short-term variability by applying the wavelet technique together with coherence filtering instead of the moving Pearson correlation method (21, 22). The authors showed a stronger relationship between the individual deviation of wavelet-based CPPopt values and poor clinical outcomes in patients with TBI compared with classic PRx-based CPPopt (22). However, no amount of filtering will account for the fact that if no sufficient variability in ABP is there, calculation based on it will not yield valid results. On the other hand, PEEP oscillations seem to be able to ensure this critical prerequisite. Therefore, it might be speculated that with PEEP oscillations, reducing PRx variability, the applicability of CA-guided therapy is improved by increasing the yield and decreasing the variability of CPPopt at the bedside (4). This will, however, require prolonged recordings as CPPopt calculation requires at least 4 h of monitoring before the first CPPopt value becomes available (23).

Limitations

We have to acknowledge several limitations of our clinical study. First, we studied the applicability of PEEP oscillations in a selected and limited group of patients. For example, a more heterogeneous sex-balanced population including patients with difficult to control intracranial hypertension and/or accompanying significant thorax trauma. This provides more insight into the applicability of PEEP oscillations. Second, for the assessment of CA estimations, no gold standard is available at the moment at the bedside, with exception of transcranial Doppler, which has not been used. However, Brady et al. (13) validated the use of PRx monitoring to detect the LLA in their animals with the application of PEEP oscillations which is reassuring. Finally, a multimodality approach, including advanced hemodynamic and respiratory measurements, could provide more insight into the complex interplay between heart, lungs, and brain and retrieve more information about the individual PEEP response in our patients.

Conclusions

Cyclic 1/min PEEP oscillations for around 30 min reduces the PRx variability at the bedside in ventilated patients with TBI with ICP levels <22 mmHg. No other clinically relevant physiological changes were observed. Reduced PRx variability might improve cerebral autoregulation-guided perfusion management methodology, but for this prolonged periods with PEEP oscillations of at least 4 h are required.

GRANTS

M. J. H. Aries and J. Tas are supported by a grant from the "Brain Battle" Foundation (HersenStrijd fonds) from the University Maastricht, The Netherlands. E. Beqiri is supported by the Medical Research Council (Grant No. MR N013433-1) and the Gates Cambridge Scholarship.

DISCLOSURES

P. Smielewski. and M. Czosnyka receive part of the licensing fees for multimodal brain monitoring software ICM+, licensed by Cambridge Enterprise Ltd, University of Cambridge, UK. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

J.T., K.D.J.B., I.C.C.v.d.H., U.S., and M.J.H.A. conceived and designed research; J.T., K.D.J.B., and M.J.H.A. performed experiments; J.T. and K.D.J.B. analyzed data; J.T., K.D.J.B., J.L.F., E.B., M.C., S.M.J.v.K., K.M.B., P.S., and M.J.H.A. interpreted results of experiments; J.T. and K.D.J.B. prepared figures; J.T., K.D.J.B., and M.J.H.A. drafted manuscript; J.T., K.D.J.B., J.L.F, E.B., M.C., R.H., I.C.C.v.d.H., S.M.J.v.K., K.M.B., P.S., and M.J.H.A. edited and revised manuscript; J.T., K.D.J.B., J.L.F, E.B., M.C., R.H., I.C.C.v.d.H., S.M.J.v.K., U.S., K.M.B., P.S., and M.J.H.A. approved final version of manuscript.

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