Renovascular reactivity measured by near-infrared spectroscopy

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SHOCK DEVELOPS WHEN OXYGEN delivery is not adequate to satisfy tissue oxygen demand. In the early postnatal period, neonates are at risk for hypotension, shock, and injury to vital organs, notably the brain and kidney (8, 24). Current neonatal hemodynamic management lacks the input of an end-organ monitoring strategy to assess the adequacy of perfusion. Our aim is to develop a clinically viable, continuous metric of renovascular reactivity to gauge renal perfusion during shock. We present the renovascular reactivity index (RVxs), which quantifies passivity of renal blood flow to spontaneous changes in arterial blood pressure. We tested the ability of the RVx to detect reductions in renal blood flow. Hemorrhagic shock was induced in 10 piglets. The RVx was monitored as a correlation between slow waves of arterial blood pressure and relative total hemoglobin (rTHb) obtained with reflectance near-infrared spectroscopy (NIRS) over the kidney. The RVx was compared with laser-Doppler measurements of red blood cell flux, and renal laser-Doppler measurements were compared with cerebral laser-Doppler measurements. Renal blood flow decreased to 75%, 50%, and 25% of baseline at perfusion pressures of 60, 45, and 40 mmHg, respectively, whereas in the brain these decrements occurred at pressures of 30, 25, and 15 mmHg, respectively. The RVx compared favorably to the renal laser-Doppler data. Areas under the receiver operator characteristic curves using renal blood flow thresholds of 50% and 25% of baseline were 0.85 (95% CI, 0.83–0.87) and 0.90 (95% CI, 0.88–0.92). Renovascular autoregulation can be monitored and is impaired in advance of cerebrovascular autoregulation during hemorrhagic shock.

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MATERIALS AND METHODS

Approval was obtained by the Animal Care and Use Committee at the Baylor College of Medicine. All procedures conformed to the standards of animal experimentation of the National Institutes of Health.

Anesthesia. Methods of anesthesia and surgical preparation have been previously described and published (2). Ten piglets, 8.9 ± 5.5 days old (mean ± SD) and weighing 3.0 ± 1.3 kg, were anesthetized with inhaled 5% isoflurane, 50% nitrous oxide, and 50% oxygen. Tracheostomy was performed, and mechanical ventilation was initiated and adjusted to maintain arterial pH between 7.35 and 7.45 and PaO2 between 200 and 300 mmHg. Maintenance anesthesia consisted of 0.8% isoflurane, 50% nitrous oxide, 50% oxygen, fentanyl (25-µg bolus followed by 25 µg/h infusion), and vecuronium (5-mg bolus followed by 2 mg/h infusion). The fentanyl infusion was adjusted to remain between 10 and 50 µg/h to keep the heart rate less than 200 beats/min and to maintain normal blood pressure during baseline recording. When the blood pressure was actively lowered by continuous removal of blood, tachycardia was permitted as an expected response to the induced reduction in preload. The primarily narcotic-based anesthetic technique, supplemented with a relatively low concentration of isoflurane, ensured the animals’ comfort while minimizing...
ing the cerebrovascular response to volatile anesthetic. Piglets were placed on a warming pad to keep their rectal temperatures between 38.5 and 39.5°C.

