The frequency response of cerebral autoregulation

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Fraser CD 3rd, Brady KM, Rhee CJ, Easley RB, Kibler K, Smielewski P, Czosnyka M, Kaczka DW, Andropoulos DB, Rusin C. The frequency response of cerebral autoregulation. J Appl Physiol 115: 52–56, 2013. First published May 16, 2013; doi:10.1152/japplphysiol.00068.2013.—The frequency-response of pressure autoregulation is not well delineated; therefore, the optimal frequency of arterial blood pressure (ABP) modulation for measuring autoregulation is unknown. We hypothesized that cerebrovascular autoregulation is band-limited and delineated by a cutoff frequency for which ABP variations induce cerebrovascular reactivity. Neonatal swine (n = 8) were anesthetized using constant minute ventilation while positive end-expiratory pressure (PEEP) was modulated between 6 and 0.75 cycles/min (min−1). The animals were hemorrhaged until ABP was below the lower limit of autoregulation (LLA), and PEEP modulations were repeated. Vascular reactivity was quantified at each frequency according to the phase lag between ABP and intracranial pressure (ICP) above and below the LLA. Phase differences between ABP and ICP were small for frequencies of >2 min−1, with no ability to differentiate cerebrovascular reactivity between ABPs above or below the LLA. For frequencies of <2 min−1, ABP and intracranial pressure (ICP) showed phase shift when measured above LLA and no phase shift when measured below LLA [above vs. below LLA at 1 min−1: 156° (139–174°) vs. 30° (22–50°); P < 0.001 by two-way ANOVA for both frequency and state of autoregulation]. Data taken above LLA fit a Butterworth high-pass filter model with a cutoff frequency at 1.8 min−1 (95% confidence interval: 1.5–2.2). Cerebrovascular reactivity occurs for sustained ABP changes lasting 30 s or longer. The ability to distinguish intact and impaired autoregulation was maximized by a 60-s wave (1 min−1), which was 100% sensitive and 100% specific in this model.

cerebrovascular autoregulation; neonatal; frequency

CEREBROVASCULAR PRESSURE REACTIVITY is the change in cerebral vascular tone that constrains cerebral blood flow during changes in arterial blood pressure (ABP). As long as ABP is maintained above a lower limit of autoregulation (LLA), pressure reactivity mitigates injurious changes in cerebral blood flow caused by changes in cerebral perfusion pressure. Although other mechanisms of cerebral blood flow regulation exist, including CO2-reactivity and flow-metabolism coupling, pressure reactivity is distinct from these and is the mediator of cerebrovascular pressure autoregulation. If ABP falls below the LLA, pressure reactivity fails, and cerebral blood flow will fluctuate as a function of ABP (7, 13, 19).

The pressure reactivity index (PRx) has been used to quantify cerebrovascular pressure reactivity as a moving correlation between slow waves of ABP and intracranial pressure (ICP) (8). The degree of reactivity and passivity of the cerebral vasculature, as measured with the PRx, has been demonstrated to relate to patient outcome after traumatic brain injury (1, 20). The PRx carries assumptions that ICP changes within the slow-wave bandwidth of PRx analysis (0.05–0.003 Hz) are caused by vascular constriction and dilation, which are in turn provoked by spontaneous excursions of ABP within that low-frequency spectral range. For instance, a substantial phase lag between slow waves of ABP and ICP results in a negative PRx and is interpreted as reactive, healthy vasculature. By contrast, a slow wave of ABP that is accompanied by a synchronous, or in-phase, wave of ICP results in a positive PRx, which is interpreted as passive, impaired cerebral vasculature.

Imprecision in the PRx measurements occurs when these assumptions are confounded (9). Irregular and spontaneous low-frequency ABP activity necessitates prolonged PRx recording times and strategies of averaging multiple measurements to yield accurate information. For time-sensitive clinical scenarios, it is desirable to have information about pressure autoregulation more rapidly. We have reported a method to increase PRx precision using induced, regular, low-amplitude sinusoidal oscillations of ABP, generated by positive end-expiratory pressure (PEEP) modulation in mechanically ventilated subjects (2).

