Positive end-expiratory pressure oscillation facilitates brain vascular reactivity monitoring

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Brady KM, Easley RB, Kibler K, Kaczka DW, Andropoulos D, Fraser CD 3rd, Smielewski P, Czosnyka M, Adams GJ, Rhee CJ, Rusin CG. Positive end-expiratory pressure oscillation facilitates brain vascular reactivity monitoring. J Appl Physiol 113: 1362–1368, 2012. First published September 13, 2012; doi:10.1152/japplphysiol.00853.2012.—The pressure reactivity index (PRx) identifies optimal cerebral perfusion pressure after traumatic brain injury. We describe a method to improve PRx precision by induced variations in arterial blood pressure (ABP) using positive end-expiratory pressure (PEEP) modulation (iPRx). Neonatal swine (n = 10) were ventilated with static PEEP and then with PEEP oscillated between 5 and 10 cmH2O at a frequency of 1/min. PRx was recorded as a moving correlation coefficient between ABP and intracranial pressure (ICP) from spontaneous ABP activity (0.05–0.003 Hz) during static PEEP. iPRx was similarly recorded with PEEP oscillation-induced ABP waves. The lower limit of autoregulation (LLA) was delineated with continuous cortical laser Doppler flux monitoring. PEEP oscillation increased autoregulation-monitoring precision. The ratios of median absolute deviations to range of possible values for the PRx and iPRx were 9.5% (8.3–13.7%) and 6.2% (4.2–8.7%), respectively (P = 0.006; median, interquartile range). The phase-angle difference between ABP and ICP above LLA was 161° (150°–166°) and below LLA, −31° (−42° to 12°, P < 0.0001). iPRx above LLA was −0.42 (−0.67 to −0.29) and below LLA, 0.32 (0.22–0.43, P = 0.0004). A positive iPRx was 97% specific and 91% sensitive for perfusion pressure below LLA. PEEP oscillation caused stable, low-frequency ABP oscillations that reduced noise in the PRx. Safe translation of these findings to clinical settings is expected to yield more accurate and rapid delineation of individualized optimal perfusion-pressure goals for patients.

cerebrovascular autoregulation: pressure reactivity: positive end-expiratory pressure: neonatal

CEREBROVASCULAR PRESSURE AUTOREGULATION is a vital, homoeostatic mechanism in the mammalian brain that constrains cerebral blood flow (CBF) during changes in arterial blood pressure (ABP). Dynamic cerebrovascular resistance (CVR), also known as pressure reactivity, mediates autoregulation.

The pressure reactivity index (PRx) was first described in 1997 as a means of monitoring cerebrovascular reactivity by moving correlation between slow waves (0.05–0.008 Hz) of ABP and intracranial pressure (ICP) (9). When autoregulation is intact, vascular constriction occurs during increased ABP, and vascular dilatation occurs during decreased ABP. Dilatation and constriction of the cerebral vasculature due to autoregulation can be trended by ICP monitoring: ICP increases during vasodilation and decreases during vasoconstriction (13). Therefore, positive ABP–ICP correlation (positive PRx) indicates pressure-passive cerebral vasculature, a state seen when cerebral perfusion pressure (CPP) is either excessive or inadequate for cerebrovascular autoregulation. Conversely, negative ABP–ICP correlation (negative PRx) indicates pressure-reactive cerebral vasculature, which is found when CPP is within range of the cerebrovascular autoregulation plateau (3). PRx monitoring can delineate optimal CPP for patients after traumatic brain injury (7, 18). Deviation from optimal CPP, as defined by PRx, is associated with death when CPP is less than optimal and with permanent neurologic disability when CPP is greater than optimal (2).