Surgery. The femoral veins were cannulated bilaterally for placement of central venous lines for drug infusion and central venous pressure (CVP) monitoring. The femoral arteries were cannulated bilaterally for placement of a pressure and blood gas monitoring line and for active removal of blood. A craniotomy was performed 4 mm rostral and 4 mm lateral to the bregma at midline for placement of an external ventricular drain catheter to monitor intracranial pressure (ICP). A second craniotomy was performed 4 mm lateral to the ventricular drain for placement of a laser-Doppler flux (LDF) probe (Moor Instruments, Devon, UK). The dura mater was incised, and the LDF probe was advanced to contact the surface of the frontoparietal cortex and secured in place with rubber washers cemented to the cranium. A third small craniotomy was performed for placement of a second LDF probe on the contralateral side of the cranium. All craniotomy sites were sealed with dental cement to preserve the integrity of the intracranial compartment. The skin was reapplied to the skull and sutured closed for heat retention. Incisions were made bilaterally just inferior to the last rib to access the kidneys. The fat and fascia were dissected away until clear visualization of the kidney was possible. A small incision was made into the kidney, and the LDF probes were placed directly into the renal cortex. The probes were positioned to avoid high baseline flux values and were secured by sutures to the skin. Pediatric oximeter probes for the INVOS near-infrared spectroscopy monitor (Covidien, Boulder, CO) were placed lateral to the craniotomy sites over the frontal and parietal lobes. An additional pair of probes was placed on the skin surface, noninvasively, overlying the bilateral kidneys in a manner that could be accomplished clinically by either palpation or ultrasound visualization. All probes were secured by veterinary tape and/or sutures and shielded with opaque black nylon until the ambient light was negligible. The inner diode detector is 2 cm from the light source and the outer diode detector is 4 cm. Our measurements are taken from the outer diode to ensure the greatest depth of tissue penetration, which is estimated to be 2 cm (3). This adequately covers the kidney depth (skin to kidney distance), which ranges from 0.5 to 1 cm in our neonatal piglet model. However, this does include interrogation of skin, fat, and muscle overlying the kidney. The present study is, therefore, limited by the assumption that kidney absorption of near-infrared light is much greater than the surrounding tissue due to the fact that the hemoglobin density is much higher in the vessel-rich kidney than the surrounding tissue, and the changes in the hemoglobin density within the reflectance arc do not need calibration to measure autoregulation. In addition, with respect to the neonate, based on normative data in preterm and term neonates, our experimental design for placement of the NIRS probes on the skin overlying the kidney would cover the range of skin to relevant range of kidney depth (1.5 to 3 cm) in human neonates (18).

Signal sampling. ABP, ICP, and LDF measurements were sampled from an analog-to-digital converter at 200 Hz using ICM+ software (Cambridge University, Cambridge, UK; www.neurosurg.cam.ac.uk/icmplus). Regional tissue oximetry (rSO2) is the United States Food and Drug Administration-approved and clinical monitoring output of the INVOS monitor. rSO2 was sampled from the INVOS digital output. rSO2 estimates tissue oxyhemoglobin saturation and is used clinically as a venous weighted trend. However, the absolute values of normal and abnormal have been the subject of substantial debate, and the monitors are mostly used as a trend in patients undergoing vascular surgery. Relative total hemoglobin (rTHb) values were calculated as (1 – optical density) from the 810 nm wavelength light-emitting diodes used in the INVOS. We previously showed this rTHb to recapitulate slow ICP waveforms when measured over the brain (14). Cerebral perfusion pressure (CPP) was calculated as (ABP - ICP), renal perfusion pressure (RPP) was calculated as (ABP - CVP), and each was recorded every 10 s as blood pressure was lowered to demise by continuous exsanguination at 10% blood volume per hour (Fig. 1).

RVx and HVx calculations. ABP and rTHb waveforms were time-integrated and resampled as nonoverlapping 10-s mean values to eliminate high-frequency waves and, specifically, wave components from pulse and respiration. Oscillatory changes that occur at frequency less than 0.05 Hz are still detected with this low-pass filter. Recurrent, spontaneous low-frequency hemodynamic oscillations between 0.05 and 0.003 Hz are found in mechanically ventilated neonates and mammals (1, 10, 21) and are the input signal for the RVx. Spontaneous ABP waves in this frequency range are of sufficient amplitude to provoke autoregulatory responses that can be seen in the ICP recordings first described by Lundberg as “B waves” (23). When
Autoregulation is intact in a vascular bed, then vasoconstriction and vasodilatation oppose these slow changes in blood pressure to constrain blood flow. The result is a phase-shift between blood volume and blood pressure at the slow wave bandwidth. Autoregulation is impaired when the constrictive and dilatory reactivity of the vascular bed is lost. By contrast, the result is a blood volume waveform that is passive to or in-phase with the blood pressure waveform (Fig. 2). The phase relationship between rTHb and ABP can be quantified in the time domain using linear correlation methods (Fig. 3) (5, 6). One advantage of the time domain technique is that can easily be set up to continuously monitor autoregulation and vascular reactivity at the variable spontaneous slow wave bandwidth. Within this slow wave bandwidth, we previously showed that changes in rTHb measured in the brain recapitulate changes in ICP and that we are able to monitor autoregulation with this uncalibrated signal (13). Because we cannot calibrate the rTHb to a measurable physiological parameter, we have limited our use of rTHb to the analysis of slow wave bandwidth specific changes in relation to ABP.