In the present study, we refined the induced-wave method by delineating the optimal frequency of ABP oscillation for the purpose of measuring pressure reactivity. Slower waves increase the time required for monitoring and, in theory, increase vulnerability to ICP changes unrelated to pressure reactivity that confound the PRx measurements. In the clinical practice of intensive care management, medical interventions such as ventilator changes, endotracheal suctioning, sedation, or even positioning will fall into this category. Faster waves risk exceeding the bandwidth of the autoregulatory mechanism. Autoregulation has been described as a high-pass filter by Zhang et al., who used transfer function analysis from spontaneous ABP waves to transcranial Doppler showing an increase in phase shift for waves slower than 14 s (0.07 Hz) (22). We hypothesized that such a frequency cutoff exists and can be experimentally measured using frequency-variant controlled oscillations of ABP in a neonatal swine model.

MATERIALS AND METHODS

Anesthesia and surgical preparation. Approval was obtained by the animal care and use committee at the Baylor College of Medicine. Neonatal swine (n = 9) aged 10–14 days, weighing 5.3 kg (4.8–7.0 kg) were anesthetized with isoflurane, intubated by tracheotomy, and

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maintained under 0.8% isoflurane, 50% nitrous oxide, and 50% oxygen. Fentanyl was infused at 50 mcg/h and D5 normal saline with 50 Meq/l sodium bicarbonate was infused at 15 ml/h. High-dose isoflurane (2 MAC), but not low-dose isoflurane (<1 MAC), is believed to ablate cerebrovascular pressure autoregulation and uncouple cerebral blood flow from metabolism (15, 21). However, nitrous oxide and fentanyl have not been shown to produce these effects. For this reason, we have consistently used a supplement of nitrous oxide and fentanyl to humanely anesthetize subjects when evaluating pressure autoregulation with a sub-therapeutic concentration of inhaled isoflurane (3–6).

Femoral arterial and venous cannulation was performed bilaterally. Arterial and central venous pressures were transduced (GE Healthcare, Little Chalfont, UK). Craniotomy was performed for placement of an external ventricular drain used to measure ICP. Additional craniotomies were performed over each parietal cortex for placement of bilateral laser-Doppler probes (Moore Instruments, Devon, UK). The laser-Doppler probe tips were advanced through dural incisions and apposed to the surface of the cortex. The drain and probes were secured in place with dental cement. Arterial, intracranial, and central venous pressures, as well as laser-Doppler signals were sampled at 200 Hz by using an analog-to-digital converter (Data Translation, Marlboro, MA) and ICM plus software (Cambridge University, Cambridge, UK; http://www.neurosurg.cam.ac.uk/icmplus).

Ventilation and PEEP modulation. A customized ventilator (Impact Eagle Transport Ventilator, Coviden, Boulder, CO) was used, and a primary wave component was applied for ventilation with a fixed tidal volume of 50 ml at a rate between 15 and 25 min⁻¹, until arterial P CO₂ (P a CO₂) was between 35 and 45 Torr. Volume controlled ventilation was used to prevent changes in minute ventilation, whereas PEEP was varied to manipulate intrathoracic pressure. PEEP was sinusoidally oscillated between 5 and 10 cmH₂O at frequencies modulated incrementally between 0.75 and 6 min⁻¹ (0.0125–0.1 Hz; see Fig. 1). Because minute ventilation is held constant by the primary respiratory wave component, P a CO₂ removal does not vary with the slower PEEP modulation, but the resultant peak inflating pressures are variant across changes in PEEP. We previously showed that the range of peak inflating pressures caused by PEEP modulation between 5 and 10 cmH₂O are within safe clinical boundaries. It is necessary to maintain constant minute ventilation in this way to prevent CO₂ reactivity in the cerebral vasculature from confounding the measurements of pressure reactivity. Using this mode of fixed minute ventilation and PEEP modulation, three wave components occur in the ABP tracing: at the cardiac cycle frequency (150 min⁻¹; 2.5 Hz), at the frequency of the primary ventilation rate (18 min⁻¹; 0.3 Hz), and at the rate of PEEP modulation, which varied between 0.75 and 6 min⁻¹ (0.0125–0.1 Hz).

