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Correlation between cerebral near-infrared spectroscopy and macro-hemodynamic changes post-fluid resuscitation in the Sus scrofa model of hemorrhagic shock

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Abstracts

***Objectives*: Current resuscitation approaches focus on macrohemodynamic circulation, whereas adequate tissue perfusion and target organ oxygen delivery should be the primary goals. This study aimed to compare the macrohemodynamic markers with microcirculation markers (cerebral oxygenation) in response to shock and fluid resuscitation.**

***Design*: This is an experimental study using an intact in vivo model of hemorrhagic shock.**

***Setting*: This study was conducted at a certified animal experimental laboratory.**

***Patients and participants*: Male domestic piglets (Sus scrofa) 6-10 weeks old were used as the model for this study.**

***Interventions*: Measurement of microcirculation in animal model of hemorrhagic shock.**

***Measurement and results*: Under anesthesia, the pressure-targeted shock was induced via venous blood drawing to reduce mean arterial pressure (MAP) by 20%, followed by normovolemic resuscitation using NaCl 0.9% of equal volume to the blood drawn. After 30 minutes, hypervolemic resuscitation using 40 ml/kg NaCl 0.9% was given. Pulse contour cardiac output (PiCCO) was used to monitor cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and oxygen delivery (DO2), while near-infrared spectroscopy (NIRS) measured cerebral saturation (SctO2). All parameters were recorded at baseline, shock, immediately following normovolemic resuscitation, hypervolemic resuscitation (hypervolemic-1), and the next 30 minutes (hypervolemic-2), and 60 minutes (hypervolemic-3). There were strong correlations between delta SctO2, delta CI, delta SVI, and delta DO2 during the hemorrhagic shock and normovolemic phase ($p<0.05$). No macrohemodynamic parameters represent the cerebral oxygenation during hypervolemic-1 up to hypervolemic-3.**

***Conclusions*: Macrohemodynamic parameters were not correlated to SctO2 as a surrogate for microcirculation in every phase. We recommend routinely monitoring microcirculation as a target goal of resuscitation in critically ill patients.**

Key words: Pediatrics, shock, NIRS, hemodynamic monitoring.

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Introduction

Approximately 10% of inpatient care among children in developed countries is caused by hypovolemic shock due to dehydration, followed by post-operative and post-traumatic hemorrhage. (1) In hemorrhagic shock, stopping the active bleeding and adequate fluid resuscitation are key managements. The ultimate aim of resuscitation is to restore tissue perfusion in which oxygen supply is compromised during hemodynamic failure. Thus, oxygen delivery through the red blood cells must successfully enter the microcirculation and reaches the tis-

sues. Currently, most resuscitation guidelines focus on the hemodynamic parameters such as cardiac output, blood pressure, and venous oxygen saturation following the administration of fluids and/or vasoactive medications. However, not all resuscitations of systemic hemodynamics are effective in normalizing microcirculatory perfusion and oxygen delivery to the cells. (2)

Near-infrared spectroscopy (NIRS) cerebral oximeter is a continuous, non-invasive, optical-based device used to estimate changes in regional tissue oxygenation. (3-5) It works by calculating oxyhemoglobin and deoxyhemoglobin concentration via measuring the light absorbance at specific wavelengths. (6) Its use has been previously validated to monitor cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO), as well as intensive resuscitation. (7-11)

This study aimed to compare macrohemodynamic-targeted resuscitation at the microcirculatory level, by measuring cerebral oxygen saturation (SctO2) using NIRS in a hemorrhagic shock model. (3-5) The use of domestic piglets (Sus scrofa) as a hemorrhagic shock model has been validated in many studies. (12) Compared to rodents, its physiological response is more comparable to humans, hence is more widely used to study hemodynamic responses in shock. (13) Using this model, we aimed to assess the effect of fluid resuscitation on cerebral oxygenation in comparison to changes in other invasive macrohemodynamic parameters. We hope this study can contribute to a deeper understanding of cerebral oxygenation as a target parameter for resuscitation.

Materials and methods

Animals

We obtained eleven male, healthy domestic piglets (Sus scrofa), aged 8-12 weeks old and bodyweight of 10-12 kg from the Faculty of Veterinary Medicine, Bogor Agricultural Institute. The exclusion criterion was any piglet that was found sick throughout the study period (none applicable for all 11 piglets). The minimal number of samples for this study was 10 according to Federer's formula. Ethical approval for this experiment was obtained from the Animal Ethics Commission of the Faculty of Veterinary Medicine, Bogor Agricultural Institute (055/KEH/SKE/III/2017). The animals were kept at the Laboratory Animal Management Unit, where there were caged and given twice daily commercially available food and free access to water. The animals were treated according to the standard management of the Faculty of Veterinary Medicine, Bogor Agricultural Institute. After data collection was performed, all animals were treated and returned to the institution. No animals were sacrificed for this study.

Interventions

The models were anesthetized using 10% ketamine HCl (20 mg/kg intramuscular [IM]) and 2% xylazine HCl (2 mg/kg IM), followed by intubation and mechanically ventilated with the following settings: 10 ml/kg tidal volume, respiratory rate of 14 times/minute, FiO2 of 60%, and positive end-expiratory pressure (PEEP) of 5 mmHg. Subsequently, a NIRS patch (OxyAlertTM NIRSensors, Covidien, United States) was installed on either side of the forehead to measure SctO2, which was measured continuously during the experiment on a monitor (Somanetics INVOS Oximeter Cerebral/Somatic, Medtronic, United States). Mean arterial pressure (MAP) was measured via the femoral artery, under heparin 1 unit/ml maintenance. The pulse contour cardiac output (PiCCO) catheter (Pulsiocath, Pulsion Medical Systems AG, Munich, Germany) was placed on the internal jugular vein and femoral artery and connected to a PiCCO Plus v4.12 monitor (Pulsion Medical Systems AG, Munich, Germany). Using PiCCO, cardiac output (CO) was measured with a 10 ml NaCl 0.9% bolus at a temperature of <8 ^{o}C. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and oxygen delivery (DO2) measurements were taken for each phase.

In the shock phase, a blood draw to reduce MAP by 20% was performed. In the normovolemic phase, resuscitation was performed using NaCl 0.9% loading as much as the blood was withdrawn to induce shock. In the hypervolemic-1 phase, loading of 40 ml/kg NaCl 0.9% was given. Hypervolemic-2 and hypervolemic-3 phases referred to 30 minutes and 60 minutes post-hypervolemic-1, respectively. Sets of three measurements were recorded for each phase, five minutes post loading in normovolemic and hypervolemic-1 phases.

Data analysis was performed using SPSS version 22.0. Normally distributed data were presented as mean±standard deviation (SD), otherwise median and ranges. Pearson correlation and paired t-test were used to analyze any correlation between normally distributed variables. Significance was set at $p<0.05$.

Results

The measurements for each variable measured during all phases of the experiments are represented in **Table 1**. Shock decreased SctO2, which was then restored to baseline level following resuscitation.

As pressure-targeted shock was induced, MAP decreased upon shock and increased following resuscitation. Meanwhile, both CI and SVI were at their lowest during shock, and their highest following hypervolemic phase 1. The highest SVRI was observed during shock and the lowest was observed following hypervolemic phase 1. Upon shock, DO2 decreased and was restored upon resuscitation. The correlation coefficient between the changes in cerebral NIRS values (delta SctO2) and changes in each hemodynamic parameter is illustrated in **Table 2**.

Figure 1 shows the trend of measured parameters in each phase. It shows directly proportional changes between delta SctO2 and delta MAP in the shock, normovolemic, and first hypervolemic resuscitation phases, but without any correlations. Meanwhile, strong correlations were observed in the second and third hypervolemic resuscitation phases (r=-0.728, p=0.013; r=-0.836, p=0.019). There was a strong correlation between delta SctO2 and delta CI, in which both cerebral NIRS and CI were decreased during the shock phase (r=0.818, p<0.001). A significant moderate correlation between delta SctO2 and delta CI was also observed during the normovolemic resuscitation phase (r=0.638, p=0.017) in which both cerebral NIRS and CI were increased.

There was a strong correlation between delta SctO2 and delta SVI during the shock phase (r=0.885, p<0.001) in which both cerebral NIRS and SVI were decreased. A moderate correlation between delta SctO2 and delta SVI was observed during the normovolemic resuscitation phase (r=0.610, p=0.023), in which both cerebral NIRS and CI were increased. In the graph, opposing changes are seen between SctO2 and SVI during the second hypervolemic resuscitation, but this was not statistically significant. It can also be seen those changes in SctO2 values are generally directly proportional to changes in DO2 at the baseline phase up to the first hypervolemic phase, and inversely proportional at the second hypervolemic phase. However, the changes in DO2 were of a larger extent compared to the changes in SctO2. The correlation coefficient showed a strong correlation between delta SctO2 and delta DO2 during the shock phase (r=0.724, p=0.003) and a moderate correlation during the normovolemic resuscitation phase (r=0.563, p=0.036).

Discussions

In this study, we studied the dynamics of MAP, CI, SVI, SVRI, DO2, and SctO2 in response to shock, normovolemic, and hypervolemic resuscitation. We looked for any correlation between SctO2 as microcirculation parameters compared to other macrocirculation parameters. Significant correlations were only found between SctO2 and CI, SVI, and DO2. While MAP did not show any correlation with SctO2 at all phases.

Despite showing a concordant trend during the shock and normovolemic phases, the correlation between MAP and SctO2 was not significant. Furthermore, in hypervolemic-2 and hypervolemic-3 phases, the trend between MAP and SctO2 changes was discordant as MAP decreased while SctO2 increased. This may be explained by the act of the autonomic nervous system to maintain stable MAP. Upon hypervolemic loading, blood pressure increased as cardiac output increased, this activated baroreceptor to return blood pressure to a stable level. (14) Also, hypervolemic loading would increase preload and impose mechanical stress on the right atrial wall. This stretch induced atrial natriuretic peptide (ANP) release, causing vasodilation. A similar trend was observed by Chappel et al in which patients who underwent volume loading had significantly higher ANP that caused interstitial shifting of intravascular fluid, clinically seen as decreased MAP. (15,16)

Interestingly, SctO2 changes across all phases were kept at relatively minimal compared to other macrohemodynamic markers. Upon hemorrhagic shock, CI decreased by around 16% due to loss of preload. Similarly, both SVI and DO2 were also decreased. In the normovolemic phase, replacement of the same volume increased CI and SVI to near baseline. However, the DO2 increase was still below the baseline value. This was expected as the blood loss was replaced by NaCl 0.9%, hence clinically there was a decrease in hemoglobin level, affecting DO2. Hypervolemic resuscitation led to a supranormal increase in CI, SVI, and slightly in DO2 (hypervolemic-1). However, in hypervolemic-2 and hypervolemic-3, CI and SVI decreased, and in hypervolemic-2 DO2 decreased below the baseline. This decrease may be explained by the increased afterload due to hypervolemic volume loading.

In the shock phase, despite a mean decrease of CI by 16% and a mean decrease of DO2 by 31%, the SctO2 was only decreased by 11% on average. A previous study in humans experiencing cerebral hypoxia during cardiac surgery reported an absolute SctO2 value of <50% or a decrease of 20% from the baseline was associated with an increased risk of cognitive function disorders, frontal lobe injuries, stroke incidence, delayed electroencephalogram (EEG) waves, as well as increased hospital length of stay and ventilator use. (17-20) Our finding demonstrated only an average of 11% decrease in SctO2 upon 20% MAP drop. This finding might be

explained by cerebral autoregulation, which depended on dynamic arterial vascular resistance. The presence of cerebral autoregulation helps to maintain a constant blood flow to brain tissues when changes in arterial blood pressure occur following circulation disorders. (21)

In response to resuscitation, we observe that hypervolemic resuscitation led to a supranormal increase in CI, SVI, and DO2 parameters but did not significantly improve SctO2 to the brain. As the primary target of resuscitation is improvement in target organ perfusion, this supports the notion that it is also important to monitor microcirculatory parameters aside from macrohemodynamic markers alone in judging the response to resuscitation. Furthermore, introducing excessive amount of fluid is not beneficial, and may even be harmful, especially in pediatric population. (22) In hypervolemic-2 and hypervolemic-3, both CI and SVI decreased. This might signify increased afterload exerted by excessive volume. We can infer that decreased MAP during hypervolemic-2 and hypervolemic-3 served as a protective mechanism to prevent further CI and SVI decrease.