The RVx was calculated as follows. A continuous moving Pearson correlation was performed between slow waves of rTHb of the kidney and ABP for the RVx. Consecutive paired 10-s averaged values from 300-s analysis periods generated 30 data points for inclusion in each Pearson coefficient used to determine the indices. Positive values of RVx indicate impaired vascular reactivity, and negative values indicate intact vascular reactivity.

We also recorded the hemoglobin volume index (HVx), which is a moving correlation between ABP and rTHb measured from cerebral NIRS. The HVx was not a study variable for this project, having been previously validated in a neonatal swine model (14). However, we present the data for informative visual comparison of the autoregulatory responses in the brain and kidney during shock.

Generating autoregulation curves. Laser-Doppler flux measurements were first normalized to a percentage of baseline, which was determined as the mean flux recording across the highest 5-mmHg span of RPP or CPP in the recording. The median RPP and CPP at baseline using this method were 67.5 mmHg (range 55 to 75 mmHg) and 62.5 mmHg (range 55 to 75 mmHg), respectively. Biologic zero flux was determined at the demise of the animal using LDF measurements from the respective organs. Ten-second mean samples of these normalized laser-Doppler recordings were plotted across RPP (kidney LDF) and across CPP (brain LDF). For visual comparison, the

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Fig. 2. ABP and blood volume relationship during slow waves. A, B, and C are taken from the corresponding labeled highlighted regions in Fig. 1. A: normal ABP (mmHg) with slow wave activity results in autoregulatory responses in both the kidney and brain. rTHbK and rTHbK are both phase shifted in relation to the ABP at the slow wave frequency. B: with small reduction in ABP brain rTHb is still phase shifted off the ABP, but the kidney rTHb begins to demonstrate passivity to ABP. C: with progressive hypotension, the ABP-rTHb phase shift attributed to vascular reactivity is lost in both the brain and kidney recordings.
dynamic measurements of autoregulation, HVx, and RVx were also binned and averaged in 5-mmHg increments of RPP and CPP (Fig. 4).

In prior studies, we used these static plots to determine the lower limit of cerebrovascular autoregulation for dichotomization of data above and below this limit; however, it is apparent that the kidney has no such lower limit of autoregulation. In addition, the flow to the kidney decays rapidly in early shock as vasoconstrictive mechanisms are activated. Therefore, we chose to use percent reduction from baseline flow in quartiles as our gold standard metric.

**Statistical analysis.** RVx and HVx were recorded every 10 s from overlapping 300-s analysis periods. For each piglet, median values for RVx, mean values of rSO2, and mean values of renal cortical red cell

Fig. 3. Vascular reactivity quantified by correlation of rTHb (AU) and ABP (mmHg). A, B, and C are taken from the corresponding recordings with similar labels in Figs. 1 and 2. A: with normal blood pressure, both rTHbB and rTHbK blood volume measurements are reactive to ABP. B: with small reduction ABP, only the kidney shows passivity quantified by positive correlation of rTHbK with ABP. C: with progressive hypotension, both the kidney and brain show passivity quantified by positive correlation of rTHb with ABP.