After physiological recordings were obtained at each increment of PEEP modulation frequency, the animals were hemorrhaged using a syringe pump at a rate of 24% blood volume/h until a decrement was observed in the the laser-Doppler recording, indicating impairment of cerebrovascular autoregulation. Once cerebral blood flow was observed to be dysautoregulated, the hemorrhage was stopped. PEEP was then modulated again at incremental frequencies between 0.75 and 6 min⁻¹ (0.0125–0.1 Hz; see Fig. 2).

A post hoc analysis of the laser-Doppler data plotted as a function of cerebral perfusion pressure was used to delineate a discrete LLA for each subject using piecewise linear regression (17). The cohort LLA was 39 mmHg (28–45 mmHg), which is consistent with precedent work in neonatal swine (12, 16). The physiological recordings taken below the LLA serve as a negative control for comparison with the recordings taken before hemorrhage, so data that were not clearly above or below this demarcation were deleted from analysis (one subject).

**ABP-ICP phase shift calculations.** The primary study variable of this experiment was the phase lag between ABP and ICP at the various frequencies of PEEP modulation. We demonstrated previously that the phase angle difference between ABP and ICP is 160° when vascular reactivity is intact and near 0° when vascular reactivity is impaired. The ABP-ICP phase shift was calculated at the frequency of the PEEP oscillation using five PEEP cycles and updated after each cycle by using overlapping recording segments. A single phase angle for each frequency, condition, and subject was rendered by averaging the 17 measurements obtained at each frequency. Oscillations in the ABP and ICP due to respiration (18 min⁻¹) and the cardiac cycle (>150 min⁻¹) were analyzed in the same way using data across the

![Fig. 1](http://jaapl.physiology.org/https://doi.org/10.1152/japplphysiol.00068.2013) Positive end-expiratory pressure (PEEP) modulation frequency is incrementally increased during normotension. PEEP was modulated at varying frequencies between 0.75 and 6 min⁻¹. Arterial blood pressure (ABP; mmHg) and intracranial pressure (ICP; mmHg) were recorded for calculation of the ABP-ICP phase angle difference at each frequency. B: Measurements were taken above the lower limit of autoregulation. Cerebral blood flow (CBF) was measured with laser-Doppler flux (%Baseline) to verify intact autoregulation during the recording. CBF was plotted as a function of cerebral perfusion pressure (CPP = ABP – ICP). Data from the entire experiment are shown with data from A highlighted as dark points. The lower limit of autoregulation is shown, determined by piecewise linear regression. Although a wide range of ABP was experienced during the recording, all data are above this limit of autoregulation and therefore representative of the “intact” state of vascular reactivity.
The Butterworth high-pass filter model was limited to the phase angle difference at frequencies much higher than traditionally used for autoregulation measurements. The intact and impaired phase-shift curves were compared by a two-way ANOVA accounting for both PEEP input frequency and state of autoregulation. Post hoc Bonferroni test was done to compare the phase shifts obtained during intact and impaired autoregulation at each frequency of PEEP input.

RESULTS

Nine animals underwent the protocol, and eight survived to give a full complement of data at every tested PEEP modulation frequency. One subject was missing data at some of the tested frequencies and was excluded from the ANOVA comparing intact and impaired states but was included in the Butterworth filter model to delineate the cutoff frequency of pressure reactivity.

Physiological data from the recordings above and below the LLAs are shown in Table 1. As expected after hemorrhage to failure of cerebrovascular autoregulation, the posthemorrhage data showed lower ABP [65 mmHg (61–68 mmHg) vs. 32 mmHg (30–34 mmHg)], higher blood lactate levels [2.0 mg/dl (1.4–2.3 mg/dl)], and a significant decrement in regional cerebral oxygen saturation (rSO2) [59% (50–65%) vs. 37% (32–45%)] measured on the left hemisphere. Importantly, the hematocrit was not significantly diluted by the hemorrhage protocol, so the decreased cerebral oxygen saturation was most likely due to decreased cerebral blood flow from failed pressure autoregulation and not a change in oxygen carrying capacity.