To date, there is no study on effectiveness of SctO2 for triage in the emergency unit or in the management of pediatric shock. This study is the first in vivo study that demonstrated the dynamics of macrohemodynamics in comparison to SctO2 in shock, during normovolemic, and following hypervolemic resuscitation in hemorrhagic shock model. The most important finding in this study was the correlation between SctO2 and other hemodynamic parameters, particularly CI, SVI, and DO2.

The popularity of NIRS to monitor microcirculation is increasing, particularly in the neonatal population and perioperative congenital heart disease patients. Even though the critical values for SctO2 or its changes from baseline is yet to be determined, the trend in SctO2 dynamics that correlates to CI, SVI, and DO2 cannot be ignored. Also, we demonstrated that macrohemodynamic parameters did not represent microcirculation status accurately. Our finding supported the routine use of NIRS as a rapid, non-invasive microcirculation monitoring as the end target of resuscitation in patients with shock. We also recommend future studies with the assessment of various regional tissue perfusion beside cerebral tissue. As well as observational studies to obtain critical values for SctO2 and its correlation to macrohemodynamic parameters, to better guide resuscitation in critically ill patients.

Limitations

Our study has some limitations. Firstly, the values for critical SctO2 or its changes from baseline have yet to be determined. The 20% MAP drop did not decrease SctO2 in our animal model, this may not be applicable to humans due to species differences. Secondly, we only measure regional brain tissue circulation. In response to shock, other regions may have different responses due to different microcirculatory regulations.

Conclusions

Most resuscitation guidelines target macrohemodynamic circulation. However, macrohemodynamic-focused resuscitation may not directly restore tissue perfusion. This study proved that MAP, CI, SVI, SVRI, and DO2 did not depict the changes and trends of SctO2 - which represents the microcirculatory status – in all phases of shock. However, the correlation could be seen in the shock and normovolemic phases. Thus, we recommend routinely monitoring microcirculatory parameters as the ultimate goal of resuscitation.

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Authors' contributions

AHP designed the experiment, analyzed the data, contributed the reagents/materials/analysis tools for this experiment, and wrote the draft and critically revised the paper. YP designed and performed the experiments, analyzed the data, contributed the reagents/materials/analysis tools for this experiment, and wrote the draft and critically revised the paper. RD oversaw the experiment and contributed to the critical revision of the paper.

Conflict of interest

No external funding was received for this study. The authors declare that they have no competing interests.

Table 1. Distribution of cerebral NIRS values and hemodynamic parameters

	Phases					
	Baseline	Shock	Normovolemic	Hypervolemic-1	Hypervolemic-2	Hypervolemic-3
SctO2 (%)	46±8.7	40.5±7.8	42.8±10.6	44.9±10.1	45.6±10.1	45.9±12.1
MAP (mmHg)	100.4±14.2	81.9±8.1	91.5±13.0	94.6±9.1	86.6±6.7	91.6±9.8
CI (l/min/m^2)	3.8±1.2	3.1±0.8	3.8±0.7	4.7±0.9	3.9±0.8	3.5±0.6
SVRI (dyn*sec/cm^5/m^2)	10246.2±3671.2	10455.4±3325.5	9034.5±2634.8	8416.1±1945.3	9705±3106.3	8941.1±5561.5
SVI (ml/m^2)	43±13.4	32.4±10.2	42.4±11.1	53.6±12.3	42.8±12.9	43.2±14.9
DO2 (ml/min)	2261±846	1459±354	2028±409	2281±526	2021±466	N/A

Legend: NIRS=near-infrared spectroscopy; SctO2=cerebral oxygen saturation; MAP=mean arterial pressure; CI=cardiac index; SVRI=systemic vascular resistance index; SVI=stroke volume index; DO2=oxygen delivery. Data is expressed as mean±standard deviations.

Table 2. Correlations between SctO2 changes and hemodynamic changes

Delta (%)		Delta SctO2					
		All phases	Shock	Normovolemic	Hypervolemic-1	Hypervolemic-2	Hypervolemic-3
MAP	r	0.011	0.053	0.164	0.066	-0.728	-0.836
	p	0.471	0.432	0.315	0.428	0.013*	0.019*
CI	r	0.438	0.818	0.638	0.253	0.440	0.202
	p	<0.001*	<0.001*	0.017*	0.226	0.088	0.276
SVI	r	0.439	0.885	0.610	0.428	0.300	0.075
	p	<0.001*	<0.001*	0.023*	0.095	0.185	0.413
SVRI	r	-0.160	-0.345	-0.151	0.221	0.099	-0.462
	p	0.119	0.124	0.328	0.257	0.393	0.076
DO2	r	0.436	0.724	0.563	0.118	0.284	N/A
	p	0.002*	0.003*	0.036*	0.365	0.199	N/A

Legend: SctO2=cerebral oxygen saturation; MAP=mean arterial pressure; CI=cardiac index; SVI=stroke volume index; SVRI=systemic vascular resistance index; DO2=oxygen delivery; r=Pearson correlation test; *=p<0.05 (1-tailed).

Figure 1a. Dynamics of delta SctO2 and MAP

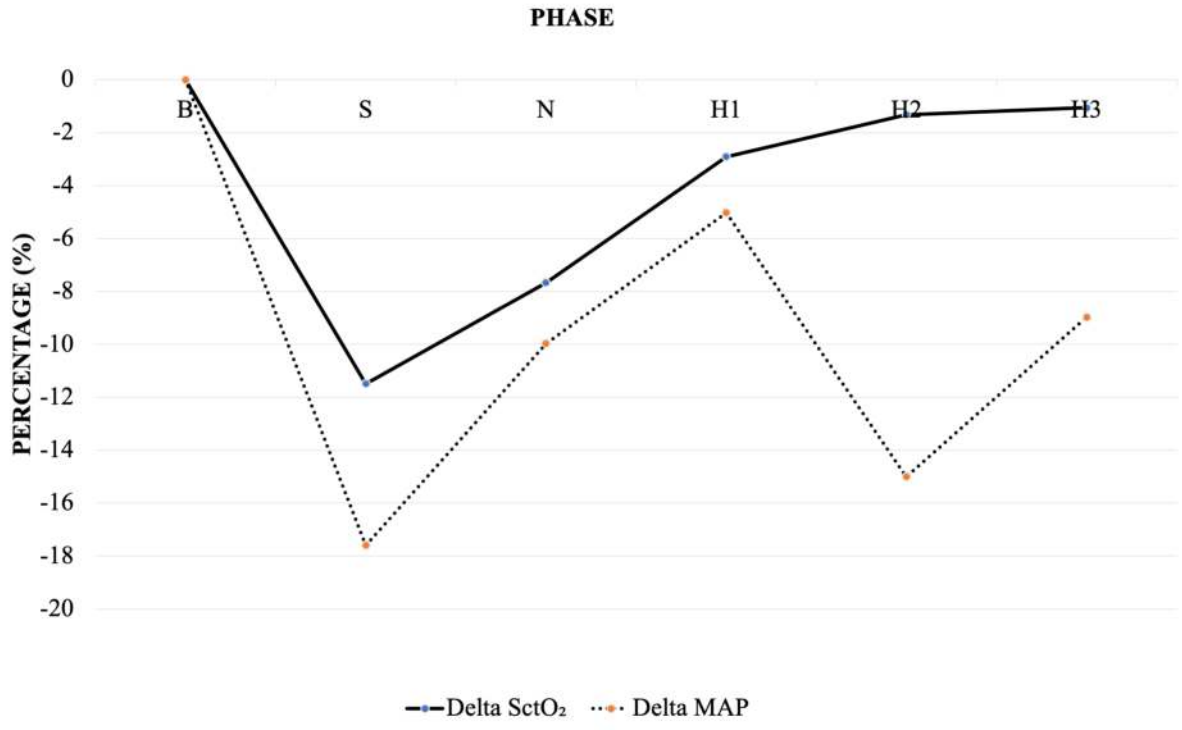
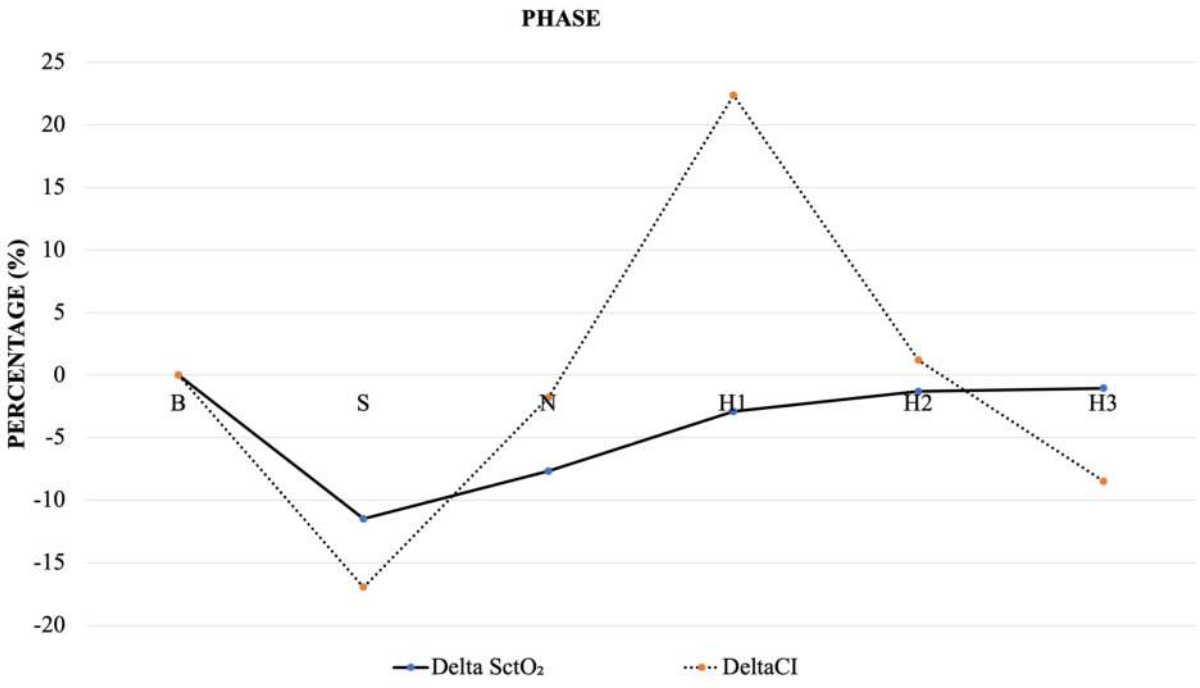


Figure 1b. Dynamics of delta SctO2 and CI



Legend: SctO2= cerebral oxygen saturation; MAP=mean arterial pressure; CI=cardiac index;B=baseline phase; S=shock phase; N=normovolemic phase; H1=hypervolemic-1 phase; H2=hypervolemic-2 phase; H3=hypervolemic-3 phase.

Figure 2a. Dynamics of delta SctO2 and SVI

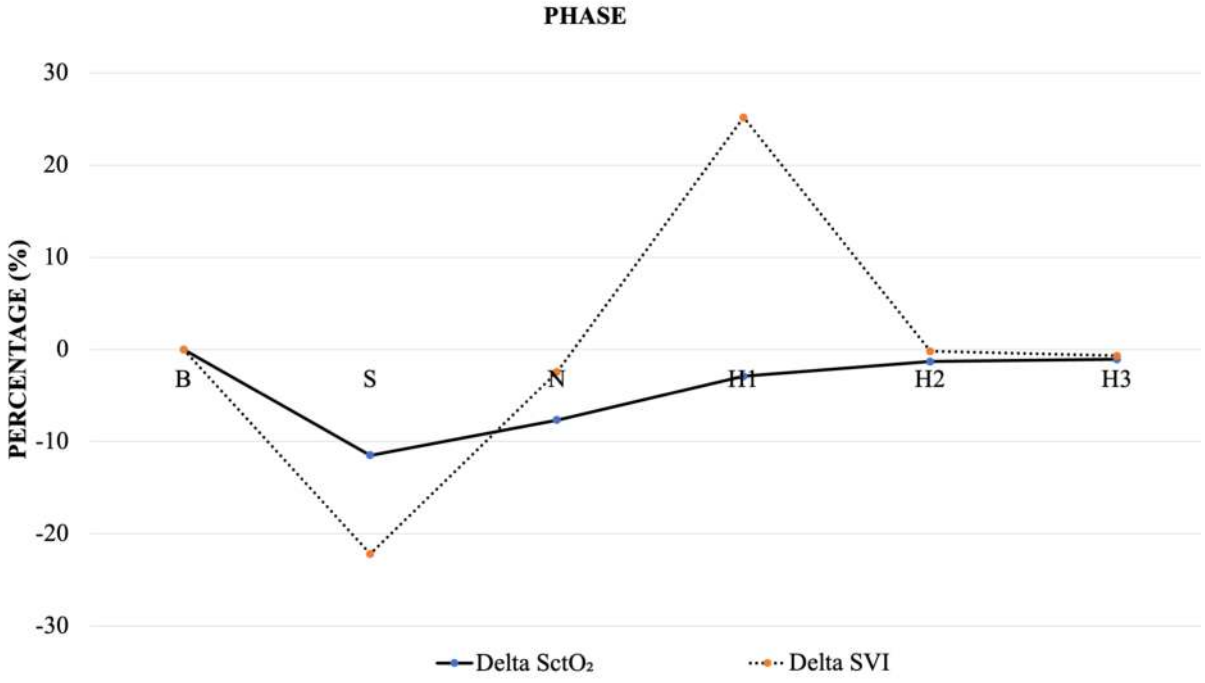
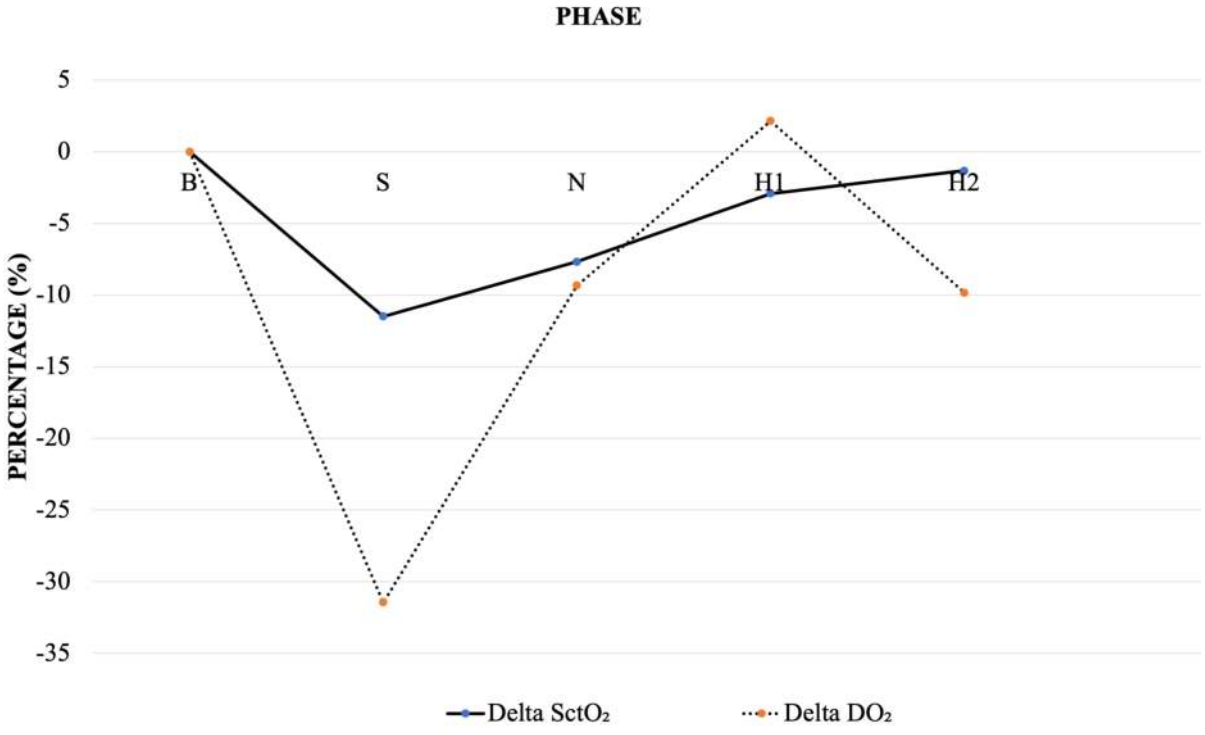


Figure 2b. Dynamics of delta SctO2 and DO2



Legend: SctO2= cerebral oxygen saturation; SVI=stroke volume index; DO2=oxygen supply; B=baseline phase; S=shock phase; N=normovolemic phase; H1=hypervolemic-1 phase; H2=hypervolemic-2 phase; H3=hypervolemic-3 phase.

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