Fig. 4. Static curves from laser-Doppler flux recordings and dynamic autoregulation monitoring in a single piglet. A: cerebral cortical laser-Doppler flux (LDFb, %Baseline) plotted across cerebral perfusion pressure (CPP, mmHg) shows a classic static autoregulation curve for the brain (top) with a defined lower limit of autoregulation. By contrast, a static autoregulation curve for the kidney (bottom) plotting renal cortical LDFK (%Baseline) across renal perfusion pressure (RPP, mmHg) lacks a discernible plateau and lower limit of autoregulation. B: static autoregulation plots can be made from recordings of dynamic autoregulation monitoring using hemoglobin volume index (HVx) and the renovascular reactivity index (RVx) by binning and averaging in 5-mmHg increments of RPP and CPP. Static plots from laser-Doppler recordings on the left are recapitulated in the HVx and RVx plots on the right.
flux were recorded from 20-min epochs and updated every 100 s. Median values were used for RVx to filter periodic, brief episodes of noise related to erratic slow wave activity. The rSO2 and laser-Doppler signals were free from this artifact, so mean values were used. RVx and rSO2 were analyzed across quartiles of renal blood flow (RBF) using Freidman’s nonparametric test for repetitive measures. Receiver-operating characteristics were performed testing these median values of RVx and mean values of rSO2 against RBF reductions in quartiles. RVx and rSO2 measurements were dichotomized as: “health” for measurements taken above each quartile RBF threshold and “disease” for measurements taken below each quartile RBF threshold. Statistical tests were performed using Prism 5 software (Graph Pad, La Jolla, CA).

RESULTS

The hemorrhagic model gave a consistent reduction in cerebral blood flow (CBF) and a somewhat more variable pattern of reduction in RBF. During shock, RBF was diminished in advance of CBF and occurred prior to clinically significant reductions in arterial blood pressure (ABP). For the kidney, a decrease in relative RBF to 75%, 50%, and 25% of baseline occurred at ABP of 60, 45, and 40 mmHg, respectively, whereas for the brain these decreases occurred at 30, 25, and 15 mmHg, respectively. Static autoregulation curves for the cohort of animals using both laser-Doppler and dynamic autoregulation monitoring are shown for comparison (Fig. 5).

With the onset of hypotension, arterial pH and blood gas tensions were maintained. Arterial blood gas measurements and serum hemoglobin, lactate, glucose, and blood urea nitrogen (BUN) concentrations are shown as a function of shock duration (Table 1). Acute hemorrhage does not cause anemia; however, serum hemoglobin concentration did fall slightly and consistently across the stages of the experiment (P = 0.01). This decrease is likely due to the administration of the intravenous fluid carrier used for anesthesia, glucose administration, and serum pH buffering. However, these very slow and subtle changes in hemoglobin are not likely to have impacted the changes in laser-Doppler flux. The “slow wave” changes in blood volume of the brain and kidney at the bandwidth of the HVx and RVx measurements are occurring more rapidly than the slow graded changes related to the fall in hemoglobin over the course of the experiment. Serum lactate levels trended upward during the experiment, a predictable effect that approached significance (P = 0.08). Other clinical variables remained controlled throughout the experiment.

RVx increased, indicating pressure passivity, with reductions in RBF. Furthermore, rSO2 decreased, indicating inadequate tissue oxygenation with reductions in RBF. Quartile analysis of both of these relationships was significant (Fig. 6, P = 0.001 and P < 0.0001, respectively). The sensitivities and specificities of both RVx and rSO2 to detect quartile reductions in RBF were quantified using receiver-operating characteristics (Figs. 7 and 8). Areas under the receiver operator characteristic
curves using RBF thresholds of 50% and 25% of baseline for RVx were 0.85 (95% CI, 0.83–0.87) and 0.90 (95% CI, 0.88–0.92), and for rSO2 were 0.91 (95% CI, 0.65–0.91) and 0.92 (95% CI, 0.90–0.93).

We observed that pressure passivity in the kidney occurred when reductions in RBF were at least 50% and that the RVx was most sensitive and specific for profound reductions in RBF. Thresholds of RVx at 80% specificity and 80% sensitivity are shown for the two lowest quartiles of RBF (Table 2). A 20-min median RVx of 0.14 was 80% sensitive for a moderate (50% of baseline) reduction in blood flow, and a 20-min median RVx of 0.34 was 80% specific for a severe (25% of baseline) reduction in RBF. In this data set then, median RVx values less than 0.14 are reassuring that RBF is more than 50% of baseline, and median RVx values greater than 0.34 are concerning that RBF is less than 25% of baseline. Intermediate values of RVx are less clear.