The phase shifts between ABP and ICP seen at each frequency measured are shown in Table 2. At higher frequencies (i.e., at the cardiac and respiratory cycle frequencies), there is negligible phase shift seen, and there is negligible difference in the phase shift measured on the left hemisphere.
Table 2. ABP-ICP phase angle differences by frequency above and below LLA

<table>
<thead>
<tr>
<th>Frequency, min⁻¹</th>
<th>ABP-ICP Phase Shift Above LLA, °</th>
<th>ABP-ICP Phase Shift Below LLA, °</th>
<th>P Value</th>
<th>AUC of ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>148 (104–169)</td>
<td>87 (62–166)</td>
<td>&lt; 0.01</td>
<td>0.61 (0.29–0.93)</td>
</tr>
<tr>
<td>0.85</td>
<td>156 (139–174)</td>
<td>77 (34–158)</td>
<td>&lt; 0.0001</td>
<td>0.76 (0.32–1.0)</td>
</tr>
<tr>
<td>1</td>
<td>156 (139–174)</td>
<td>30 (22–50)</td>
<td>&lt; 0.0001</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>1.2</td>
<td>143 (129–164)</td>
<td>61 (30–103)</td>
<td>&lt; 0.0001</td>
<td>0.97 (0.89–1.0)</td>
</tr>
<tr>
<td>1.5</td>
<td>126 (121–153)</td>
<td>32 (16–89)</td>
<td>&lt; 0.01</td>
<td>0.97 (0.89–1.0)</td>
</tr>
<tr>
<td>2</td>
<td>99 (76–157)</td>
<td>33 (14–90)</td>
<td>&lt; 0.01</td>
<td>0.84 (0.65–1.0)</td>
</tr>
<tr>
<td>3</td>
<td>41 (16–93)</td>
<td>63 (35–87)</td>
<td>&gt; 0.05</td>
<td>0.53 (0.23–0.83)</td>
</tr>
<tr>
<td>6</td>
<td>40 (24–50)</td>
<td>69 (45–100)</td>
<td>&gt; 0.05</td>
<td>0.84 (0.65–1.0)</td>
</tr>
<tr>
<td>(18) Resp</td>
<td>35 (15–50)</td>
<td>42 (21–153)</td>
<td>&gt; 0.05</td>
<td>0.64 (0.32–0.90)</td>
</tr>
<tr>
<td>(≥150) Pulse</td>
<td>28 (26–35)</td>
<td>38 (23–41)</td>
<td>&gt; 0.05</td>
<td>0.67 (0.39–0.96)</td>
</tr>
</tbody>
</table>

Values are means (range). Phase shifts are presented as median with IQR. P value is obtained from Bonferroni post hoc analysis of two-way ANOVA, and area under curve (AUC) of receiver operator characteristic analysis (ROC) is shown with 95% confidence interval.

between phase shifts measured above vs. below the LLA. Starting at 2 min⁻¹ (0.03 Hz) and increasing with frequency decrements, a phase shift is observed in the animals with CPP above LLA, and this shift is not observed in the control measurements obtained below LLA.

The frequency-response of the ABP-ICP phase shift was used to demonstrate the high-pass filter function of pressure autoregulation and rendered a cutoff frequency of 1.8 min⁻¹ (95% confidence interval of 1.5–2.2) when fit to the Butterworth model [0.03 Hz (0.025–0.036 Hz)] (see Fig. 3).

Maximal phase shift was seen at a frequency of 1 min⁻¹ (0.017 Hz), where sensitivity and specificity of the ABP-ICP phase angle to detect impaired autoregulation were both 100% for a threshold greater than 95°. The phase shift responses were significantly more changed across frequency in the intact autoregulation data set compared with the impaired autoregulation data set (P < 0.001 by two-way ANOVA for both frequency and state of autoregulation).

