COMPARISON OF CIRCULATORY STRESS INDICATORS IN A SWINE MODEL

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Abstract

It is known that stress in humans involves both the cardiovascular, central and autonomous nervous systems. Dysregulation of either system may lead to a wide spectrum of diseases, including vegetative disturbances. Currently, there are no diagnostic techniques allowing clinicians to distinguish whether observed changes in blood pressure or heart rate are caused by physiological events, such as exercising, a psychological condition, such as anxiety, or a pathophysiological condition, such as hemorrhage. Such differential diagnostic knowledge would be extremely useful in medical practice, especially for emergency and military medicine. Although the primary purpose of the present study was to compare haemostatic bandages, the study offered an opportunity to create a set of variables characterizing mild circulatory stress, such as hemorrhagic shock. Therefore, during the bandage study, we also looked at the variables from the point of view of combat casualty care by investigating possible early warning signs of hemorrhagic shock.

The purpose of the present study was 1) to compare the indicator of vegetative balance (Kerdo-index) to a known circulatory stress (mild bleeding); 2) to develop a multimodal quantification of circulatory stress.

Methods: An abdominal aortotomy was performed on anesthetized pigs (n=15), after which four treatment groups were created. Eight circulatory variables were calculated from measurements of electrocardiogram and

blood pressure measurements of the femoral and carotid arteries. Data were stored electronically for offline processing. Baseline values were compared to values measured 30 and 60 minutes after injury.

Results: Of the eight circulatory variables calculated, shock index was the most sensitive measure of circulatory perturbation, but no differences in shock index were noted among the four treatment groups. There were significant differences among the four groups in systolic and diastolic blood pressure and in vegetative balance (Kerdo-index).

Conclusion: Calculation of shock index and vegetative balance (Kerdo-index) may be useful in quantifying cardiovascular stress.

Key-words: circulation, bleeding, vegetative balance, Kerdo-index, shock index, cardiovascular stress, swine.

Introduction

Bleeding is a major cause of morbidity and death after trauma (*Clifford*, 2004). Although hemorrhage is the leading cause of death for combat casualties, catastrophic hemorrhage is rarely a pre-hospital combat medical management problem, since it tends to cause death before medical care can be provided. In civilian environments, most seriously injured victims can be reached and transported by emergency medical services personnel within minutes; in combat, it often takes hours simply to transport casualties off the battlefield. In combat situations, even if the transport distances are small, the hazardous nature of the forward combat areas frequently prevents medical personnel from quickly reaching the wounded (*Carr*, 2004).

In medical practice, pulse oximetry is the most widely used noninvasive monitoring modality (*McMorrow* and *Mythen,* 2006). A known limitation of pulse oximetry is that when hypotension is present, peripheral vasoconstriction may cause the pulse oximetry signal to be distorted or lost (*Sinex*, 1999). Consequently, when hemorrhage is present, there is a need to measure additional modalities and to calculate new variables for life sign monitoring. Here we present results obtained from calculating several modalities not widely used in detecting the consequences of progressive hemorrhage.

It is known that anxiety and stress in humans involve both the cardiovascular and central nervous systems. Dysregulation of either system may lead to a wide spectrum of diseases including vegetative disturbances. Currently, there are no diagnostic techniques to distinguish between blood pressure changes caused by circulatory disturbances and disturbances caused by anxiety/stress (*Giardino, Friedman* and *Dager,* 2007).

The Shock Index (SI) is the ratio of the heart rate to systolic blood pressure. 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 (*Yealy* and *Delbridge*, 1994). The formula of SI calculation is as follows: (heart rate in beats per minute) / (systolic blood pressure in mm Hg). In interpreting results, normal is 0.5 to 0.7; elevated SI: (> 0.9) was found helpful by *Rady* et al. (1994) to identify patients in the emergency care units requiring admission and/or intensive care despite apparently stable vital signs. Persistent elevation of the SI has been associated with a poor outcome in critically ill patients (*Cancio* et al., 2008).

Calculation of the Kerdo-index (*Kerdo*, 1966), modified by Sipos (*Bodo* et al., 1995), is as follows: (1- diastolic blood pressure /heart rate) + 100. In the Kerdo-index, values above 100 indicate sympathicotonia, and values below 100 indicate parasympathicotonia.

Our objectives were 1) to compare the indicator of vegetative balance (modified Kerdo-index) to a known circulatory stress (mild bleeding), and 2) to find a comprehensive approach to quantify circulatory distress.

Our hypothesis was that the best haemostatic bandage is one that causes the least change in circulatory variables.

Methods

Female Yorkshire pigs (32.44 ± 3.31 Kg; n=15) were anesthetized with isoflurane and prepared for surgery and monitored during the procedure as described previously (*Rothwell* et al., 2005). At the initiation of the experiment, warmed lactated Ringer's solution was infused at a rate of 8 mL/min. The femoral and carotid (ascending pharyngeal artery – APA - in pig) arteries were exposed to permit placement of a Millar pressure sensor (Millar Instruments, Inc., Houston, TX) (carotid artery) and a three port catheter (femoral artery) for blood pressure monitoring (systemic arterial pressure, SAP) and for collection of arterial blood for coagulation tests.

Procedures

Anesthetized pigs were placed in dorsal recumbency. A midline abdominal incision was performed and the spleen removed (*Sondeen*, *Coppes* and *Holcomb*, 2003). The abdominal aorta was isolated at the level of the kidneys, and a 4.4 mm hole was made in the aorta as previously described (*Rothwell* et al., 2005). The dressings were applied manually to the wound site and pressure (100 mmHg measured by manometer) applied for 4 min-

utes. Blood from the injury site was collected by suction into closed containers and pre-weighed surgical sponges were used to absorb the remainder. During the experiment, if the subject's mean arterial pressure dropped below 60 mm Hg, infusion with warmed lactated Ringer's solution was increased to 25 mL/min. The experiment was designed to continue for 60 minutes after the end of bleeding. Physiology data was collected with Ponemah instrumentation (Data Sciences, Inc., St. Paul, MN). If bleeding had not stopped when MAP dropped below 20 mm Hg, the animal was euthanized. After the last set of measurements, the animal was euthanized with a lethal dose (1 mL/5kg) of euthanasia solution (Veterinary Laboratory Inc, Lenexa, KS). At the end of the experiment, the exposed section of the aorta was removed for examination for the presence or absence of clots. Four bandage preparations were utilized in this study: control – gauze; liposome; salmon; and ¼ fibrin/thrombin (¼ fib/th); for further details see *Wang* et al. (2000) and *Rothwell* et al. (2005).

Data processing

Estimated blood volume was calculated as 6.5 % of weight. Shed blood volume was calculated as percentage of body weight. The following analog physiological signals were stored: carotid arterial and femoral blood pressure, electrocardiogram (EKG), exhaled CO_2 and isoflurane concentrations. Data processing was performed with custom-made software (DataLyser, L. Baranyi; Walter Reed Army Institute of Research). Measurements were made before bleeding (baseline), 30 and 60 minutes thereafter. Pulse wave variables were measured with Datalyser, typically during a 30-second period; in case of artifacts, eight pulse waves were measured. Changes were calculated and expressed as percentage of baseline. Student t-test in Excel (Microsoft, Redmond, WA) was used for statistical evaluation. $P< 0.05$ was considered significant.

The following circulatory variables were measured and calculated (see below and Figure 1):

1. Systolic blood pressure
2. Diastolic blood pressure
3. Pulse pressure (Systolic - Diastolic blood pressure)
4. Heart rate (HR)
5. Time interval between peaks of carotid (C) and femoral (F) pressures
6. Time interval between EKG R peak (EKG) and femoral artery (F) pulse peak

7. Shock index
8. Kerdo-index

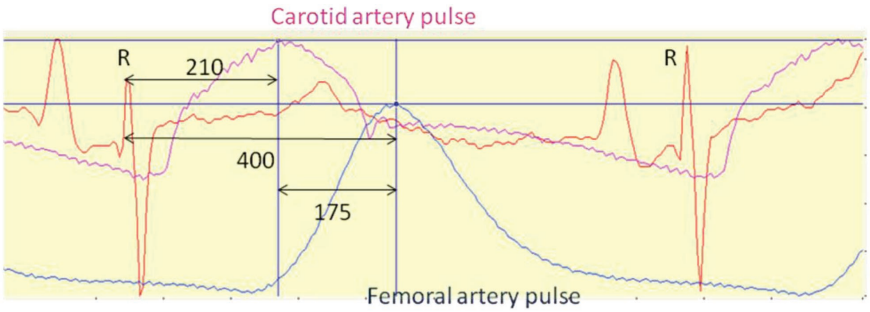


Figure 1: Pulse variables

R: EKG R peak. Vertical bars indicate carotid and femoral artery peaks. Arrows and numbers indicate intervals in millisecond: EKG R – carotid peak interval: 210 ms; EKG R – femoral peak: 400 ms; carotid peak - femoral peak: 175 ms. Time window: 1270 ms; Pig 15, file 15-1.exp.

Results

Shed blood volume alone did not indicate differences among haemostatic bandages (Figure 2). There was no significant difference in mean weight of groups compared to the control group.

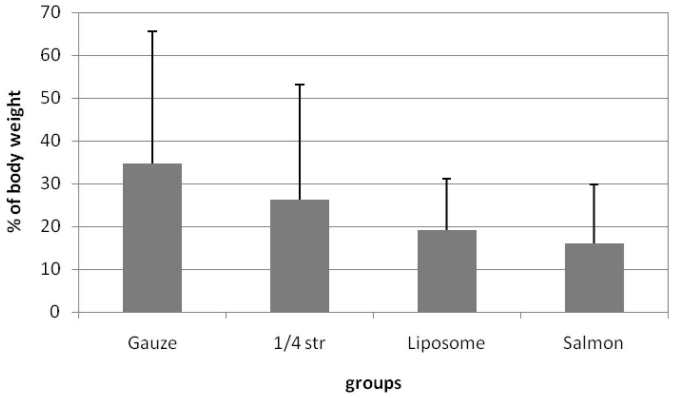


Figure 2: Shed blood volume in experimental groups. There was no statistically significant difference compared to control (gauze) group.

As an overall measure of circulatory perturbation, the shock index (SI) was the most sensitive. Significant differences were found between mean

value of SI for all three bandage treatments, for systolic and diastolic blood pressures and for the Kerdo-index.

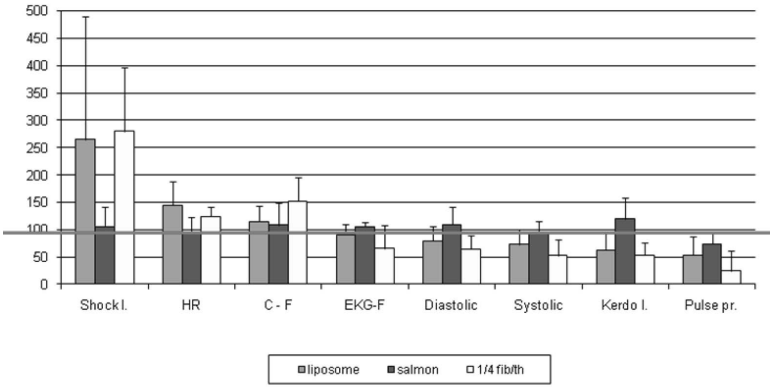
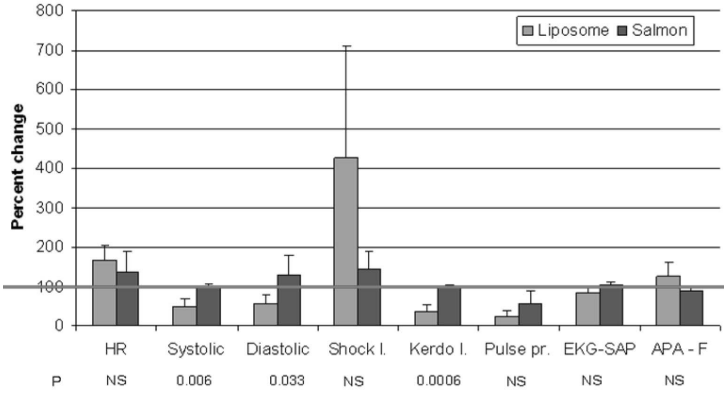


Figure 3: Changes in circulatory variables 30 minutes after injury. Changes in SI, heart rate, carotid-femoral interval, EKG-femoral interval, diastolic, systolic pressures, Kerdo-index and pulse pressures were compared among bandage formulations and among circulatory modalities. No change (horizontal line) = 100%.

The SI was the parameter with highest percentage change, but no differences in SI were noted among the bandage groups. A partial explanation for this result may be that SI was abnormally high under control conditions (extreme physiological stress imposed by the aorta bleeding model).



NS = non-significant. No change (horizontal line) = 100%.

Figure 4: Changes in circulatory variables in the salmon and liposome groups 60 minutes after injury. Changes in circulatory parameters were examined 60 minutes following injury and treatment with the salmon or the liposome dressings. Statistical significance was calculated to determine the difference in performance between the original salmon protein bandage formulation and the protein-liposome formulation as judged by circulatory parameters.

Based on analysis of the systolic and pulse pressures and the Kerdo and shock indices, there was no difference detected between the performance of the liposome and the ¼ fib/th bandage formulation. There were differences between the original salmon formulation, the liposome and the ¼ fib/th groups using these calculations.

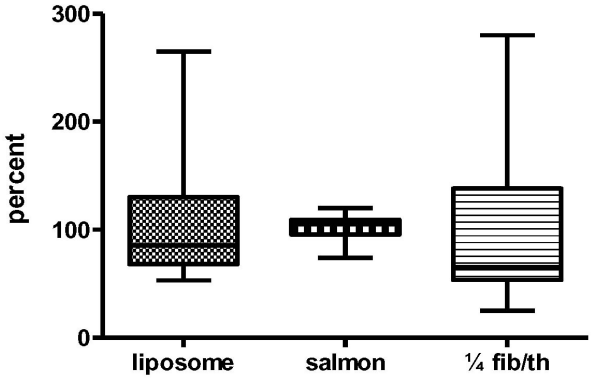


Figure 5: Summative percentage changes of eight circulatory variables 30 min after damage. Summation of changes in the circulatory variables showed that the salmon group had the smallest percentage change. Coefficient of variation for groups was as follows: 62.40%, liposome; 13.48%, salmon; 80.86%, 1/4 fib/th.

Discussion

Hemorrhagic shock is the leading cause of death in civilian and combat trauma. Effective hemorrhage control and better resuscitation strategies have the potential to save lives. Uncontrolled hemorrhage is the leading cause of preventable combat-related deaths. The vast majority of these deaths occur in the field before the injured can be transported to a treatment facility. Early control of hemorrhage remains the most effective strategy for treating combat casualties (*Alam* et al., 2005). A desirable method is still unavailable to estimate blood loss, which can be a helpful guide in resuscitation. Therefore, during the bandage study, we also looked at our variables from the point of view of combat casualty care as well by investigating possible early warning signs of hemorrhagic shock.

Visually estimated blood loss has long been known to be imprecise, inaccurate, and often underestimated, which may lead to delayed diagnosis and treatment. Error in estimating blood loss is dependent on actual blood loss volume. Both medical students and experienced faculty demonstrate similar errors (*Dildy* et al., 2004). External blood loss estimation by ambulance and hospital personnel is generally too inaccurate to be of clinical use (*Tall* et al., 2003). The epidemiology, cellular basis, and etiology of trauma-

related deaths were detailed elsewhere (*Sauaia* et al., 1995, *Hoffman*, 2004, *Cothren* et al., 2007). Similarly, in animal studies, it was reported that alterations in blood pressure variables can be detected only after each animal has lost over 36% of estimated initial blood volume (*Westphal* et al., 2007)

In combat casualty and civilian trauma victims with traumatic exsanguination, the potential for successful resuscitation from severe traumatic hemorrhagic shock is not only limited by the "golden one hour" but also by the "brass (or platinum) 10 minutes". One research challenge is to determine how best to prevent cardiac arrest during severe hemorrhage, before control of bleeding is possible. Another research challenge is to determine the critical limits of an optimal treatment for protracted hemorrhagic hypotension, in order to prevent "delayed" multiple organ failure after haemostasis and all-out resuscitation (*Shoemaker* et al., 1996). Our research addressed these concerns.

Initially, we hypothesized that the best bandage tested would result in minimum blood loss. However, our results showed otherwise (see Figure 2). Therefore, we needed to introduce other circulatory variables to differentiate among several haemostatic bandages (e.g. EKG and blood pressures – see Methods and Figure 1). Of the eight circulatory variables calculated, shock index (SI) was the most sensitive measure of circulatory perturbation, but no differences in SI were noted among the four bandage treatment groups. However, there were significant differences among the four bandage groups in systolic and diastolic blood pressure and in vegetative balance (Kerdo-index). The salmon group showed the least changes and was therefore determined to be the best hemostatic bandage. This result coincided with results based on non-circulatory variables.

The background of our approach in calculating variables indicating central and autonomic nervous system variables simultaneously is based on the anatomic and physiological fact known as 'co-location' and on the interaction of vital structures within the brainstem.

The autonomic nervous system

The body of an animal can be divided into somatic and visceral portions. The somatic portion interacts with the external environment through the skeleton-muscular system under the control of the cerebral cortex. The internal environment (inside the body) is regulated by the autonomic nervous system under supervision of the hypothalamus and brain stem nuclei. Specifically, the Autonomic Nervous System (ANS) supervises heartbeat, digestion, defecation reflexes, blood vessel constriction, etc. The word "au-

tonomic" implies that the ANS is independent of the cerebral cortex and not subject to conscious control. This is largely true, but people have trained themselves to gain conscious control of their heart rates, for example (Best 1). The modified Kerdo-index turned out to be a useful contributor in determining circulatory stress.

The reticular activating system

Activity of the cerebral cortex is dependent upon both specific sensory input and nonspecific activating impulses from the brain stem. The source of these activating impulses is the reticular formation of the brainstem (i.e., medulla, pons and midbrain). The reticular formation comprises much of the brainstem core, known as the tegmentum. The reticular formation not only contributes to the activation of the cortex but is also important for maintaining muscle tone of "antigravity muscles", assisting in regulation of breathing and heartbeat, and modulating the sense of pain. Although the ascending and descending reticular activating systems are well integrated, the latter tends to be centered in the medulla, whereas the former is found more in the pons and the midbrain (Best 2).

Interaction of central and autonomic nervous systems

The anatomy of the brainstem (medulla oblongata and pons), where the centers of the cardio-respiratory and vegetative nervous systems are co-located, explains the interaction between these systems. Another area of overlapping is the ascending reticular activation system. These systems help explain why any central nervous system activation involves heart rate, respiratory and vegetative changes, simultaneously. Researchers and clinicians who want to measure emotion or anxiety need to consider not only heart-related changes but other physiological measures as well. For example, an increase in heart rate can be a physiological consequence of exercise, but heart rate change can also be a consequence of hemorrhage. It is not possible to differentiate between these conditions based on heart rate measurement alone.

The interaction of general arousal (reticular activating system) and autonomic nervous system can be found elsewhere (*Jennings* and *Coles,* 2006; *Lacey* and *Lacey*, 2007). Additional details of the interactive nature of cardiovascular and behavioral events see (*Obrist* et al., 2007). Here we mention only a few facts revealed by using brain imaging methods naming involved brain regions of interaction.

Converging data from human functional imaging in healthy subjects, neuropsychological studies of brain-damaged patients, and non-human neurophysiology indicate that emotional processing is linked to anatomically distinct and well-defined brain regions. A main characteristic of emotion-related brain regions (orbitofrontal cortex, anterior cingulated cortex, amygdala, insula) is their reciprocal anatomical connectivity with each other as well as with neuromodulatory systems (e.g., serotonergic dorsal raphe, cholinergic nucleus basalis of Meynert, and dopaminergic ventral tegmentum) and with other brain areas involved in sensory, motor, and cognitive functions. These structures mediate the representation of stimulus values, the affect-leaden enhancement of sensory processing, and the predictions of values associated with actions in order to bias decision-making in uncertain situations (*Szily* and *Kéri*, 2008).

Arterial Stiffness (AS)

Pulse transit time is a distance between the EKG R peak and a peak of a pulse wave, see Figure 1. It is an index of arterial stiffness, measured during exercise (*Kounalakis* and *Geladas*, 2009). It was reported also that carotid-femoral pulse wave velocity is a direct measure of arterial stiffness (*Laurent* and *Boutouyrie*, 2007). Velocity pulse wave speed is an important biomarker of arterial stiffness and cardiovascular disease risk in man (*Quinsac* et al., 2007). Patients with anxiety had significantly higher carotid mean arterial pressure (MAP) %, brachial-ankle pulse wave velocity arterial stiffness index %, MAP, and diastolic BP of the extremities compared to controls (*Yeragani* et al., 2006). Blood pressure measurements provide information regarding risk factors associated with cardiovascular disease, but only in a specific artery. This can be determined by measurement of arterial pulse wave velocity (propagation time/distance). Separate from any role as a surrogate marker, AS is an important determinant of pulse pressure, left ventricular function and coronary artery perfusion pressure. Proximal elastic arteries and peripheral muscular arteries respond differently to aging and to medication (*Graham* et al., 2008). For further details on mechanisms, pathophysiology, and therapy of arterial stiffness, see (*Zieman*, *Melenovsky* and *Kass*, 2005; *Wilkinson*, *Franklin* and *Cockroft*, 2004). In this study we used various ways to measure AS (between EKG R and carotid as well femoral pulse wave peaks). It turned out to be a useful contributor in determining circulatory stress.

Most recently, in a study similar to our work using multiple variables, Convertino used physiological hemorrhage model, resulting in a conclusion proposing that derived indices based on currently available technol-

ogy for continuous monitoring of specific hemodynamic, autonomic, and/or metabolic responses could provide earlier recognition of hemorrhage than current standard vital signs and allow intervention before the onset of circulatory shock (*Convertino* et al., 2008).

For a demonstration of involvement of multiple organs/systems in hemorrhage, we here present a polygraphic recording from a swine hemorrhage (Figure 6) to illustrate how the cardiovascular, central and autonomous nervous systems act together and how the manifestation looks from the point of view of various measured modalities. Mean arterial pressure decreased to 40 mmHg during 15 minutes and was maintained by closed loop control at 40 mmHg (see upper trace, left side). In the first phase of hemorrhage, few modalities showed compensatory, transitory amplitude increase (POX, Car fl, Skin bf, REG). All traces characterize various phases of hemorrhage compensation. The involvement of various organs is presented quantitatively by different traces. The transient pulse oximetry amplitude increase ended when heart rate increase indicated the next phase of compensation. From the cerebral blood flow point of view, compensation has three phases, characterized by three levels of carotid flow amplitude. The cardiac output change reflected only two phases. This recording demonstrates the insufficiency of the clinical approach in following/recording arterial pressure or cardiac output alone in case of a hemorrhagic patient. It is impossible to see the whole picture when considering only a single modality. The immediate action taken by clinicians in emergency care or in the intensive care unit, when considering a single modality, might be neglect vital information and lead to incorrect treatment. We can demonstrate this situation with a Cushing response phenomenon.

The Cushing response

The Cushing reflex or triad is a cardiovascular response to increased intracranial pressure, a decrease in cerebral blood flow. Cerebral ischemia, a major complication of cerebral hemorrhage, causes a massive discharge of sympathetic outflow. The symptoms are hypertension, bradycardia and decreased or irregular respiration (*Anonymous,* 2004). The danger of these symptoms is not only the direct life threatening condition for the patient; misleading information, such as increased SAP, can cause the clinician to believe that the patient is improving, when in fact, the decreased cerebral perfusion pressure is actually causing brain ischemia. During postoperative care following neurosurgery, traumatic brain injury or hemorrhage, patients are typically in a comatose condition. In such cases, an increase in SAP can be easily misinterpreted as an improvement in the status of the patient.

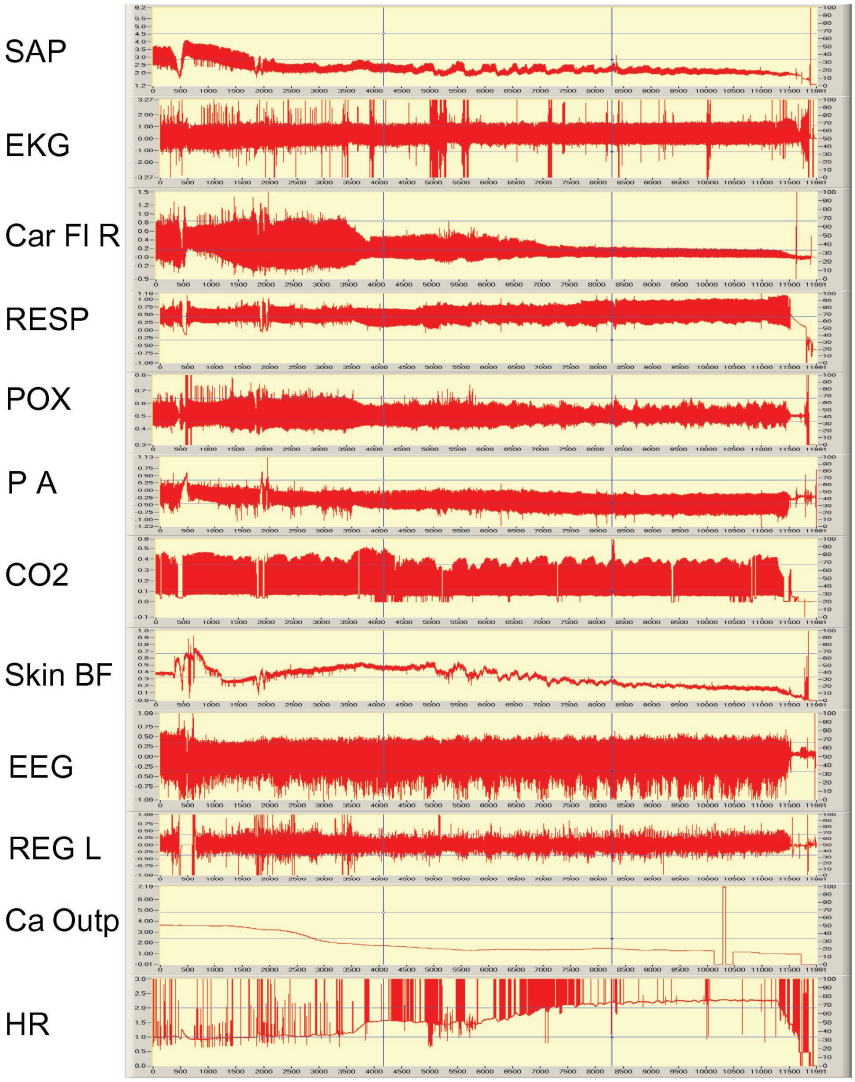


Figure 6: Polygraphic traces during hemorrhage. Time window, 199.8 minutes; pig ID: 7-13-06. Abbreviations: SAP (systemic arterial pressure); EKG (electrocardiogram); Car fl R, right carotid (ascending pharingeal) artery flow, measured by Doppler ultrasound; Resp, respiration, measured by a thermal sensor placed into the intubation tube; POX, pulse oximeter; PA, pulmonary artery pressure; CO_2, exhaled CO_2 concentration; Skin bf, skin blood flow by laser Doppler; EEG, electroencephalogram; REG L, rheoencephalogram, left side; Ca Outp, cardiac output; HR, heart rate; PA and Ca Outp were measured by a Swan-Ganz catheter.

Without intervention, SAP increase can lead to herniation and death (*Bakay* and *Lee*, 1965). Related clinical aspects can be found elsewhere (*Prall*, *Nichols* and *Munro*, 1995; *Jones,* 1989; *Strandgaard* and *Paulson* 1989, 1995; *Griswold* et al., 1981).

Conclusion

Shock index and vegetative balance (Kerdo-index) may be useful in quantification of cardiovascular stress. Responses of the sympathetic nervous system are rarely isolated phenomena and always require interaction with other functional systems in CNS. Thus, in some circumstance, responses of the sympathetic nervous system are part of the whole response, for example, in defense reactions. In some cases, other systems are called up to support the whole response (Sun, 1995). The progress of computerization in medicine have already devices with microprocessors not only measure a modality but also calculate derived variables. Such devices exist, for example BIS and LiDCOrapid monitors, which give adequate information on the depth of anesthesia, expressing level of sedation in both a numerical scale and a hemodynamic status (*Anonymous*).

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