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Measurement of cerebral blood flow autoregulation with rheoencephalography: a comparative pig study

Michael Bodo [1,4], Leslie D. Montgomery [2], Frederick J. Pearce [1], Rocco Armonda [3]

1. *Walter Reed Army Institute of Research, Silver Spring, MD, USA*
2. *LDM Associates, San Jose, CA, USA*
3. *National Naval Medical Center, Bethesda, MD, USA*
4. *E-mail any correspondence to: mbodo@tulane.edu*
   Current position: Tulane University School of Medicine, New Orleans, LA, USA

Abstract

Neuromonitoring is performed to prevent further (secondary) brain damage by detecting low brain blood flow following a head injury, stroke or neurosurgery. This comparative neuromonitoring study is part of an ongoing investigation of brain bioimpedance (rheoencephalography-REG) as a measuring modality for use in both civilian and military medical settings, such as patient transport, emergency care and neurosurgery intensive care. In a previous animal study, we validated that REG detects cerebral blood flow autoregulation (CBF AR), the body's physiological mechanism that protects the brain from adverse effects of low brain blood flow (hypoxia/ischemia). In the current descriptive pig study, the primary goal was to compare measurements of CBF AR made with REG to measurements made with other neuromonitoring modalities: laser Doppler flow (LDF); intracranial pressure (ICP); absolute CBF; carotid flow (CF); and systemic arterial pressure (SAP). Challenges administered to anesthetized pigs were severe induced hemorrhage (bleeding) and resuscitation; CO_2 inhalation; and positive end expiratory pressure (PEEP). Data were stored on a computer and processed offline. After hemorrhage, the loss of CBF AR was detected by REG, ICP, and CF, all of which passively followed systemic arterial SAP after bleeding. Loss of CBF AR was the earliest indicator of low brain blood flow: loss of CBF AR occurred before a decrease in cardiac output, which is the cardiovascular response to hemorrhage. A secondary goal of this study was to validate the usefulness of new automated data processing software developed to detect the status of CBF AR. Both the new automated software and the traditional (observational) evaluation indicated the status of CBF AR. REG indicates the earliest breakdown of CBF AR; cessation of EEG for 2 seconds and respiration would be used as additional indicators of loss of CBF AR. The clinical significance of this animal study is that REG shows potential for use as a noninvasive, continuous and non-operator dependent neuromonitor of CBF AR in both civilian and military medical settings. Human validation studies of neuromonitoring with REG are currently in progress.

Keywords: Cerebrovascular reactivity, bioimpedance, REG, carotid flow, CBF, LDF, ICP, pig

Introduction

Physiological Background of CBF

The brain requires a continuous, uninterrupted blood supply to meet its energy requirement. Of the body's organs, the brain is uniquely dependent on a continuing adequate supply of substrate (glucose, oxygen). In a resting individual, the central nervous system consumes 20% of the oxygen and 25% of the glucose utilized by the body. So small is the brain's store of energy-generating substances that at normal rates of adenosine phosphate production, the brain's store of oxygen would be exhausted in less than 3 minutes. Under normal physiological conditions, 15% of the resting cardiac output perfuses the brain, an amount more than adequate to meet the brain's energy requirement. Also, the brain can conserve energy and decrease its energy demand by switching off many of its metabolic processes before the reserves have been compromised, that is, before delivery of substrate decreases below 'critical' values. On the other hand, the brain cannot tolerate significant increases in the volume of the skull's contents such as those caused by bleeding and swelling (Fitch, 1999).

Relationship between Hemorrhage and Cerebral Blood Flow

Hemorrhagic shock (hypotension) is the leading cause of death in both civilian and military injuries. A patient with both a severe head injury and hypotension is four times more likely to die than a patient with a head injury alone (Manley et al, 2001). Despite the brain's well developed autoregulation (Strandgaard, Paulson, 1984), its vital functions are impaired when the CBF autoregulatory reserve is exhausted by prolonged hypovolemic conditions (hemorrhage).

Afferent neural input to the brain seems to be elevated during shock, which may lead to increased tissue metabolism and the accumulation of metabolites. Low CBF combined with elevated neuronal activity and cellular metabolism produces an imbalance between oxygen delivery and oxygen utilization (Kovach, 1988). The cerebrovascular response to hemorrhage balances autoregulatory vasodilatation and sympathetic vasoconstriction (Pearce, D'Alecy, 1980). During hemorrhage, CBF heterogeneity (Komjati et al, 1996) and hypovolemic cerebral hyperemia were observed (Waschke et al, 1996). Continuous monitoring of CBF AR predicted a better patient outcome than intermittent monitoring (Rivere-Lala et al, 2017).

Background of Rheoencephalography (REG)

The term 'rheoencephalography' was first applied by Jenkner (1962) to refer to the use of bioimpedance to estimate brain circulation. According to the US Food and Drug Administration (FDA), "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" (Anonymous, 1997).

