Thoracic, peripheral, and cerebral volume, circulatory and pressure responses to PEEP during simulated hemorrhage in a pig model: a case study

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Abstract

Positive end-expiratory pressure (PEEP) is a respiratory/ventilation procedure that is used to maintain or improve breathing in clinical and experimental cases that exhibit impaired lung function. Body fluid shift movement is not monitored during PEEP application in intensive care units (ICU), which would be interesting specifically in hypotensive patients. Brain injured and hypotensive patients are known to have compromised cerebral blood flow (CBF) autoregulation (AR) but currently, there is no non-invasive way to assess the risk of implementing a hypotensive resuscitation strategy and PEEP use in these patients.

The advantage of electrical bioimpedance measurement is that it is noninvasive, continuous, and convenient. Since it has good time resolution, it is ideal for monitoring in intensive care units (ICU). The basis of its future use is to establish physiological correlates. In this study, we demonstrate the use of electrical bioimpedance measurement during bleeding and the use of PEEP in pig measurement.

In an anesthetized pig, we performed multimodal recording on the torso and head involving electrical bioimpedance spectroscopy (EIS), fixed frequency impedance plethysmography (IPG), and bipolar (rheoencephalography – REG) measurements and processed data offline. Challenges (n=16) were PEEP, bleeding, change of SAP, and CO₂ inhalation. The total measurement time was 4.12 hours.

**Systemic circulatory results:** Bleeding caused a continuous decrease of SAP, cardiac output (CO), and increase of heart rate, temperature, shock index (SI), vegetative - Kerdo index (KI). Pulse pressure (PP) decreased only after second bleeding which coincided with loss of CBF AR. Pulmonary arterial pressure (PAP) increased during PEEP challenges as a function of time and bleeding.

**EIS/IPG results:** Body fluid shift change was characterized by EIS-related variables. Electrical Impedance Spectroscopy was used to quantify the intravascular, interstitial, and intracellular volume changes during the application of PEEP and simulated hemorrhage. The intravascular fluid compartment was the primary source of blood during hemorrhage. PEEP produced a large fluid shift out of the intravascular compartment during the first bleeding period and continued to lose more blood following the second and third bleeding. Fixed frequency IPG was used to quantify the circulatory responses of the calf during PEEP and simulated hemorrhage. PEEP reduced the arterial blood flow into the calf and venous outflow from the calf.

**Head results:** CBF AR was evaluated as a function of SAP change. Before bleeding, and after moderate bleeding, intracranial pressure (ICP), REG, and carotid flow pulse amplitudes (CFa) increased. This change reflected vasodilatation and active CBF AR. After additional hemorrhaging during PEEP, SAP, ICP, REG, CFa signal amplitudes decreased, indicating passive CBF AR. 1) The indicators of active AR status by modalities was the following: REG (n=9, 56 %), CFa (n=7, 44 %), and ICP (n=6, 38 %); 2) CBF reactivity was better for REG than ICP; 3) REG and ICP correlation coefficient were high (R² = 0.81) during CBF AR active status; 4) PRx and REGx reflected active CBF AR status. CBF AR monitoring with REG offers safety for patients by preventing decreased CBF and secondary brain injury.

We used different types of bioimpedance instrumentation to identify physiologic responses in the different parts of the body (that have not been discussed before) and how the peripheral responses ultimately lead to decreased cardiac output and changes in the head. These bioimpedance methods can improve ICU monitoring, increase the adequacy of therapy, and decrease mortality and morbidity.
Introduction

**PEEP**

PEEP is a respiratory/ventilation procedure that is used to maintain or improve breathing in clinical and experimental cases that exhibit impaired lung function. PEEP has been applied to such cases, including, acute respiratory distress syndrome (ARDS) [1], stroke [2], after heart surgery [3], to support breathing of elderly patients [4], and during animal experimentation [5].