Current strategies for PRx monitoring require prolonged recordings of multiple PRx measurements averaged across time (for event detection) or across CPP (for CPP optimization) (8). Such averaging is necessary to reduce noise in PRx due to inherent, incoherent, physiologic variability of ABP and ICP slow waves (10). We sought to improve the precision of PRx using controlled periodic slow-wave activity. For clarity, we refer to PRx values observed during the imposition of these controlled slow waves as induced PRx (iPRx). We compared precision of PRx with iPRx recorded from anesthetized neonatal swine by inducing regular ABP oscillations with sinusoidal variations in positive end-expiratory pressure (PEEP) during volume-controlled ventilation.

We further hypothesized that the iPRx would be replicated by continuous measurement of the phase-angle difference between ABP and ICP (hereafter, ABP–ICP phase shift) at the frequency of our imposed PEEP oscillation. Accuracy of the iPRx and ABP–ICP phase shift was assessed against a gold-standard determination of the individual lower limits of autoregulation (LLAs) derived from laser Doppler cortical blood flow monitoring.

METHODS

Anesthesia and surgical preparation. Approval was obtained by the Animal Care and Use Committee at Baylor College of Medicine. Neonatal swine (n = 10) were anesthetized with isoflurane, intubated by tracheotomy, and maintained under 0.8% isoflurane, 50% nitrous oxide, and 50% oxygen. Fentanyl was infused at 50 mcg·kg−1·h−1.
carried by 0.45 normal saline with 5% dextrose and 50 Meq/l sodium bicarbonate added at 4 cc·kg⁻¹·h⁻¹.

Femoral arterial and venous cannulation was performed bilaterally. ABP and central venous pressure (CVP) were transduced with a clinical monitor (GE Healthcare, Little Chalfont, UK).

Craniotomy was performed for placement of an external ventricular drain, transduced as a fluid-filled column. Additional craniotomies were performed over each parietal cortex for placement of bilateral laser Doppler probes (Moor Instruments, Devon, UK). The laser Doppler probe tips were juxtaposed to the underlying cortex. The drain and probes were secured in place with dental cement.

Subjects were given 20 cc/kg normal saline and recovered from surgery for 30 min while maintained under general anesthesia at normothermia (38–39°C) with arterial blood gas measurements of pH 7.37–7.43, pCO₂ 38 – 42 mmHg, and pO₂ 150 – 200 mmHg.

Ventilation. A customized ventilator was used (Impact Instrumentation, West Caldwell, NJ). A primary wave component was applied for ventilation, which was a fixed tidal volume of 50 cc at a rate between 15 and 25 min⁻¹. Volume control ventilation prevented changes in minute ventilation with varying PEEP. A secondary wave component was introduced into the PEEP control. PEEP was oscillated between 5 and 10 cmH₂O in a sine-wave pattern with a period of 60 s.

Signal sampling and pressure reactivity monitoring. Recordings were made from analog outputs of ABP, ICP, CVP, and bilateral laser Doppler flux using an analog-to-digital converter (Data Translation, Marlboro, MA), all sampled at 200 Hz with ICM+ Brain Monitoring Software (Cambridge University, Cambridge, UK, http://www.neurosurg.cam.ac.uk/pages/ICM/about.php), which was also used for subsequent waveform analysis.

PRx and iPRx recording. ABP and ICP were low-pass filtered by recording 10-s mean values. The PRx and iPRx were calculated as a Pearson’s coefficient of 30 consecutive samples, defining the analysis epoch at 300 s. There is no high-pass filter per se, but the PRx and iPRx are calculated from overlapping 300-s epochs updated at 60-s intervals, limiting the contribution of wave activity slower than 0.003 Hz. The difference between the PRx and iPRx is the presence of hemodynamic activity caused by the oscillating PEEP valve.

ABP–ICP phase-shift recording. PEEP oscillation occurred at a frequency of 0.0167 Hz (60 s). ABP–ICP phase shift is the phase-angle difference between ABP and ICP recordings at the frequency of their maximum cross-spectral amplitude between 0.015 and 0.018 Hz to allow a small drift in the PEEP oscillation frequency. The average phase-angle difference was calculated from 300-s epochs (five PEEP wave periods) without overlap in the averaging and was updated at 150 s.