The original REG device was a four-electrode system, later modified to two electrodes. In clinical practice, the electrical impedance method has been used in cardiology to measure cardiac output and peripheral circulation. REG is based on monitoring pulse synchronous changes in cranial electrical impedance over time. The significant physiological information derived from the REG signal relates to vasoconstriction and vasodilatation in the brain, which are shown by decreases and increases in REG pulse amplitudes, respectively. The units of these amplitude changes are measured in Ohms.

Unlike measurements using electrocardiogram and electroencephalogram (EEG), there are no normative values associated with REG, which is influenced by many factors (Moskalenko et al, 1980).

REG amplitude values are measured by placing two or four electrodes on the skull, requiring the current to pass through brain tissue as well as cerebrospinal fluid and blood, which are better conductors than the brain.

Purpose of measuring positive end-expiratory pressure (PEEP)

Increasing PEEP is known to increase O_2 saturation by increasing ventilation; however, PEEP is also known to depress cardiac output (Angerpointner et al, 1977, Muench et al, 2005, Solodov et al, 2016). Increasing PEEP may decrease SAP and CBF.

Materials and methods

Pigs (N=13; mean weight 69.4, sd 2.3 kg) were anesthetized with isoflurane and propofol/ketamine anesthesia. The anesthesia levels of the pigs were monitored with two devices: a bispectral index (BIS) device (A-2000, Aspect Medical Systems, Newton, MA) and an anesthesia monitor (RGM 5250, Datex-Ohmeda, Louisville, CO). During surgery, the BIS number was 30–60; during hemorrhage and resuscitation and other CBF challenges, the BIS number was 60–80.

SAP was measured with a Microtip disposable pressure transducer inserted into the femoral artery, with a transducer control unit (Millar Instruments, Houston, TX) and with a Digi-Med Blood Pressure Analyze (Micro-Med, Louisville, KY).

CF was measured on the right carotid artery ('ascending pharyngeal artery' in pigs), using a T201ultrasonic blood flow meter (Transonic Systems, Ithaca, NY).

ICP was monitored with an ICP Express device (Codman, Raynham, MA).

Brain blood flow was recorded with laser Doppler flowmeter (PeriFlux 4001; Perimed; Jarfalla, Sweden) and with a tissue perfusion monitor (Bowman 500, Hemedex, Cambridge, MA).

A pulmonary artery catheter (CCOmbo, Edwards Life Sciences, Irvine, CA) was introduced via external jugular vein and connected to a cardiac output monitor (Vigilance, Edwards Life Sciences, Irvine, CA).

Central venous (CVP) and pulmonary artery pressure (PAP) were measured with a disposable transducer (Argon Medical Devices, Athens, TX) and Digi-Med Blood Pressure Analyzer (Micro-Med, Louisville, KY). Pressure transducers were calibrated with a water column (0 and 100 mmHg).

Respiration (CO_2, pressure and volume) was monitored with CO_2SMO respiratory profile monitor (Novametrix – Respironix, Carlsbad, CA).

Oxygen saturation was measured with Pulse Oximeter 8600 (Plymouth, MN).

REG was measured with a bipolar KR-Ea RHEO Preamp (OTE Galileo, Italy). Two custom stainless steel REG electrodes 40 mm in length were constructed for implantation in the skull. Inter-electrode resistance was 2.83 (mean) and 1.54 (sd) ohm (n=14). After removal of skin, using the burr-hole surgical technique, 1mm holes were drilled 10-20mm apart parasagittaly on the right side of skull above and below the fronto-parietal sutura.

Electrodes were fixed to the skull with Vetbond tissue adhesive (3M, St. Paul, MN) and instant adhesive 454 (Loctite, Hartford, CT). Data were sampled with 200 Hz analogue digital conversion rate using a DREW system (Institute of Surgical Research, San Antonio, TX) and a DASH-18 (Astro-Med, West Warwick, RI) with an analogue digital converter card (PCI 6052E, National Instruments, Austin, TX) with 16 bit resolution. Serial port data sampling rate was 12 samples per minute. Data were processed offline using Excel (Microsoft, Redmond, WA) and DataLyser software, based on LabWindows (National Instruments, Austin, TX). DataLyser was developed to display, store and quantify analogue physiological signals. REG calculation was published previously (Bodo et al, 2010).

CBF AR responses were evaluated during the following CBF manipulations: hemorrhage and resuscitation (n=8 pigs; 34 challenges); CO_2 inhalation (n=16); PEEP with 10, 15 and 20 cm H_2O pressures (n=5 pigs; 57 challenges); Trendelenburg and reverse Trendelenburg position; and transitory SAP decrease and increase caused by changes in anesthesia.

A computerized system was used to induce hemorrhage (isobaric model, Wiggers, 1950) and to reach and maintain SAP (40 mmHg mean). For resuscitation Hextend and saline were used.

Cerebrovascular reactivity was evaluated as a function of SAP change: in case of identical phases, CBF AR was considered as passive; in case of inverted phase, CBF AR was considered as active. Evaluated modalities were as follow: CF pulse, CF mean, REG 1st derivative, CBF, LDF, ICP, CVP, PAP, oxygen saturation waveform and exhaled CO_2 concentration. Dubious and artifact contaminated signals were excluded from evaluation. Person's correlation coefficient (PCC) for ICP (PRx) and REG (REGx) were calculated in DataLyser to indicate the active or passive status of CBF AR, similar to what was used in the original ICM+ program (Czosznyika et al, 1997, Anonymous).