**DISCUSSION**

The results of the experiments presented here have two implications. First, RBF is impaired during hemorrhagic shock in advance of any disturbance to CBF and before clinically significant reductions in ABP. Thus monitoring of ABP and even cerebral autoregulation monitoring are insufficient to provide meaningful goal-directed therapy targets for infants with shock. Second, RBF impairment from hemorrhagic shock can be detected using the RVx, a noninvasive, continuous monitoring index. The RVx has the potential to provide data about the relative splanchnic circulation to aid in the management of early shock.

When shock is compensated, blood pressure is maintained by neurohormonal compensatory mechanisms, including the sympathetic nervous system, vasopressin, and angiotensin. These mechanisms increase systemic vascular resistance and preserve CBF at the expense of splanchnic and renal perfusion. In the early postnatal period, critically ill neonates are exposed to a variety of causes of shock, including cardiac dysfunction, sepsis, hypovolemia, anemia, hypoxia, and abnormal peripheral vasoregulation (14, 19). Given these factors, the neonate is extremely vulnerable to multisystem organ dysfunction, including gut and renal hypoperfusion injury. In a shock state, blood pressure may or may not be reduced, and blood flow changes are organ specific. Although blood pressure is one determinant of tissue delivery, there is limited utility in using blood pressure as the sole marker of systemic and regional perfusion (13).

Renovascular autoregulation is physiologically distinct from, but similar to, cerebrovascular autoregulation. Both systems are vital, protective mechanisms exist that constrain blood flow to support oxidative metabolism while preventing injurious microvascular hypertension. The cerebral vasculature has autoregulatory mechanisms to preserve glucose, oxygen, and pH homeostasis, and metabolic flow-coupling, in addition to pressure autoregulation, which is considered in this manuscript and described in isolation (Fig. 6). Pressure autoregulation in the cerebral vasculature is mediated by a myogenic response to transmural arterial pressure changes. By contrast the kidney has at least a dual-layered pressure autoregulation system: a myogenic response of the renal vascular smooth muscle (9, 26) and tubuloglomerular feedback (16, 27). These autoregulation
mechanisms occur at distinct frequencies, but both are responsive to changes in renal perfusion pressure.

Detailed laboratory studies of these separate layers of vascular regulation have involved frequency-modulated, repetitive perturbations of ABP or manipulations of fluid in Henlé’s loop (7, 12, 20, 25). The RVx is measured in the time domain, with a low-pass filter cutoff and sampling epoch giving a comparatively wider range of spontaneous slow waves analyzed: 0.05–0.003 Hz. This relatively blunt metric treats the separate autoregulatory elements in the kidney as a single unit, detecting overall pressure passivity, not failure of an individual component of reactivity. Thus we cannot say which mechanism dominates our findings. The time-domain correlation method was chosen largely because of precedent clinical success in monitoring cerebrovascular autoregulation (22). In addition, those studies demonstrated a positive correlation of ABP, and intracranial blood volume indicates absent vascular reactivity, and negative correlation indicates intact vascular reactivity. Absolute thresholds of these relatively new modalities are not yet delineated.

The RVx uses NIRS-based trends of tissue hemoglobin density as a surrogate of renal blood volume. We previously measured cerebrovascular reactivity using the same technique with cortical reflectance NIRS (14). Although cerebral autoregulation monitoring was the framework used to develop the RVx, differences between renovascular and cerebrovascular physiology during shock preclude the use of RVxs in the way that cerebral autoregulation monitoring has been used. In the brain, optimizing pressure is sufficient to maintain CBF, but ABP maintenance is necessary and insufficient to maintain RBF. RBF is extraordinarily large to sustain filtration at the glomerulus. Although the kidneys make up only 2% of body mass, they receive almost 25% of cardiac output (4). Our data support a model in which the brain is perfusion-pressure dependent, whereas the kidney is more dependent on cardiac output (17). The vasoactive neurohumoral axes activated by circulatory compromise, including sympathetic tone increase, activation of the renin-angiotensin cascade, and release of vasopressin, cause profound reductions in RBF while ABP is preserved. The vasoconstrictive actions of these axes exert less effect on cerebral vascular tone than splanchnic and renal tone.