The application of PEEP first affects the lungs and pulmonary system. PEEP increases lung volume, alveolar recruitment, and lung compliance thereby reducing the work of breathing [6]. The increase in intrathoracic pressure then depresses the diaphragm extending the effects of PEEP to internal organs [7] and the peripheral circulatory system [8]. PEEP decreases hepatic, splanchnic, and gastric perfusion. PEEP increases systemic circulatory resistance, increases peripheral pooling, and reduces venous return to the heart [9]. Reduced venous return decreases right ventricular preload and increases right ventricular afterload which has the net effect of decreasing the right ventricular stroke volume [10]. In turn, the reduced output from the right ventricle leads to a reduced stroke volume in the left ventricle and a reduction in cardiac output [10]. Decreased cardiac output affects the cerebral circulatory system by increasing intracranial pressure and reducing cerebral perfusion pressure and thereby reducing cerebral blood flow [11].

As stated by [12]: “The effects of mechanical ventilation have been evaluated, but most studies focused on a single variable or circulation regardless of interactions and compensatory mechanisms that should require the simultaneous assessments of multiple circulations.”

Detailed descriptions of the effects of PEEP on individual physiologic systems are given in the Deranged Physiology series [12] of clinical notes. Malbrain [13] gives a description of the impact of intra-abdominal pressure on end-organ function and shows the interaction between multiple physiologic systems.

Shekerdemian and Bohn [8] have proposed a simplified three-compartment model of the cardiovascular effects of mechanical ventilation. However, the above articles do not provide a detailed description of the peripheral [calf] circulation or the intracranial responses to PEEP.

**Hemorrhage**

Hemorrhage is a leading cause of death in both civilian and military trauma [15-17]. In spite of significant advancements in the pathophysiology of hemorrhagic shock [HS] and its treatment, the mortality rate remains high [17]. Extensive bleeding due to unintentional injury remains the principal cause of death for US civilians [18]. Hemorrhagic shock remains a leading cause of morbidity and mortality from battlefield injuries [18]. In a rat study, it was documented, that brain injury together with hemorrhagic shock causes persistent impairment of CBF and brain tissue oxygen tension, increasing the probability of cortical spreading depolarizations that likely contribute to secondary neuropathology and compromise neurological recovery [19].

Continuous monitoring of hemodynamic, autonomic, and/or metabolic responses may provide earlier recognition of hemorrhage than standard vital signs and allow interventions before the onset of hypovolemic shock [20]. The Shock index (SI) is the ratio of heart rate (HR) to systolic arterial pressure (SAP) and may be more useful in early hemorrhage than either vital sign alone [21]. The vegetative balance - Kerdo index [22] was useful in the quantification of cardiovascular stress in hemorrhagic shock [23].

**EIS**

Hemorrhage and PEEP is not only a CBF manipulation but also triggers a change in body water compartments (intra- and extra-cellular and vascular fluid shift) which can be measured by BIS non-invasively. The EIS (Z-Scan-2, U.F.I. Inc, Morro Bay, CA) used in this study, combines a fixed frequency Impedance Plethysmograph [IPG] and a multi-frequency electrical impedance spectrograph (EIS) into one unit. The IPG mode was used to quantify the total segmental conductive volume and associated circulatory parameters [24]. The EIS mode was used to monitor segmental intracranial and extracellular compartment volumes as is done by other EIS devices. However, our proprietary software was then used to divide the extracellular compartment volume into its intravascular and interstitial components. The electrical bioimpedance spectrographic mode was validated [25] and used [26,27] to monitor fluid shifts between the intracellular, interstitial, and intravascular compartments during dialysis. This instrumentation was used in this study to monitor relative changes in interstitial and intravascular compartment volumes during simulated hemorrhage and the use of PEEP [28].

**REG**

Early bioimpedance research began with thoracic [cardiac] measurements, which were soon followed by measurements of brain circulation. The term “rheoencephalography” was first used by Jenkner to refer to this technique and more recently the Food and Drug Administration definition has been stated that “A rheoencephalograph is a device used to estimate a patient’s cerebral circulation by electrical impedance methods with direct electrical connections to the scalp or
neck area” [29]. The original REG devices were a four-electrode system, later modified to two electrodes. The electrical impedance method (measuring blood flow by alternating current) is known in clinical practice however, it is used mostly in cardiology to measure cardiac output and peripheral circulation (summative blood flow in the limbs). REG is based on monitoring pulse synchronous variations in cranial electrical impedance over time. REG pulse wave amplitude is due to the conductivity differences between brain tissue, and cerebrospinal fluid and blood, with blood and cerebrospinal fluid being better conductors than the brain and other “dry” tissue. The significant physiological information derived from the REG signal relates to vasoconstriction and vasodilation in the brain. This is manifested by decreasing and increasing REG, amplitudes, respectively. The early publication described that REG can be used to detect brain arteriosclerosis and elevated ICP [30]. The units of these amplitude changes are measured in Ohms, however, there are no normative values associated with the REG amplitude values due to the many factors that can affect it [31].