The calculation followed these steps: 1) divide each channel into a series of 10 second "epochs"; 2) calculate the mean value over each epoch ("slow oscillations"); 3) extract five minute (30 point) "sliding windows" from the slow oscillations, at one minute intervals; 4) calculate the PCC between corresponding windows from each channel; 5) generate a new channel from the series of sliding window correlations (1 point/minute).

CBF AR is active if PCC is close to -1 and passive if PCC is close to +1. PCC numbers from DataLyser were copied and pasted into a GraphPad Prism spreadsheet (La Jolla, CA), where statistical analysis (two-way ANOVA) was performed.

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

Hemorrhage

Before bleeding, active CBF AR was reflected by REG, ICP, and CF pulse amplitude; after bleeding, these modalities passively followed decreases in SAP. Mean carotid flow failed to detect the status of CBF AR, as shown in Tables 1 and 2 (see inversion of CFa and CFm numbers shown for active and passive CBF AR). Of the measurement modalities that reacted to SAP change (ICP, REG, CBF, LDF, CF), reactions varied (Table 1). In the hemorrhage group, the ratio of active/passive CBF AR was highest for the CF pulse, pO_2 and REG. The loss of CBF AR preceded cardiovascular collapse, which indicates hemodynamic decompensation, when SAP decrease correlated with heart rate and a decrease in cardiac output (Figure 4).

Positive end-expiratory pressure (PEEP)

For the PEEP group (Table 2), ICP, CVP, PAP and REG showed the highest active/passive ratios. Under control conditions, the decrease in SAP caused by PEEP administration was associated with increases in the amplitude of the REG, CF, and ICP signals, showed vasodilatation, which reflects active CBF AR. CBF and LDF often passively followed SAP (Figure 1). After hemorrhage during PEEP, the signal amplitudes registered for REG, CF and ICP showed corresponding decreases in SAP, indicating decreased CBF, which reflects passive CBF AR.

CO_2 inhalation

CO_2 inhalation caused a transient increase in CBF, ICP, REG and LDF but not in CF (Figure 2).

Person's correlation coefficient (PCC)

One purpose of this study was to compare results obtained using a new computerized method with the results obtained by traditional calculation methods, after measurement of changes in CBF AR for several modalities. Both the new and the traditional computerized evaluations indicated the active status of CBF AR. PEEP with normal SAP caused a decrease in SAP. Both PRx and REGx showed active CBF AR; PCC decreased to minus 1 (Fig 1). Following bleeding during PEEP, ICP and REG showed a shift from active to passive CBF AR status. There was a partial correlation between PRx and REGx (Fig 3). The comparison of the brain modalities by calculating their PCC resulted in partially identical pictures: REG was compared to ICP, LDF and CBF; CBF was compared to LDF; ICB was compared to LDF. A two-way ANOVA analysis showed a percent of total variation of 5.42 (P=0.0016) for all modalities and 17.58 (P=0.6603) for time points (1/min; n=65 min). Related changes in body compartment volumes during simulated hemorrhage and resuscitation, measured by bioimpedance are described by (Montgomery et al, 2019).

Table 1: Summary of CBF AR changes during challenges in hemorrhage group. CBF AR status was calculated as the relationship to SAP change: identical change of modality CBF AR was considered as passive (-); in case of inverted phase, CBF AR was considered as active (+). Artifact contaminated signals, mixed change or lack of signal were excluded from evaluation (0). Legend: SAP: systemic arterial pressure; CFa: carotid flow pulse amplitude; mean: CFm: mean pulse amplitude; REG1d: REG first derivative; CBF: absolute blood flow; LDF: laser Doppler flow; ICP: intracranial pressure; CVP: central venous pressure; PAP: pulmonary arterial pressure; pO_2: pulse oximetry pulse amplitude; CO_2: exhaled CO_2 concentration; +: increase - i.e. identical change; -: decrease - i.e. opposite phase; 0: no data or artifact, no change; Trendelenburg: Trendelenburg position; rTrendelenburg: reverse Trendelenburg position; iso-prop transit: transition of anesthesia from isoflurane to propofol; A/P ratio: ratio of active/passive CBF AR status.