Fig. 1. Comparing pressure reactivity index (PRx; arbitrary units), induced PRx (iPRx), and arterial blood pressure (ABP; mmHg)–intracranial pressure (ICP; mmHg) phase shift (∆φAI; °) in a normotensive, normally autoregulating animal. PEEP, positive end-expiratory pressure (cmH₂O). PEEP oscillated between 5 and 10 cmH₂O after a period of standard ventilation at PEEP 5 cmH₂O. In this subject, slow-wave activity in both the ABP and ICP is erratic until PEEP oscillation begins, at which time, both recordings have low-amplitude waveforms with the input period of 60 s. PRx is unstable and requires a prolonged average to yield a value near 0 (0.12 in this recording). iPRx is more stable (averaging −0.57 in this recording). ABP–ICP phase shift is not meaningful until the PEEP oscillation has been on for 5 cycles, and thereafter, ∆φAI is a stable value near 150°, indicating intact pressure reactivity.

Fig. 2. Recording iPRx and ABP–ICP phase shift as the lower limit of autoregulation (LLA) is crossed. PEEP (cmH₂O); ABP (mmHg); ICP (mmHg); iPRx (arbitrary units); ∆φAI (°); cerebral blood flow (CBF; % baseline). In this subject, induced slow waves at the PEEP oscillation frequency are seen in the ABP tracing during gradual hemorrhage. Native slow-wave activity is evident in the ICP and is slower than the 1/min PEEP oscillation frequency. In this subject, induced slow waves at the PEEP oscillation frequency are seen in the ABP tracing during gradual hemorrhage. Native slow-wave activity is evident in the ICP and is slower than the 1/min PEEP oscillation frequency. A stable, negative PRx and an ABP–ICP phase shift of 150° are seen as ABP is lowered until a critical threshold is crossed, at which time, PRx becomes positive, and ABP–ICP phase shift drops to 50°.
60-s intervals. The absolute value of ABP–ICP phase shift was recorded to prevent phase wrapping at 180°. During intact autoregulation, ABP–ICP phase shift is near 180°, which wraps to negative 180° and causes a false average phase shift of 0°. With the use of the absolute phase shift, the value solves the problem of phase wrapping for the purpose of automating the phase-angle calculation in a monitor. However, it can cause underestimation of the actual phase-angle difference when the value approaches 180°, which could degrade the sensitivity of the ABP–ICP phase shift to detect impaired autoregulation. Each determinant of ABP–ICP phase shift has a corresponding synchronous value of PRx. ABP–ICP phase shift has no meaning without the PEEP oscillation, so it cannot be compared with synchronous traditional PRx measurements. The effects of PEEP oscillation on slow-wave activity in the ABP, ICP, and CVP tracings were quantified by determining the fundamental amplitude of these tracings across the frequency range 0.015–0.018 Hz.

**Precision analysis.** After recovery at normotension and without PEEP oscillation, recordings of PRx were made for 60 min. This was followed by 60 min of PRx and ABP–ICP phase-shift recordings with PEEP oscillation as described (Fig. 1).

Normotensive newborn piglets have robust pressure reactivity and intact cerebrovascular autoregulation (5, 13). The present study therefore compares the precision of the three metrics in the normal state of pressure reactivity. Precision was quantified for each of the three metrics in each subject as median absolute deviation (MAD)/range of possible values (RPV). The RPV used for the PRx and iPRx is −1 to 1. The RPV for ABP–ICP phase shift is 0°-180° due to the absolute value function applied to prevent phase wrapping at 180°.

**Accuracy analysis.** We measured accuracy in iPRx and ABP–ICP phase shift to detect CPP below the LLA. This was done in all of the animals by continuing the recording through hypotension. PEEP oscillation was left on while the subjects were hemorrhaged by syringe-pump withdrawal at a rate of 12% calculated blood vol/h. This rate gives a graded reduction in ABP to demise over 3–4 h (Fig. 2).

Cortical laser Doppler flux recordings during hemorrhage were used to delineate the LLA by a previously published method, commonly used in our lab (3, 4, 13, 15). Flux measurements are plotted across CPP, and the LLA is determined by piece-wise linear regression as the intersection of the two best-fit lines with the lowest residual squared. This analysis identifies for each subject a single CPP, above which static autoregulation is intact and below which static autoregulation is impaired, so the sensitivity and specificity of the dynamic indices iPRx and ABP–ICP phase shift can be derived by separating data above and below this standard CPP demarcation (Fig. 3).

The LLA standard was validated further by verifying a normal static rate of autoregulation across the CPP range of LLA to LLA + 15 mmHg. Laser Doppler plots were normalized to a percentage of baseline (average flux at a mean CPP 50–60 mmHg) and biologic zero flux (average flux at demise). CVR is calculated as CPP divided by cortical blood flow (% baseline flux). The slope of CVR plotted across CPP normalized to baseline is the static rate of autoregulation (%ΔCVR/%ΔCPP). Values of the static rate of autoregulation when autoregulation is intact are close to 1, and values <0.5 indicate impaired autoregulation (17).

**Statistics.** Gaussian distribution was not assumed for the sample size in this study, so nonparametric tests were used for all comparisons, and data are reported as medians and interquartile ranges (median, IQR). An alpha of 0.05 was set for significance. All statistics and graphics were performed with GraphPad Prism version 5 (GraphPad Software, San Diego, CA). PRx without PEEP oscillation and then iPRx and ABP phase shift with PEEP oscillation were measured serially in the same subjects in the first part of the experiment. Therefore, precision was compared for the three metrics, accounting for both subject and metric differences with the Friedman test to account for repetitive measures and nonparametric assumptions.

To delineate the accuracy of iPRx and ABP–ICP phase shift to detect CPP below LLA, both metrics were categorized and averaged in 5-mmHg bins of CPP for each subject (18). CPP was defined as health or disease based on the Doppler-derived determination of LLA. A receiver-operator characteristic (ROC) test was done, rendering an area under ROC curve (AUC) for each metric.

Variables requiring PEEP oscillation (iPRx, ABP–ICP phase shift, and the fundamental amplitudes of slow-wave activity in the ABP, ICP, and CVP recordings) are potentially confounded by changes in cardiac preload. Therefore, we examined all of the PEEP oscillation-
dependent variables across three states of preload—normotension, hypotension above the LLA, and hypotension below the LLA—using the Friedman test to account for repetitive measures and nonparametric assumptions.

Physiologic measurements, blood chemistries, and the ventilating pressures [mean airway pressure (Pawmean); peak inflating pressure (PIP)] were averaged across the following conditions of the protocol: normal ventilation, PEEP oscillation, and hemorrhage. These physiologic measures were compared with the Friedman test for comparison of repetitive measures across the three experimental conditions. ABP was compared between the first two experimental conditions only: normal ventilation and PEEP oscillation with the Wilcoxon matched-pairs signed-rank test. ABP was actively modulated during hemorrhage, so this condition was not included in the comparison of ABP measurements.

RESULTS

Comparing PRx, iPRx, and ABP–ICP phase shift at normal ABP. ABP and ICP recordings before PEEP oscillation revealed sporadic slow-wave activity. The resultant PRx was 0.06 (0.16 to 0.03) and demonstrated variability typical of PRx monitoring. PEEP oscillation caused stable low-amplitude variation in both ABP and ICP waveforms. During PEEP modulation, iPRx became constrained around a significantly more negative value of 0.42 (0.67 to 0.29), more consistent with intact cerebrovascular reactivity (P = 0.03). ABP–ICP phase shift was 150° (142°–160°) during normotension, consistent with intact autoregulation (Fig. 1).