Various correlations have been established between REG and CBF (volume, flow, or pressure, detailed by Jenkner [32]). The consensus from a review of published REG literature is that the REG signal represents volume change. REG pulse amplitude is quantified most frequently using its derivative or integral [33, 34]. Both variables are sensitive to changes in CBF induced by perturbations such as CO₂ inhalation, Trendelenburg position, carotid occlusion, and hemorrhage. The REG pulse amplitude relationship to cerebral blood volume was previously documented in humans with the radio-iodinated human serum albumin method during CO₂ inhalation [35]. As a result of this study, it was determined that the REG pulse wave amplitude increased reflecting the intracranial volume increase. In vitro study clearly confirmed this statement [36]. Earlier studies [31, 32] made an initial effort to establish pathophysiological correlates to REG [30, 34] but did not mention CBF AR. Previous studies documented that REG reflects cerebrovascular reactivity [40], has a correlation to ICP [35, 38], laser Doppler flow [39], carotid flow [40] and can be used for patient monitoring instead of ICP [42]. It was documented that REG indicated cerebral vasospasm before systemic reaction caused by complement activation/cytokine storm in pigs [42]. We described multimodal CBF AR changes during hemorrhage and various SAP changes in pigs [43].

Considering the above, the goals of this descriptive case study were:

1) to use extensive invasive and noninvasive techniques to provide multiple system responses to PEEP, including the calf in intracranial regions,
2) to demonstrate how the use of different types of bioimpedance instruments [bipolar implanted electrodes for rheoencephalography, fixed frequency impedance plethysmography, and multi-frequency impedance spectroscopy can give additional information during clinical and experimental studies, and
3) to define primary parameters that can be used to assess the responses of various physiologic systems to the application of PEEP.

Materials and Methods
Following surgical implantation of catheters and sensors, under anesthesia, the following CBF AR challenges were used: hemorrhage, PEEP, CO₂ inhalation, and transitory SAP change during switching isoflurane anesthesia to propofol (n=16 challenges). After measurements, the pig was euthanized by lethal hemorrhage. The pig (68.7 kg) was anesthetized with isoflurane and propofol/ketamine anesthesia and spontaneously breathing. Details were described previously [43].

Simulated Hemorrhage

The amount of blood withdrawn during the simulated hemorrhage test is shown in Figure 1. The baseline period [0-90 min] is followed sequentially by three bleedings: each at elapsed times of 80, 150, and 210 min. Bleedings were performed in three steps, each time 15 % of the estimated blood volume (0.669 L) was withdrawn; after the second bleeding it was 1.339 L (30 %), and the third time total removed volume was 2.009 L (45%).

Application of PEEP
Sequential levels of PEEP were administered three times during the experiment to counteract the physiologic effects of the simulated hemorrhages. Each series of PEEP consisted of increased levels of the applied pressure of 10, 15, and 20 cm H₂O. The first series of PEEP took place before the first bleeding. The second and third PEEP took place at the time of initiation of the first and second bleed periods. A ventilator (Invent 201, VersaMed, Pearl River, NY) generated PEEP with 10, 15, and 20 cm H₂O pressures lasting about 8 minutes three times, separated with breaks.