Pig #	Challenge	SAP	CFa	CFm	REG1d	CBF	LDF	ICP	CVP	PAP	pO_2	CO_2
1	hemorrhage	-	+	-	0	+	0	-	-	-	+	-
	resuscitation	+	+	+	+	0	0	+	0	0	0	+
	lethal bleeding	-	-	-	+	0	0	-	-	-	-	-
2	hemorrhage	-	0	0	0	+	-	+	-	0	+	-
	resuscitation	+	0	0	0	-	+	+	0	0	+	-
	CO_2 inhalation	+	0	0	0	0	+	+	+	0	+	+
	lethal bleeding	-	0	0	0	+	-	-	-	0	-	-
3	CO_2 inhalation	+	-	+	-	+	0	+	+	0	-	+
	iso-prop transit	+	-	+	-	+	0	+	+	0	-	+
	hemorrhage	-	+	-	+	0	-	+	-	0	+	-
	resuscitation	+	+	+	+	+	+	+	+	0	0	+
	CO_2 inhalation	+	-	-/+	-	+	0	+	+	0	0	+
	CO_2 inhalation	+	-	-/+	-	+	+	+	+	0	-	+
4	CO_2 inhalation	0	-	-	0	+	0	+	+	0	+	+
	hemorrhage	-	+	+	+	+	0	-	-	0	+	0
5	iso-prop transit	+	-	+	+	+	+	+	+	+	+	0
	CO_2 inhalation	+	-	-/+	0	+	+	0	+	+	-	+
	CO_2 inhalation	+	-	-/+	+	+	+	+	+	+	-	+
	Trendelenburg	-/+	0	+	0	-	-	+	+	0	+	0
	rTrendelenburg	+	+	+	-	+	+	-	-	0	0	0
	hemorrhage	-	-/+	-/+	0	+	-	-	-	0	-	-
6	iso-prop transit	+	-	+	-/+	-/+	0	-/+	-/+	+	0	0
	CO_2 inhalation	-	+	-	0	+	0	+	+	0	0	+
	CO_2 inhalation	-	+	-	0	+	0	+	+	0	0	+
	hemorrhage	-	+	-	-	+	0	-	-	-	-/+	-
	CO_2 inhalation	0	0	0	+	+	0	+	+	+	-/+	+
	CO_2 inhalation	0	0	0	0	+	0	+	0	0	0	+
	CO_2 inhalation	0	+	+	0	+	0	+	0	0	0	+
	CO_2 inhalation	0	+	+	0	+	0	+	0	0	0	+
11	iso-prop transit	+	-	+	-	0	+/-	-	+	+	-	-
	hemorrhage	-	+	-	+	0	-	+	0	-	+	-
	resuscitation	+	+	+	+	0	+	+	+	+	-	0
14	iso-prop transit	+	-	0	-	+	+	-	-	0	-	-/+
	hemorrhage	-	+	-	+	-	-	+	0	-	+	-
	CBF AR active		**18**	**1**	**12**	**9**	**0**	**9**	**4**	**0**	**14**	**4**
	CBF AR passive		**5**	**17**	**6**	**11**	**16**	**17**	**18**	**11**	**6**	**17**
	A/P ratio		**3.6**	**0.1**	**2.0**	**0.8**	**0.0**	**0.5**	**0.2**	**0.0**	**2.3**	**0.2**

Table 2: Summary of CBF AR changes during challenges in PEEP group. CBF AR status was calculated as the relationship to SAP change. (See Table 1 for legend).

CBF AR	CFp	CFm	REG1d	CBF	LDF	ICP	CVP	PAP	pO_2	CO_2
Active	21	4	22	21	8	28	25	22	14	27
Passive	8	31	6	11	9	9	9	12	17	10
A/P ratio	**1.75**	**0.33**	**1.83**	**1.75**	**0.67**	**2.33**	**2.08**	**1.83**	**1.17**	**2.25**