PEEP modulation significantly improved precision of PRx monitoring. The ratios of MAD/RPV for the PRx, iPRx, and

![Fig. 4. Comparing the precision of PRx, iPRx, and ABP–ICP phase shift. Median absolute deviation normalized to the range of possible values (MAD/RPV; %) was reduced in the iPRx (6.2%; 4.2%–8.7%) and ABP–ICP phase shift (6.4%; 4.8–8.4%) when compared with traditional PRx (9.5%; 8.3–13.7%). Box whiskers are median, interquartile, and range; P = 0.006.](image)

![Fig. 5. Normalizing iPRx and ABP–ICP phase shift to the LLA. CPP (mmHg); LLA (mmHg); CBF (% baseline); iPRx (correlation units); ΔφAI (°). A and B: CBF normalized to LLA gives a visual assessment of the validity of the 2 best-fit lines’ method to determine LLA. C: iPRx values above the LLA are negative, and iPRx values below the LLA are positive, indicating impaired vascular reactivity. D: ABP–ICP phase-shift values above the LLA show a large phase-angle difference, indicating intact vascular reactivity. Below the LLA, the phase shift is small, indicating pressure passivity.](image)
ABP–ICP phase shift were 9.5% (8.3–13.7%), 6.2% (4.2–8.7%), and 6.4% (4.8–8.4%), respectively (P = 0.006; Fig. 4).

Comparing iPRx and ABP–ICP phase shift against the LLA. Previous studies comparing PRx against LLA have demonstrated accuracy, and PRx is linked to outcome in multiple studies (3, 6, 13, 18). This study was not designed to detect a difference in accuracy among PRx, iPRx, and ABP–ICP phase shift but rather to report the accuracy obtained with PEEP oscillation. The group LLA was 29.7 mmHg (26.1–36.4 mmHg), and hemispheric differences were small (3.9 mmHg; 1.2–5.9 mmHg). These values are similar to our previously reported LLA determinations in neonatal swine (3–5, 13). Intact autoregulation above LLA was verified by static rate of autoregulation of 0.79 (0.51–0.87), suitable for defining health in a ROC analysis. CBF, iPRx, and PRx are shown normalized to LLA in Fig. 5.

ROCs. Thresholds at 95% sensitivity and 95% specificity for iPRx and ABP–ICP phase shift were determined. For iPRx, a threshold value of ~0.04 was both 95% sensitive and 95% specific for CPP below the LLA. For ABP–ICP phase shift, a phase-angle difference <115° was 95% sensitive for CPP below the LLA, and a phase-angle difference <103° was 95% specific for CPP below the LLA. AUCs were 0.988 for both iPRx and ABP–ICP phase shift (Fig. 6).

**PEEP-dependent variables and cardiac preload.** The transfer of PEEP amplitude to the fundamental amplitudes of the ABP, ICP, and CVP was minimally (but statistically, significantly) influenced by the state of cardiac preload as shown in Table 1. However, the change in fundamental amplitude of these coherent, induced waves did not affect the phase relationship between ABP and ICP, which is the determinant of both iPRx and ABP–ICP phase shift. Therefore, iPRx and ABP–ICP phase shift were not different when comparing the normal preload state and mild hypotension, but hypotension below LLA caused a significantly more positive iPRx, explained by the significantly lower ABP–ICP phase shift (Table 1). ABP–ICP phase shift is artificially elevated by the absolute value function needed to control phase wrapping at the limit of 180°. This causes a false increase in ABP–ICP phase shift when autoregulation is impaired, and the value is near zero but did not impair the ability of ABP–ICP phase shift to discriminate intact from impaired vascular reactivity. To report the actual phase-angle difference between ABP and ICP during impaired autoregulation, a separate, more accurate but impractical calculation of phase angle, using a 360° phase-limited analysis, was done (Table 1).

**Physiologic changes with PEEP oscillation and hemorrhage.** Safe translation of this methodology to clinical practice de-
Table 1. Comparing positive end-expiratory pressure (PEEP) oscillation-dependent variables

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Hypotension &gt; LLA</th>
<th>Hypotension &lt; LLA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔABP</td>
<td>3.2 (2.3–4.2)</td>
<td>4.0 (3.8–5.2)</td>
<td>3.1 (2.0–4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔICP</td>
<td>0.43 (0.25–0.48)</td>
<td>0.51 (0.31–0.60)</td>
<td>0.24 (0.17–0.29)</td>
<td>0.02</td>
</tr>
<tr>
<td>ΔCVP</td>
<td>0.69 (0.56–0.80)</td>
<td>0.74 (0.61–0.84)</td>
<td>0.75 (0.67–0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔPRx</td>
<td>−0.39 (−0.49 to −0.33)</td>
<td>−0.42 (−0.67 to −0.29)</td>
<td>0.32 (0.22–0.43)</td>
<td>0.0004</td>
</tr>
<tr>
<td>ΔΨFAI</td>
<td>150 (142–160)</td>
<td>161 (150–166)</td>
<td>−31 (−43 to 12)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LLA, lower limit of autoregulation (mmHg); ΔABP, fundamental amplitude of the arterial blood pressure (ABP) at the PEEP oscillation frequency (mmHg); ΔICP, fundamental amplitude of the intracranial pressure (ICP) at the PEEP oscillation frequency (mmHg); ΔCVP, fundamental amplitude of the central venous pressure (CVP) at the PEEP oscillation frequency (mmHg); ΔPRx, induced pressure reactivity index with oscillating PEEP; ΔΨFAI, phase-angle difference between ABP and ICP at the PEEP oscillation frequency (°). Values are given as median and interquartile range (IQR). P values shown are with Friedman test for repetitive measures.

DISCUSSION

Cerebral vascular reactivity monitoring has the potential to inform the most fundamental variable of care for patients with brain injury: where to target CPP. Outcome studies have shown that both survival and neurologic outcome are associated with constraint of CPP within this optimal range (2, 18).

To measure vascular reactivity to ABP, a change in ABP must occur, and to monitor vascular reactivity, a repetitive change in ABP must occur. Traditional PRx measurements rely on spontaneous ABP oscillations across a low-frequency bandwidth corresponding to low-frequency waves described in ICP tracings by Lundberg (Lundberg’s slow waves) (19). Functional cerebral vasculature reacts to ABP changes lasting more than 10 s and is too slow to react against ABP changes lasting <4 s (1). Lundberg’s slow waves (typically between 20 s and 200 s) are slow enough to provoke a full cerebrovascular reaction, but they occur with irregular periodicity and amplitude, which is sometimes problematic for pressure reactivity monitoring. In this study, we present a method to monitor cerebrovascular autoregulation by inducing low-amplitude ABP waves with a slow PEEP modulation.

Intrathoracic pressure changes, whether from spontaneous breathing or mechanical ventilation, cause low-amplitude changes in ABP, and previous studies have attempted to use respiratory ABP waves to measure autoregulation (14, 16). However, typical respiratory frequencies are too fast to fully engage the autoregulatory mechanism. As a result, the phase-angle difference between ABP and cerebral blood volume (or flow), measured at the respiratory frequency, can only weakly discriminate intact from impaired autoregulation (~30°–70° intact vs. ~0°–50° impaired) (11, 12, 16). The high-pass frequency response of the autoregulatory mechanism suggests

Table 2. Physiologic measurements by experimental condition

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PEEP Oscillation</th>
<th>Hemorrhage</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>76 (70–83)</td>
<td>72 (60–78)</td>
<td>n/a</td>
<td>0.005</td>
</tr>
<tr>
<td>ICP</td>
<td>9.4 (7.8–12.5)</td>
<td>10.9 (7.1–12.4)</td>
<td>10.3 (6.8–13.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>CVP</td>
<td>4.3 (2.3–5.2)</td>
<td>4.1 (3.4–7.1)</td>
<td>4.0 (3.1–5.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pmean</td>
<td>9.8 (8.4–10.8)</td>
<td>10.8 (9.4–12.5)</td>
<td>10.6 (9.2–11.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>PIP</td>
<td>17.1 (14.3–19.6)</td>
<td>18.3 (15.1–20.3)</td>
<td>16.8 (13.9–18.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>PIPPEEP5</td>
<td>14.4 (12.2–16.4)</td>
<td>19.6 (16.1–20.9)</td>
<td>4.0 (3.1–5.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>PIPPEEP10</td>
<td>19.6 (16.1–20.9)</td>
<td>74.7 (7.43–7.49)</td>
<td>38 (33–41)</td>
<td>0.07</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 (7.34–7.45)</td>
<td>7.46 (7.43–7.49)</td>
<td>7.47 (7.42–7.48)</td>
<td>0.07</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>39 (36–53)</td>
<td>39 (36–43)</td>
<td>38 (33–41)</td>
<td>0.7</td>
</tr>
<tr>
<td>PaO₂</td>
<td>220 (200–246)</td>
<td>229 (215–263)</td>
<td>241 (216–256)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hb</td>
<td>9.8 (7.5–10.5)</td>
<td>9.7 (8.4–11.1)</td>
<td>7.5 (6.7–8.4)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Na</td>
<td>141 (139–142)</td>
<td>140 (138–143)</td>
<td>139 (136–143)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Values are presented as median and IQR. ABP (mmHg); ICP (mmHg); CVP (mmHg); Pmean, mean airway pressure (cmH₂O); PIP, peak inflating pressure (cmH₂O); PIPPEEP5, PIP at the nadir of the PEEP cycle during PEEP oscillation (cmH₂O); PIPPEEP10, PIP at the peak of the PEEP cycle during PEEP oscillation (cmH₂O); PaCO₂, arterial CO₂ tension (mmHg); PaO₂, arterial O₂ tension (mmHg); Hb, arterial blood hemoglobin concentration (mg/dl); Na, arterial blood sodium concentration (Meq/l); n/a, not applicable. *P values are obtained from the Friedman test, except for ABP, which is obtained from the Wilcoxon matched-pairs signed-rank test.
that improved differentiation between passive and reactive states can be obtained by decreasing the respiratory rate. Lewis et al. (14) slowed spontaneous respiration to a rate of six breaths/min in adult volunteers. Under these conditions, the phase-angle difference between ABP and middle cerebral artery flow velocity was found to be highly correlated to a synchronously obtained correlation method inclusive of Lundberg’s slow waves. Slow breathing methods are difficult to apply in pediatric practice, since respiratory rates are routinely set between 15 and 30 breaths/min.

The method presented here effectively separates the respiratory function of the ventilator from the autoregulation interrogation function by programming an additional wave component into the ventilator. This additional wave component was adjusted to be slower than respiration and within the frequency range of Lundberg’s slow waves. Consistent, low-amplitude ABP and ICP waves resulted, persistent across a range of cardiac preload states. The phasic relationship between these coherent ABP and ICP waves was predictive of the state of autoregulation. Intact and impaired autoregulation was distinguished by a separation of 192° phase-angle difference between ABP and ICP (128°–204°, median, IQR).

One limitation of this study is the use of 50-cc tidal volumes, the lowest possible setting of volume-mode ventilation provided by the ventilator. In a 3-kg piglet, a 50-cc tidal volume is 17 cc/kg, which is larger than traditional tidal volumes of 8–12 cc/kg. Large tidal volumes did not cause excessive inflation pressures. Nonetheless, there is room to question the reproducibility of our results during ventilation with lower tidal volumes.

In conclusion, the introduction of PEEP modulation to induce a persistent, low-frequency ABP wave was safely applied in a neonatal swine model. PEEP modulation, by causing a consistent ABP slow wave, increased the precision of traditional PRx monitoring. Approximately 35% of the noise at baseline was removed when comparing PRx with iPRx. The accuracy of iPRx and ABP–ICP phase shift to discern the LLA is reported with near-infrared cerebrovascular autoregulation using near-infrared spectroscopy. Stroke 38: 2818–2825, 2007.

REFERENCES