Data processing
EIS data was stored on a laptop with a 100 Hz sampling rate. Physiological signals were sampled with a 200 Hz analog-digital conversion rate using DASH-18 (Astro-Med, West Warwick, RI). The total recorded time was 4.12 hours in 3 files. Serial (and analog) data were collected with DREW (Army Institute of Surgical Research, San Antonio, TX) with a 12/min sampling rate. Analog signals were processed offline with DataLyser, an in-house developed program. DataLyser is based upon LabWindows/CVI program (National Instruments, Austin, TX) specifically developed to display, store, and quantify analog physiological signals.
REG integral was calculated after creating the first derivative and turning negative numbers into positive. Running integral calculation was used to smooth the trace with 60-sec windows. PRx and REGx calculations were made identically as was given in the ICM+ program [44, 45]. In case REG was used instead of ICP it was called REGx [45]. Data processing involved 1) visual evaluation of CBF AR responses during SAP changes; 2) automated calculation of CBF AR status; 3) comparing REG integral and ICP mean values during 15 and 20 cm H2O PEEP; 4) status of systemic circulation was compared by student t-test, involving 30 minutes data at the start and the end of the recording. SAP and CO were compared by their correlation coefficient involving time window from 14:00 till 17:40; 5) pulse pressure (PP) was calculated as systolic-diastolic blood pressure; 6) calculation of shock index (SI: Heart rate in beats per minute/Systolic blood pressure) [46] and Kerdo index - KI: (1 – diastolic blood pressure/heart rate) + 100 [23] modified by Sipos [47] was calculated covering 4.12 hours recording time. Statistical analysis was performed in Excel (Microsoft, Redmond, WA). Probability was considered significant at P <0.05.

Ethical approval
The research related to animals use has been complied with all the relevant national regulations and institutional policies for the care and use of animals.

Results
The results of this study are presented in two sections below. The first part will give the results of the invasive and non-invasive instrumentation that was used to quantify the physiologic responses of the various body systems to the application of PEEP during simulated hemorrhage. The second part will present parameters and displays that can be used by physicians at the bedside to monitor the effects of PEEP during treatment procedures.

Results are presented in the sequence of responses in various bodily systems as described in the introduction. The results are presented that are most directly affected by the administration of PEEP and are related to the hypothesis that PEEP reduces venous return to the heart which in turn leads to reduced cardiac output.

Mean pulmonary arterial pressure (PA-M) is shown in the figures below to provide consistent insight into the various parameter value changes during the simulated hemorrhage periods.

**Physiologic responses to PEEP**

**Pulmonary Circulation**

**Systemic (calf) circulation**

**EIS-related results**
The impedance spectroscopy used in this investigation first quantifies the intracellular and extracellular resistance of the calf. These resistance values are then used to calculate the individual compartment volumes which are then plotted in Figure 3, normalized to the mean of the values during the period before the first bleeding.

Positive values indicate fluid transfer out of each compartment and negative values indicate fluid transfer into each compartment. No fluid transfer took place between any of the three fluid compartments prior to the first bleeding. A large amount of fluid was transferred from the interstitial and intracellular compartments into the intravascular space following the first bleeding. Smaller amounts of fluid were transferred between the three compartments after the first bleed period (Figure 4).

IPG-related results

Note that calf blood flow is not affected by PA-M before the first bleeding. PA-M does cause an increase in %BF following the first sequence of PA-M and then %BF decreases during subsequent bleed periods. PA-M does produce an increase in %BF during the second and third bleed periods (Figure 5).

Note that both TIN and TOUT increase before the first bleeding. TIN remains relatively constant during the first and second bleed periods while TOUT decreases following the first bleeding and continues to decrease throughout the rest of the experimental duration (Figure 6).

Figure 4. Fluid transfer in and out of the cells (Fc), interstitial space (Fi), and intravascular compartment (Fb) vs. elapsed time.

Figure 5. Mean pulmonary arterial pressure (PA-M) and calf percent blood flow (%BF) vs. elapsed time.

The CCO values were multiplied by 100 so they would fit the same range of the linear Y-axis CO numbers. The SAP and CO decreased during the time of recording because of bleedings. Their correlation was 0.58. The difference was statistically significant between the start and end of SAP (P=0.0005; for CO was P<0.0001 (Figure 1.) During the recording time, PP and PAP change invertedly: PP decreased, while PAP increased as a function of bleeding (Figure 2). Their correlation was low during the total recorded time (R^2 0.003) but increased after 2^{nd} bleeding (R^2 0.511). The difference was statistically not significant (P=0.236) between the start and end for PAP but significant for PP (P=0.0003) (Figure 7).

Cardiac output is the product of stroke volume (SV) and heart rate (HR). Heart rate increases following the first bleeding. However, this increase was found to be a result of increased internal temperature of the pig, perhaps due to the effect of the anesthesia used (Figure 8).

Stroke volume changes were the predominant factor affecting the cardiac output (CCO). Stroke volume was therefore used to represent the effect of PEEP on the heart during simulated hemorrhage (Figure 9).
vasodilatation, which reflects active CBF AR. CBF and LDF signals often passively followed SAP. After hemorrhaging during PEEP, the signal amplitudes registered for REG, CF, and ICP showed corresponding decreases in SAP, indicating decreased CBF, which reflects passive CBF AR. The sequence of active AR was led by REG (n=9, 56 %), followed by CFA (n=7, 44 %) and ICP (n=6, 38 %).

CBF AR parameters are given in Table 1. CBF AR status was calculated as the relationship to SAP change: identical change of modality CBF AR was considered as passive (-); in the case of inverted phase, CBF AR was considered as active (+). Artifact contaminated signals, mixed change (+/-), or lack of change (0) were excluded from evaluation. Legend: SAP: systemic arterial pressure; CFA: carotid flow pulse amplitude; mean: CFm: carotid flow mean; REG1d: REG first derivative; CBF: absolute blood flow; LDF: laser Doppler flow; ICP: intracranial pressure; CVP: central venous pressure; PAP: pulmonary arterial pressure; PO2: pulse oximetry pulse amplitude; CO2: exhaled CO2 concentration; +: increase - i.e. identical change; -: decrease - i.e. opposite phase; 0: no data or artifact, no change; iso-prop transit: transition of anesthesia from isoflurane to propofol.

Twenty cm H2O PEEP caused SAP decrease which triggered an increase of ICP, carotid flow (CFA), and REG pulse amplitudes – Figure 11. The first step of REG data processing was creating the 1st derivative of REG pulse amplitude which eliminated the slow oscillation, caused by respiration. The next step was to turn up (+) negative values of the 1st derivative of REG. After it, a running integral was calculated with 60 sec time windows. For the REG integral and ICP values (Table 2), the correlation coefficient was 0.81. Bottom trace: mean carotid flow. NB: CFm does not reflect CBF AR. Pig CBF 9, file 13:32; time window: 5175-5790.9 (615.94) sec.

Hemorrhage elicited 1) a decrease in SAP and transitory increases in ICP, REG, and CF amplitude; 2) PEEP resulted in a decrease in SAP and increases in ICP, REG, and CF amplitude; 3) PEEP after hemorrhage caused decreases in SAP, ICP, REG, and CF amplitudes. When CBF AR was present, it was detected by an increase of ICP, REG, and CFa. Following severe hemorrhage, CBF AR was lost; ICP, REG, and CFa passively followed SAP decrease.

**CBF AR test**

**Effect of 20 cm H2O PEEP, after 2nd hemorrhage**

Blood loss of about 1.3 L with an estimated shed blood volume of 30%. Hemodynamic status: SAP 90/67; mean 75 mmHg. CBF AR impaired. ICP passively follows SAP increase, except transient active AR at the start of SAP decrease, during 50 sec. SAP decrease elicited a decrease in CFa and REG integral. Pig CBF 9, file 16:30; time window: 1600-2200 (600) sec (Figure 12).
Table 1. Summary of CBF AR changes.

| Challenge           | SAP | CFa | CFm | REG1d | CBF | LDF | ICP | CVP | PAP | CO2 | pO2 |
|---------------------|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|
| iso-prop transit    |     |     |     |       |     |     |     |     |     |     |     |
| PEEP 10             | +   | -   | -   | -     | +   | -   | -   | +/- | 0   | -   |     |
| PEEP 15             | -   | +   | -   | +     | +   | +   | -   | 0   | +   |     |     |
| PEEP 20             | -   | +   | -   | +     | +   | +   | -   | -   | -   |     |     |
| hemorrhage 1        | -   | +   | -   | +     | +   | +   | -/+ | +   | -   |     | -/+ |
| PEEP 10             | 0   | 0   | -/+ | +     | 0   | 0   | +   | -   | +   |     | -/+ |
| PEEP 15             | -   | -/+ | -/+ | +     | +   | 0   | +   | -   | +   |     | -/+ |
| PEEP 20             | -   | -/+ | -/+ | +     | +   | -/+ | +   | -   | +   |     | -/+ |
| CO2 inhalation      | +   | 0   | 0   | 0     | +   | 0   | +   | 0   | +   |     | -/+ |
| hemorrhage 2        | -   | +   | +/- | +     | -   | 0   | -   | +   | +   | 0   | +/- |
| PEEP 10             | 0   | 0   | +   | -     | 0   | +   | -   | -   | -   | +   | -/+ |
| PEEP 15             | +   | -   | +   | -     | 0   | +   | +   | -   | -   | +   | -/+ |
| PEEP 20             | -/+ | -   | -   | +     | +   | +   | +   | -   | -   | +   | -/+ |
| hemorrhage 3        | -   | +   | -   | +     | +   | 0   | -   | -   | -   | +   | 0   |
| PEEP 10             | +   | 0   | 0   | 0     | 0   | 0   | +/- | 0   | +   | +   | -/+ |
| lethal bleeding      | -   | +/- | -   | +/-   | -   | -   | -   | +/- | +/- | +   | +/- |

**CBF AR active**

7 1 9 4 3 6 3 4 5 3

Figure 11. Continuous analog parameters (as a strip chart) vs. time. CBF AR is active.
Figure 12. Continuous analog parameters (plotted as a strip chart) vs. time. CBF AR is passive.

Table 2. Percent changes of mean ICP and REG integral during 15 and 20 cmH₂O PEEP before first (1) and after first bleedings (2), and after second bleeding (3). Values are in percentage of their own baseline. Measurement was made at the highest values. Note that after 2nd bleeding REG values are negative, indicating that CBF AR is passive.

|       | ICP 15 cm H₂O | ICP 20 cm H₂O | REG 15 cm H₂O | REG 20 cm H₂O |
|-------|---------------|---------------|---------------|---------------|
| 1     | 132           | 148           | 15            | 31            |
| 2     | 133           | 148           | 28            | 40            |
| 3     | 74            | 48            | -19           | -41           |

Discussion

In this descriptive study, we demonstrated the use of three types of bioimpedance methods by measuring torso, peripheral, and brain circulation, noninvasively and correlated to invasive measures. Related results of this pig group are detailed previously [43, 48]. Recent results indicate that 1) EIS reflects body fluid shifts; 2) IPG quantified the circulatory responses of the calf; 3) REG accurately reflects cerebrovascular responsiveness (CBF AR) similarly to ICP and carotid flow pulse amplitude. The clinical importance of our findings was pointed out previously: The potential for PEEP to evoke neurologic complications in patients who have an intracranial disease and that the presence of the pulmonary disease may attenuate these deleterious side effects [50].

PEEP

Increased intrathoracic pressure due to PEEP has the potential for reducing SAP. Such change could critically reduce cerebral perfusion pressure [CPP] CPP=SAP-ICP [49]. PEEP will be expected to decrease cardiac output mostly by decreasing venous return and right ventricular stroke volume. Hence PEEP and hypovolemia would tend to amplify the decrement in CO. However, we have a venous capacitance (as high as 25% blood volume) that can be called upon and other compensatory mechanisms and could mask some effects of true hypovolemia (especially as it relates to blood pressure). With that in mind, the exact relationship between PEEP and CO is variable. Of note,
Clinical aspects

Intensive care unit (ICU) monitoring typically involves invasive (SAP) and noninvasive: electrocardiogram, (ECG) oxygen saturation (pO₂), temperature, respiration, carbon dioxide (CO₂) methods. Bedside monitors show these traces and calculate numerical values. A ventilator is a separate device in which several respiratory variables are needed to set up, such as PEEP pressure, volume, frequency, etc. Additionally, in neurocritical care, invasive monitoring is ICP, laser Doppler flow (LDF), brain O₂/temperature, quantitative CBF; noninvasive monitoring is near-infrared spectroscopy (NIRS), electroencephalogram (EEG), transcranial Doppler (TCD). For details see [54, 55]. ICP is monitored, but not for every patient. It is desired that biometry would be used for brain and cardiorespiratory ICU monitoring since it is continuous, noninvasive, convenient, and cheap.

During hemorrhage lost blood volume is compensated by interstitial fluid movement into intravascular space while hemorrhagic shock is compensated. Compensation involves an increase in heart rate. After additional blood loss compensation capacity is exhausted and starts a decrease of SAP and after a transient increase of heart rate, it is decreasing (Figure 14). Practical problems were demonstrated previously [43, 57].

A recent guideline [60] states: “We recommend that less invasive devices are used, instead of more invasive devices, only when they have been validated in the context of patients with shock. Best practice”. But searching this document with keywords: “cerebral blood flow” resulted in no-hit! In other words, CBF is not interesting to be monitored in circulatory shock?

However, it was published, that serious hypotension combined with a severe head injury can increase mortality by a factor of four [60]. American Academy of Neurology 2017 Guideline [53]; Neurocritical Care Society Standards [62]; Guidelines [62-64]; the protocol for the treatment of SARS-CoV-2 [65] does not mention “cerebral blood flow” or “PEEP” but sometimes cerebral perfusion.

Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure that affects approximately 200 000 patients each year in the United States, resulting in nearly 75 000 deaths annually. Globally, ARDS accounts for 10% of intensive care unit admissions, representing more than 3 million patients with ARDS annually [52].

ARDS exerts a substantial disease burden, with 40% of patients dying in hospitals. Diverse factors, including patient-related factors such as age and illness severity, country-level socioeconomic status, and ventilator management and ICU organizational factors each contribute to the outcome from ARDS. Addressing these issues provides opportunities to improve outcomes in patients with ARDS [64]. Monitoring CBF AR during PEEP is an option to decrease ICU mortality. Probably it would be helpful in the management of severe hypoxic respiratory failure, too [66]. An experimental study demonstrated, that CBF AR is progressively impaired during septic shock [70].

Shock and Kerdo index

The SI is the ratio of the HR to SBP. The index is a sensitive indicator of left ventricular dysfunction and can become elevated following a reduction in left ventricular stroke work. The SI can be used in the emergency care and intensive care units to identify patients needing a higher level of care despite vital signs that may not appear
strikingly abnormal [68]. Persistent elevation of the SI has been associated with a poor outcome in critically ill patients [69]. The SI is a sensitive indicator of left ventricular dysfunction and displays variability in critical patients displaying normal vital signs [68]. In our current study, the greatest increase in SI was seen after 3rd bleeding. This increase coincided with a heart rate and temperature increase. KI values are indicative of autonomic dysfunction [71]. Kerdo index was modified by Sipos previously [47]. The KI values above 100 indicate sympathicotonia, and values below 100 indicate parasympathicotonia. Both SI and modified KI were increased, SAP and CO were decreased during recording time. PAP reaction during PEEPs increased. PP decrease after 2nd bleeding was identical to loss of CBF AR, indicated by REG. It is a practical experience that pig stress (hemorrhagic shock) reaction involves an increase in body temperature. It is opposite to human and rat reactions. Calculation of shock index and vegetative balance (KI) was useful in quantifying cardiovascular stress [70, 71].

**CBF**

PEEP and Cerebral Perfusion Pressure [CPP]. About 20–25% of patients with brain injury developed ARDS, which was associated with high mortality. Guideline for mechanical ventilation in ARDS recommended low tidal volume and moderate to high levels of PEEP. Nevertheless, the use of PEEP in brain injury led to an increase in intrathoracic pressure, impeded venous return, and reduced cerebral venous drainage from superior vena cava. Finally, these effects induced high ICP and CPP. However, in clinical studies, these effects occurred only when applying PEEP more than 15 cm H₂O in hypovolemic patients [72]. Higher CBF AR response of REG can be explained that REG reflects better the arteriolar blood volume change than the Doppler, which measures a big vessel flow [73]. NB: the organ of CBF AR is the arteriola [74, 75]. A recent MRI study described loss of grey matter in cortical areas directly connected to primary olfactory and gustatory cortex after 19 infection, compared to pre-Covid-19 status [76]. It can be hypothesized that there were CBF-related changes as well, which can be detected with REG much cheaper.

It was demonstrated that BOLD MRI can reflect an early impairment of cerebrovascular reserve after aneurysmal subarachnoid hemorrhage [77]. Since REG reflects CBF AR it is expected that will be able to reflect the same way the impairment of cerebrovascular reserve, tested by CO₂ inhalation; REG correlated well (AUC= 0.84 with p<0.0001) to laser Doppler flow during CO₂ inhalation [78].

The clinical importance of these findings is that REG can be measured more conveniently and continuously in humans than Doppler ultrasound. Therefore, the measurement of CBF AR by REG has the potential for use as a life sign monitoring modality in neurocritical care units as well as in the military environment.

**Military relevance**

Additionally, to civilian cases, military medicine offers practical use for bioimpedance, since the dominant cause of death is hemorrhage and TBI [15, 79-82]. Brain-injured patients are known to have compromised CBF AR but currently, there is no non-invasive way to assess the risk of implementing a hypotensive resuscitation strategy in the brain-injured patient [83]. A previous study demonstrated that REG can be used to identify the autoregulatory breakpoint to determine the limit for permissive hypotension. Bioimpedance monitoring can be a help during the transport of wounded service members, independently of the Covid pandemic [84, 85].

In civilian clinical practice, invasive SAP and ICP monitoring are typically used to detect the status of CBF AR. However, in military medical practice, these invasive modalities cannot be used during the transport of injured, deployed military personnel. Moreover, in military medical practice, resuscitation techniques used to treat injured service members on the battlefield can result in the unintended consequence of secondary brain injury. After brain/blunt injury cerebral vascular reactivity (CVR) can be lost, which is a bad prognosis. In the absence of the ability to maintain cerebral perfusion, a state of hypotension results in significant ischemia and secondary brain injury. Currently, however, there is no way of assessing the risk of implementing a hypotensive resuscitation strategy in a patient suspected of having traumatic brain injury [60, 87, 89]. If normal CVR is found to be present, then lower blood pressures/cerebral perfusion pressures can be tolerated. Conversely, if CVR is absent, then blood pressures must be maintained at a higher level to prevent cerebral ischemia. A meta-analysis revealed significant benefits of hypotensive resuscitation relative to mortality in traumatic hemorrhagic shock [61]. Damage control resuscitation is the overall guiding concept to emerge from the recent military experience [87]. A Guideline states: “If blood pressure [BP] monitoring is available, maintain target systolic blood pressure 80-90 mmHg” [88].

Traumatic brain injury is a frequent component of the combat casualty’s injury profile in addition to hypovolemic hypotension. Furthermore, disruption of CBF AR has been recently associated with poorer outcomes, however, currently; there are no non-invasive approaches to evaluate the status of cerebral autoregulation. A major diagnostic limitation for the blast-induced head-injured patient is the inability to image the cranium using MRI due to the possibility of embedded metal fragments from improvised explosive devices. Additionally, CT angiography sometimes fails to detect vasospasm due to the associated metal artifact. Based on previous results, REG seems to be a practical noninvasive and continuous monitoring modality of traumatic brain and blast injuries, since REG signal seems to be insensitive to the presence of metal fragments [92].
REG monitoring on the battlefield is possible by using a miniaturized REG amplifier [90]. By using additional modalities (ECG, respiration) can help the medic in end-of-life decision making [91, 92]. A study described, that 87.3% of all injury mortality occurred in the pre-medical treatment facility environment [93]. It is also stated, that “To impact the outcome of combat casualties with potentially survivable injury, strategies must be developed to mitigate hemorrhage on the battlefield” Monitoring CBF AR during transport and afterward is one potential tool to decrease combat morbidity and mortality, which caused by secondary brain damage.

Conclusions
1) We used multiple invasive and noninvasive procedures to present an integrated sequence as to how PEEP affects the different regions/organs of the body – at three levels of PEEP after bleeding
2) Illustrated how different bioimpedance measurements can provide a fuller characterization of physiologic responses to clinical and environmental stress - bipolar to monitor cerebral circulation, the fixed frequency at 50KHz to measure total segment volume and hemodynamic state, impedance spectroscopy to quantify fluid compartment volumes, and fluid transfer between compartments. Lastly, (perhaps) calculation of phase angle and/or cell membrane capacitance to investigate cell hydration.
3) Identified those methods/parameters that can best be used during bedside monitoring and for research.
4) We demonstrated that the use of PEEP in brain-injured and hypotensive patients is safe only if CBF AR is monitored.
5) REG indicated the point at which CBF AR is lost
6) The use of the Shock and Kerdo indices can quantify cardiovascular and autonomic stress responses before vital signs are abnormal.

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Disclaimer
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Conflict of interest
Authors state no conflict of interest.

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