**DISCUSSION**

This study utilizes a new technique of PEEP manipulation to induce ABP oscillations for delineating the frequency response of pressure-autoregulation in the piglet brain. Using this technique, we demonstrated the high-pass filter function of pressure-autoregulation, which is unresponsive to high-frequency ABP oscillations but reacts to sustained ABP oscillations. Specifically, in this neonatal swine protocol, we demonstrated a cutoff frequency at 1.8 min⁻¹ (0.03 Hz), above which pressure autoregulation is not engaged. Furthermore, we demonstrated a maximal response at 1 min⁻¹ (0.017 Hz), and oscillations at this frequency rendered phase shifts between ABP and ICP with 100% sensitivity and specificity for detecting impaired autoregulation.

The findings of this study have relevance to the ongoing effort to develop clinically viable monitors of pressure autoregulation. Based on these data, the ideal frequency of ABP oscillation for autoregulation monitoring would be 1 min⁻¹ (0.017 Hz). ABP oscillation at the respiratory frequency has been attractive historically for measurement of pressure autoregulation because of consistent regularity during mechanical ventilation (10, 11, 14, 18). However, our data suggest that pressure reactivity is not consistent at this frequency, and measurement of the transfer function between ABP and cerebral blood flow and/or volume at this frequency will not reliably delineate the state of autoregulation. The degree of overlap comparing intact and impaired subjects at these high frequencies is too great to have confidence in metrics at this frequency for prospective clinical decision-making regarding CPP management.

Interestingly, our data provide further validation for the PRx, which has previously been shown to effectively delineate perfusion pressures that optimize outcome after traumatic brain injury. The PRx is a time-domain analysis; however, filters are used to remove pulse and respiratory frequency variations, and the analysis epochs are typically 4–5 min (7, 8). Therefore, the PRx is measuring positive and negative correlations between ABP and ICP across a range of frequencies that is well below the cutoff frequency of 1.8 min⁻¹ (0.03 Hz) and inclusive of the optimal frequency of 1 min⁻¹ (0.017 Hz).

Frequencies lower than 1 min⁻¹ (0.017 Hz) showed some deterioration in ability to distinguish intact from impaired states of autoregulation. This may be due to the effects of confounding native slow-wave activity, unevenly distributed between the ABP and ICP waveforms. We observed that the native slow-wave activity had greater amplitude than the 3- to 4-mmHg ABP waves induced with our ventilator method. Native slow-wave activity near the frequency of the smaller input wave could result in distortion of the phase angle calculations at the PEEP input frequency. Alternatively, some of the animals may not have been sufficiently hypotensive during testing at the lowest frequencies below LLA, a limitation of the piecewise regression method used to determine LLA. This method assumes a binary state of autoregulation (present or absent), and pressure reactivity is more likely to decay over a
The frequency response of cerebral autoregulation is a critical mechanism that helps maintain cerebral blood flow (CBF) within a narrow range, even when systemic blood pressure changes. This autoregulation is particularly important in the neonatal and pediatric population, where alterations in blood pressure can be more detrimental due to the developing cerebrovascular system.

In neonatal swine models, researchers have used a combination of mechanical variables and near-infrared spectroscopy to measure the frequency response of autoregulation. By applying cyclic pressure changes, they were able to determine the ideal frequency for cerebral blood flow regulation, which is around 0.03 Hz. This optimal frequency is used to optimize cerebral blood flow during mechanical ventilation, particularly in the context of positive end-expiratory pressure (PEEP).

The method described in the text involves using a cyclic pressure change to modulate arterial blood pressure. This modulation is designed to stress the autoregulatory mechanisms, allowing for an assessment of their frequency response. The frequency that is optimal for cerebral blood flow regulation is found to be around 0.03 Hz in neonatal swine models.

In summary, the application of a novel method to measure autoregulation in neonatal swine models has enabled the identification of an optimal frequency for cerebral blood flow regulation. This is crucial for optimizing cerebral perfusion during mechanical ventilation, particularly in the context of PEEP, as it allows for the maintenance of cerebral blood flow within a critical range, even under invasive conditions. The findings from these studies have significant implications for clinical practice, particularly in neonatal intensive care units, where maintaining cerebral perfusion is a critical aspect of patient management.