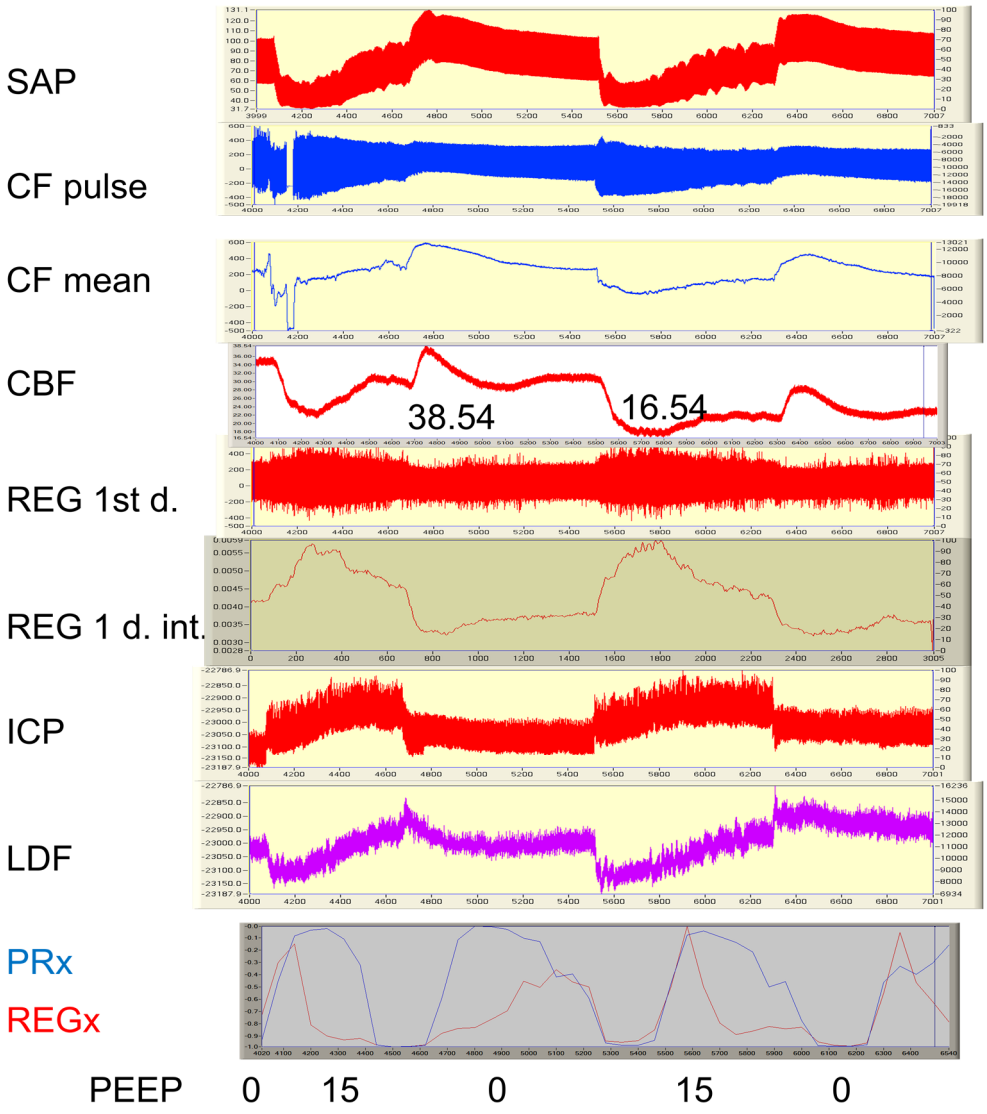

Fig. 1: Effect of 15 water cm PEEP. According to the CBF AR definition, here CBF AR is active and reflected by CF pulse amplitude, REG 1st derivative, its integral and ICP. CBF AR is passive in traces CF mean, LDF and CBF (quantitative CBF; unit ml/100gr/min). **Both calculated CBF AR indexes (PRx from ICP and REGx from REG) show active (-1) status at the same time.** Legend: SAP: systemic arterial pressure; CF pulse: carotid flow pulse; CF mean: mean CF; CBF: absolute blood flow (ml/100 g/min), numbers indicating maximum and minimum values; REG 1st d.: REG first derivative; REG 1st d. int: integral of REG 1st derivative; ICP: intracranial pressure; LDF: laser Doppler flow (brain). PRx: Person's correlation coefficient calculated from SAP and ICP; REGx: Person's correlation coefficient calculated from SAP and REG. PEEP units are in water cm. Pig ID: CBF 13, file 13:53; time window 4000-7007 s.

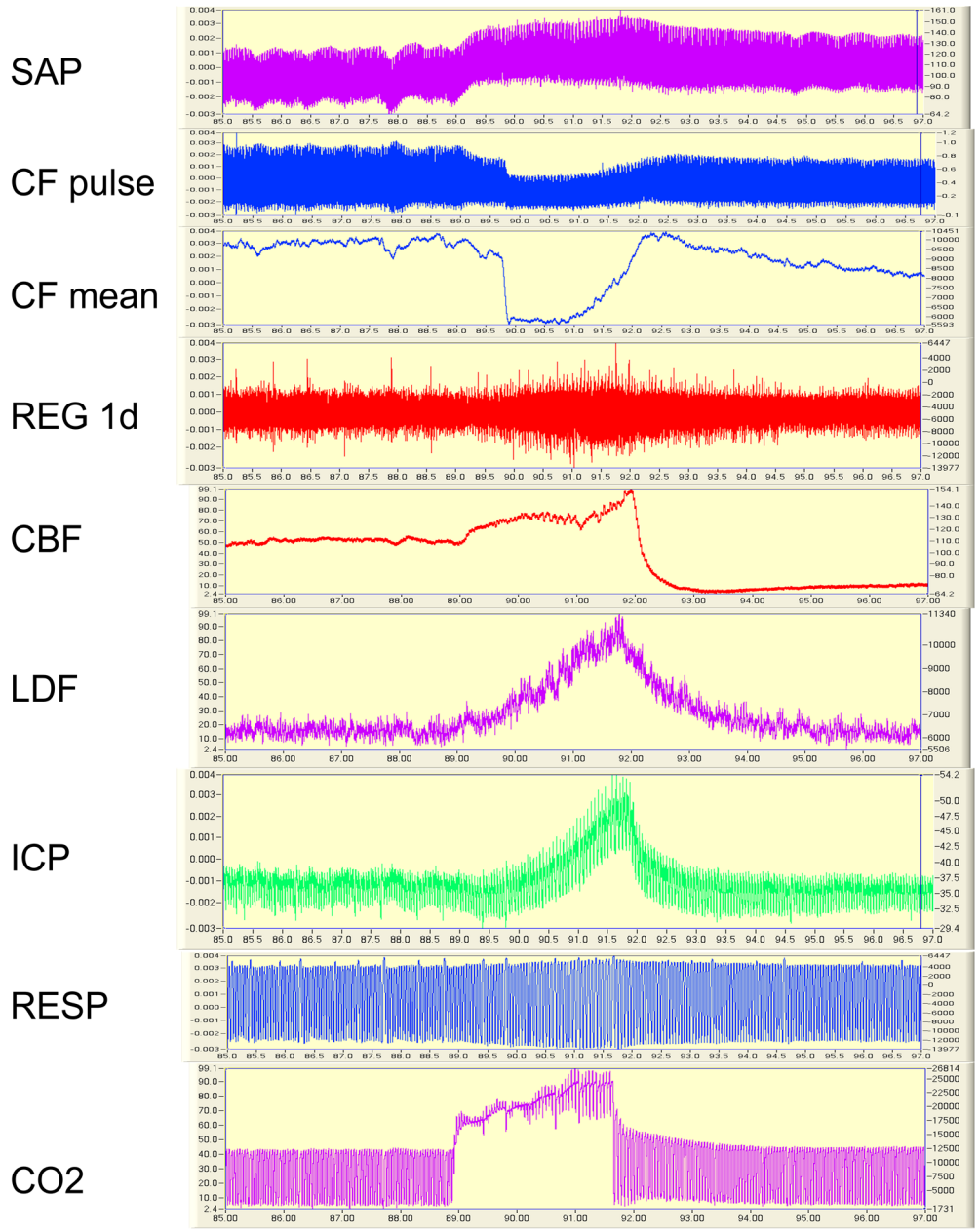

Fig. 2: Polygraphic traces during CO_2 inhalation. Abbreviations are as in Fig 1. RESP: respiration. As a function of CO_2 increase, ICP, CBF, LDF, REG 1st derivative and SAP increased; both CF pulse amplitude and mean value decreased. Pig recording of 5/22/07; time window 85-97 min.

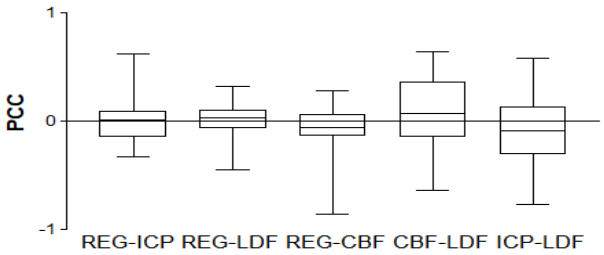

Fig. 3: Box diagram of Pearson's correlation coefficients between measured modalities. Recording of analog signals showed SAP decrease after 8 minutes and plateau at 40 mmHg during the rest the of recording (from 22 till 71 m); simultaneous decrease of mean CF, ICP, brain tissue O_2, exhaled CO_2 concentration; transient increase of CBF, CF and pulse oximeter amplitudes; REG followed SAP decrease and showed transient increase; LDF involved artifact, was unable to visually evaluate change. Pig # 1, file # 2. Input data (time points) are representing 65 min.

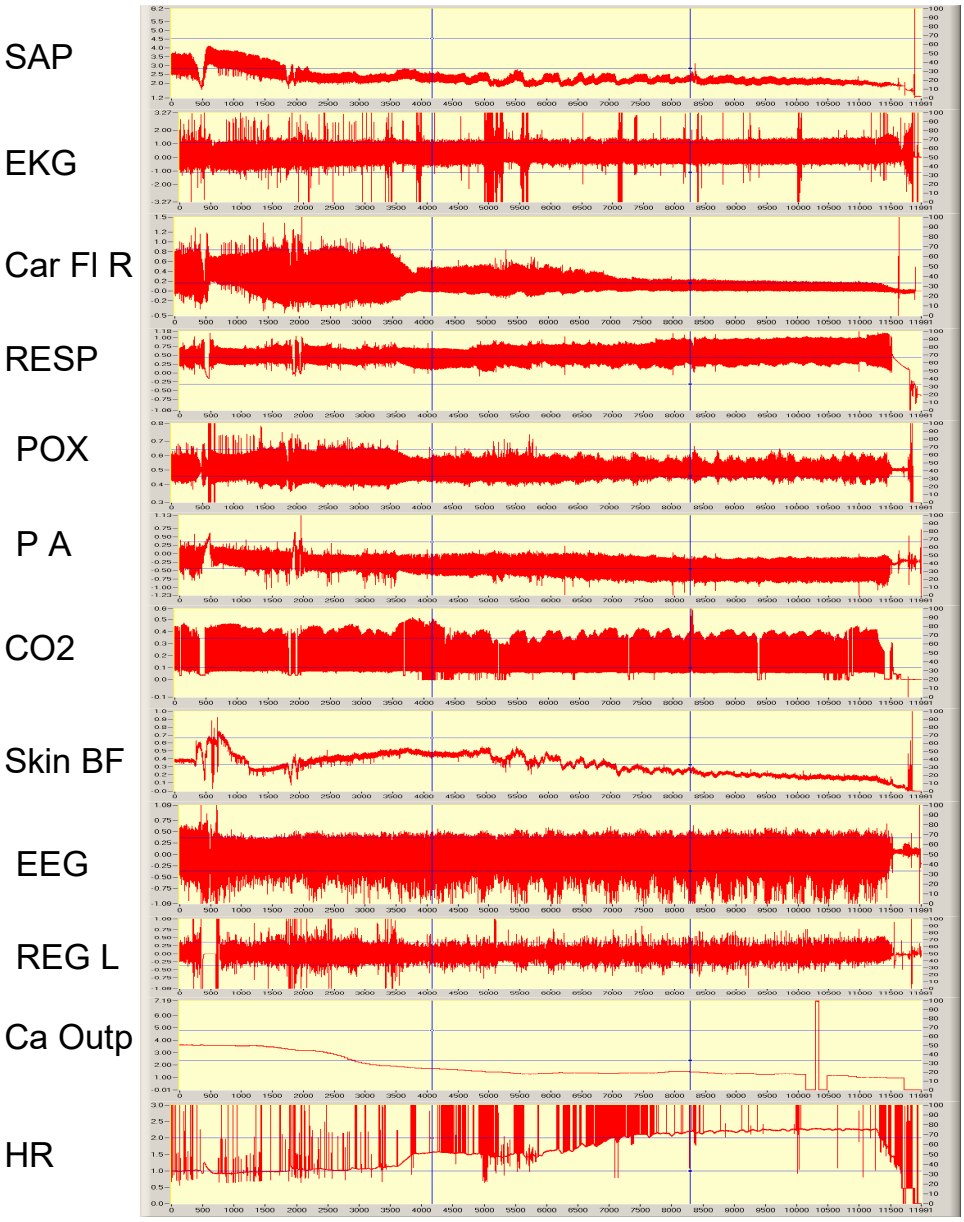

Fig. 4: Polygraphic traces during hemorrhage. Mean arterial blood pressure was 40 mmHg, maintained by a computer controlled system. In the first phase of hemorrhage carotid flow pulse (Car FI R), pulse oximeter signal (POX) and skin blood flow (Skin BF- measured by LDF; both sensors were placed on nose). REG showed compensatory amplitude increase. The involvement of various organs is represented by different traces. Traces characterize various phases of hemorrhage compensation. The transient POX amplitude increase ended when heart rate (HR) increase indicated the next phase of compensation. There were 3 compensation phases, characterized by 3 levels of CF, HR and respiratory wave amplitudes (RESP). Cardiac output (Ca Outp) reflected only two phases. The pig recording of 7/13/06; time window 199.8 min.

Discussion

Issues in neuromonitoring

An optimal life sign monitor would detect a patient's earliest pathological changes. In response to severe blood loss, the brain is the body's most sensitive organ. The goal of this study was to detect CBF AR during hemorrhage and other CBF challenges. Hemorrhagic shock is the leading cause of death in both civilian and combat-related military injuries (Bellamy et al, 1996, Shoemaker et al, 1996); for details of hemorrhagic shock see (Udeani, 2015, Schiller et al, 2017, Rickards 2015). The ideal brain monitor would be one that detects CBF decrease and its reactivity non-invasively and continuously. REG, the technique for measuring CBF AR described in this study, shows promise as a non-invasive, mobile, and continuous non-operator dependent means of evaluating an unconscious patient.

Although neuromonitoring would be valuable for use as a general life sign monitor during patient emergency transport and treatment, neuromonitoring is not typically performed in the practice of emergency medicine in either civilian or military medical environments. A principal goal of neuromonitoring after a stroke or head injury is to prevent secondary brain damage caused by interrupted blood supply to the brain (hypoxia/ischemia). Monitoring cerebral blood flow reactivity to determine the status of CBF AR is an appropriate primary parameter to evaluate cerebral

resuscitation due to a systemic or regional cerebral injury leading to possible irreversible brain damage. Monitoring CBF AR is a suitable practice to help ensure adequate resuscitation during both emergency and hospital intensive care.

The superiority of a resuscitation strategy that targets maintenance of CBF and function in the context of cardio-pulmonary resuscitation has been demonstrated by P. Safar (1998).

Hypotensive resuscitation following a traumatic brain injury (TBI) calls for a mean SAP of 90 mmHg (Anonymous, 2003), which does not guarantee adequate CBF. Without the ability to monitor CBF autoregulation, the use of permissive hypotension (Beekley, 2008) may itself cause secondary brain damage.

There are two related background problems of CBF monitoring. First, there is a technical problem concerned with the comparison of CBF assessment methods since some methods yield approximations of global flow assessment (e.g. cerebral oximetry, REG) while others are local measures (e.g. LDF, Hemedex).

Our study overcame this problem by measuring these signals simultaneously and describing their relationship. Similarly to our results, a human study described mild differences among the CBF monitoring methods used (Zeiler et al, 2018). Second, there is a biological problem: the essential nature of CBF is heterogeneity during both physiological and pathological conditions. This is why changes in the global and local flow data can show divergent directions. A further complication is that what is true within the physiological range of CBF regulation can be false during pathological CBF states, for example in the case of increased ICP or hypotension. This means that during edema formation (ICP increase, CBF decrease), REG may not reflect decreased cerebral perfusion pressure but may instead reflect the increased water content of the cranial cavity (McHenry, 1965, Bodo et al, 1986).

To clarify such misleading information during neuromonitoring, we found that measuring a combination of signals simultaneously shows promise. In recent clinical practice, Doppler ultrasound is used for CBF monitoring. However, the Doppler measurement takes several minutes to perform, must be repeated several times daily and is operator dependent. Traditional Doppler probes are not designed for continuous monitoring. Flat probes are available but difficult to maintain for continuous monitoring, and the holding frame for conventional Doppler probes is inconvenient for continuous monitoring. In nonclinical applications such as physiological status monitoring for military combat casualty care, neither Doppler technique is adequate. Further studies of neuromonitoring CBF AR are in progress.

Anatomical background of cerebral blood flow autoregulation

The physiological basis of cerebrovascular reactivity concerns arterioles, the last small branches of the arterial system, which alter blood flow in response to tissue needs. Arterioles act as control valves through which blood is released into or withheld from capillaries (Guyton, 1991; Kontos et al, 1978). Anatomically, the arteriole has a strong muscular wall capable of closing a vessel completely to restrict blood flow or to dilate a vessel several fold to increase blood flow to capillaries and tissue. The fact that CBF is heterogeneous may explain our recorded variations during the various administered challenges. For example, CBF is typically lower in brain white matter than in grey matter. Also, during each administered challenge, the sensors of all measured modalities were on different areas of each pig's head.

REG correlations and data processing

A secondary goal of this study was to validate the usefulness of new automated data processing software developed to detect the status of CBF AR; we calculated differences in CBF AR among each of the measured modalities. Both the automated software and the traditional (observational) evaluation indicated the active status of CBF AR. Various correlations have been established between REG and CBF (volume, flow or pressure, detailed by Jenkner (1986). The consensus from a review of published REG literature is that the REG signal represents volume change. In an in vitro study, we established a correlation between the REG pulse wave (bioimpedance) and both flow and volume (Bodo et al, 2010). The REG pulse wave is quantified most frequently by using its derivative (Jacquy et al, 1974; Hadjiev, 1968) or integral. Both variables are sensitive to changes in CBF induced by perturbations such as CO_2 inhalation, carotid occlusion, and hemorrhage. The relationship between the REG pulse amplitude to cerebral blood volume was previously documented in humans; we used the radio-iodinated human serum albumin method during CO_2 inhalation (Bodo et al, 1986). In that study, we determined that the observed increase in REG pulse wave amplitude reflected an intracranial increase in blood volume. Earlier studies attempted to establish pathophysiological correlates with REG (McHenry, 1965; Hadjiev, 1968; Moskalenko, 1980; Jenkner, 1986). However, these studies did not include measurements of CBF AR. The first study demonstrating that REG can be used for CBF AR detection was published in 2010 (Brady et al). In this study we used a computer program (ICM+) for monitoring of CBF AR with ICP and REG. CBF AR was not included in a previously developed program for REG data processing (Montgomery et al, 2011). Successful REG data processing (signal averaging) was used in the computerized Cerberus system

(Bodo et al, 1995). The initial test of our automated program to calculate CBF AR was reported previously (Bodo et al, 2010). Like the ICM+ program, our automated software uses slow waves of ICP and SAP to calculate Pearson's correlation coefficient. The goal is to substitute invasive modalities (ICP, SAP) for noninvasive measurements (REG for ICP). We are currently initiating a study using peripheral bioimpedance as a noninvasive substitute for SAP. In the present study, we analyzed the pulse oximeter waveform for this purpose (Table 2).

Conclusion

The clinical significance of the present animal study is that REG, a noninvasive, continuous neuromonitoring modality, shows similar results to those of invasive monitoring modalities used to measure CBF AR following hemorrhage. The study also indicates that loss of CBF AR in response to severe hemorrhage is the earliest indicator of ischemia/ hypoxia, the causes of secondary brain damage; loss of CBF AR occurred before a decrease in cardiac output, the cardiovascular response to hemorrhage.

This animal work has demonstrated that REG has the potential for use as noninvasive brain monitor to identify the autoregulatory breakpoint for individual patients to determine their limit for permissive hypotension and has produced a signal analysis algorithm that allows real-time monitoring of the integrity of CBF AR. In order to overcome limitations of REG as a brain monitoring modality, we propose the simultaneous use of REG, EEG and respiration monitoring. REG is useful to indicate the earliest breakdown of CBF AR breakdown; cessation of EEG for 2 seconds, then final respiration would be used as additional indicators of further decrease of CBF (Bodo et al, 2013). Additionally, REG is useful for detecting spreading depression (Hartings, 2017, Bodo et al, 2010). Human validation studies of REG are currently in progress.

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Disclaimer

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted under an approved animal use protocol in an AAALAC accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, NRC Publication, 2011 edition. This work was supported by the U.S. Army Medical Research and Materiel Command (D43_0025_2005_WRAIR) and SBIR Grants 1 R43 HL074524-01 and 2 R44 HL074524-02A2.

Conflict of interest

The authors state no conflict of interest

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