When comparing the brain and kidney autoregulation for an individual piglet at varying blood pressure states, it is apparent that renovascular reactivity is lost early in hemorrhage, even before significant reductions in ABP in Fig. 3. At a mild hypotensive state, vascular reactivity is lost in the kidney while preserved in the brain. This observation held true across all piglets. Furthermore, as illustrated in Fig. 5, RBF is near 25% of baseline while the brain continues to maintain adequate perfusion. Although clinically blood pressure is often used a surrogate indicator for renal perfusion, the present results suggest that the blood pressure measurement does not accurately reflect the renal blood flow. Therefore, unlike brain autoregulation monitoring, RVx may not help to elucidate optimal perfusion pressures, but is more likely to have a role as an early marker to detect pathologic elevations in splanchic tone.

When evaluating the RVx as a test to discriminate between shock states, the RVx has good specificity but poor sensitivity. It would best be suited as part of a multi-modal shock assessment platform based on these properties but likely not as useful as a standalone test.

The data for the ROC curves suggest the kidney rSO2 has good functionality over blood pressure to detect RBF; however, saturation-dependent methodologies are susceptible to confounders of the rSO2 reading such as variations in cardiovascular shunting, intrapulmonary shunting, and other acute changes that effect arterial oxygenation. The benefit of using rTHb to look at changes in hemoglobin volume within the kidney is it permits a saturation-independent metric and evaluates the vascular tone of kidney rather than the blood flow. Thus the measurement is much less confounded than the rSO2 measurement and more likely to reflect the autoregulatory state of the kidney in a wide spectrum of diseases.

The peculiarities of renal perfusion during shock will also mandate separate studies of the different etiologies of shock, especially vasoplegia. The hemorrhagic model presented was

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**Table 2. RVx thresholds for identification of moderate and severe reductions in renal blood flow**

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<thead>
<tr>
<th>RVx</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>Moderate reduction (50% of baseline renal blood flow)</td>
<td></td>
<td></td>
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<tr>
<td>0.14</td>
<td>80% (77–83)</td>
<td>67% (64–70)</td>
</tr>
<tr>
<td>0.24</td>
<td>74% (71–78)</td>
<td>80% (77–82)</td>
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<tr>
<td>Severe reduction (25% of baseline renal blood flow)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.34</td>
<td>85% (79–87)</td>
<td>80% (79–83)</td>
</tr>
<tr>
<td>0.39</td>
<td>80% (75–84)</td>
<td>86% (84–87)</td>
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RVx, renovascular reactivity index.
chosen for ease of reproducibility, appropriate for an initial study of the RVx. In addition, we recognize that hemorrhage and hypovolemia are most prominent in neonates undergoing surgical treatments and are relatively uncommon causes of neonatal shock. In the preterm neonate, where sepsis and myocardial dysfunction are more common during transition to extraterrestrial life, we cannot conclude that the renal vasculature will behave as it did in these piglets with hemorrhagic shock. This animal model effectively demonstrates changes in RBF from baseline, but cannot elucidate the clinical consequences of these changes. An important evaluation of this and other monitors of organ perfusion is to determine abnormal values and duration of abnormal values associated with deleterious patient outcomes.

In conclusion, this study provides evidence that renovascular reactivity can be measured in a continuous, noninvasive fashion. Passivity in the renal vasculature, quantified by the RVxs, is associated with profound reductions in RBF in this neonatal swine model of shock. Impairment of RBF in a shock state occurs in advance of disturbance to cerebral blood flow, and ABP is not descriptive of renovascular compromise.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES