ORIGINAL ARTICLE

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Does hyperbaric oxygen therapy positively change organic dysfunctions in bitches with sepsis caused by cystic endometrial hyperplasia-pyometra

Oxigenioterapia hiperbárica altera positivamente a disfunção orgânica de cadelas com sepse por hyperplasia endometrial cística-piometra

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ABSTRACT: Experimental models have shown positive outcomes associated with hyperbaric oxygen therapy (HO) when it comes to reducing mortality rates in sepsis patients. The aim of the present study is to assess HO impact on the microperfusion of sepsis bitches with Cystic Endometrial Hyperplasia-Pyometra (CEH-P) based on SOFA SCORE (*Sequential Organ Failure Assessment*) to quantify and monitor organic dysfunction degree. Eight (8) bitches diagnosed with CEH-P were included in the study; they were randomly split into two groups: G1 (ovariohysterectomy + clinical therapy) and G2 (ovariohysterectomy + clinical therapy + HO). All bitches in G2 were subjected to three HO sessions, at 24-h time interval between sessions. All animals showed at least one organic dysfunction due to sepsis. Animals in G2 presented significant improvement in clinical conditions and initial 51% reduction in SOFA scoring. On the other hand, animals in G1 recorded 29% reduction in this variable. Hyperbaric therapy was effective in reducing bitches' organic dysfunction with sepsis caused by CEH-P; however, it did not have significant reflex on Central Venous Oxygen Saturation ($SvcO_2$).

KEYWORDS: Hyperbaric therapy, SOFA score, central venous oxygen saturation ($SvcO_2$)

RESUMO: Modelos experimentais têm demonstrado resultados positivos associados à oxigenioterapia hiperbárica (OH) com relação a redução da mortalidade em pacientes sépticos. O objetivo deste estudo foi avaliar o impacto da OH na microperfusão de cadelas com Hiperplasia Endometrial Cística-Piometra (HEC-P) em quadro de sepse, utilizando a escala SOFA (*Sequential Organ Failure Assessment*) para quantificar e monitorar o grau de disfunção orgânica. Foram incluídas oito cadelas com diagnóstico de HEC-P, distribuídos aleatoriamente em dois grupos iguais: G1 (ovariohisterectomia + terapia clínica) e G2 (ovariohisterectomia + terapia clínica + OH). No total, as cadelas do G2 foram submetidas a três sessões de OH, com intervalo de 24 horas entre as sessões. Todos os animais apresentaram ao menos uma disfunção orgânica devido a sepse. Observou-se que os animais do G2 apresentaram melhora significativa nas condições clínicas e redução da pontuação SOFA inicial em 51%. Em contrapartida, os animais do G1 demonstraram redução de 29%. A terapia hiperbárica foi eficaz na redução da disfunção orgânica de cadelas em sepse por HEC-P, porém, não repercutiu significativa na Saturação Venosa Central de Oxigênio ($SvcO_2$).

PALAVRAS-CHAVE: Terapia hiperbárica; SOFA score; Saturação venosa central de oxigênio ($ScvO_2$)

INTRODUCTION

Cystic Endometrial Hyperplasia-Pyometra (CEH-P) is a high-incidence illness in veterinary medicine and animals suffering from this pathology are often hospitalized with sepsis symptoms or with septic shock with installed organic dysfunction (Filho *et al.*, 2020; Hagman, 2022). In clinical terms, these patients present hypovolemia and arterial hypotension caused by dehydration and systemic vasodilation, which lead to lower cardiac output (Kislitsina *et al.*, 2019).

Any hemodynamic change leading to lower oxygen supply - be it caused by intravascular volume reduction (preload), arterial and venous vasodilation (afterload), and

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myocardial depression (contractility), or by causes leading to hypermetabolism - triggers unbalance in systemic oxygen input, given the lower demand for oxygen (Rivers *et al.*, 2001). Consequently, cells get into hypoxia and tissue hypoperfusion states, and this frame compromises microperfusion. Cells develop ischemia followed by tissue failure if the tissue-oxygen demand is not fulfilled (Conti-patara *et al.*, 2012; Singer *et al.*, 2016).

Tissue ischemia is one of the main consequences of sepsis development (Minasyan, 2022) due to the release of bacterial toxins, inflammatory mediators and free radicals (Wu *et al.*, 2018). Tissue ischemia accounts for inducing cells to seek other metabolic pathways, such as anaerobic metabolism activation, to achieve energy acquisition (Oley *et al.*, 2020). However, the anaerobic pathway is much lesser efficient in producing adenosine triphosphate (ATP), besides producing nitric oxide and lactic acid, which lead to metabolic acidosis (Gouveia *et al.*, 2022).

It is possible correlating Central Venous Oxygen Saturation ($SvcO_2$) to tissue hypoxia level at severe cases due to reduced oxygen supply to tissues. SvcO2 values lower than 70% are featured by higher oxygen extractions (Taylor & Tibby, 2020; Minasyan, 2022).

Hyperbaric oxygen therapy (HO) consists in administering 100% oxygen within pressurized environment at rates higher than 1 Absolute Atmosphere (ATA). This procedure improves oxygen diffusion and increases its availability for tissues (Takahashi *et al.*, 1992; Yamanel *et al.*, 2011). Systemic inflammation processes, increased antimicrobial activity, burn infections, osteomyelitis, chronic wound healing, improved tissue perfusion in hypoperfused and ischemic tissues are the main methods recommended as treatment or adjuvant therapy (Memar *et al.*, 2019).

Although HO effects are complex and remain little assessed in veterinary medicine, some studies have shown their positive outcomes in several diseases and their benefits to therapeutic effects on inflammatory cytokines (decrease in interleukins-1 and 6, decrease in tumor necrosis factor), necrotic tissue healing, tissue perfusion improvement in low oxygen supply tissues, besides helping responses to infection processes, such as sepsis (Kirby *et al.*, 2019; Yang *et al.*, 2020).

Therefore, the aim of the present study was to use HO as adjuvant therapy method to treat sepsis in CEH-P bitches based on using $SvcO_2$ as microperfusion evaluation parameters and SOFA score to quantify and monitor organic dysfunction.

MATERIALS AND METHODS

The study was approved by the Ethic Committee on Animal Use (CEUA) of Federal University of Santa Maria – Rio Grande do Sul State (UFSM – RS), under registration n. 9462020221.

Eight (8) bitches under sepsis treatment at the Veterinary Hospital of Federal University of Santa Catarina (HVU-UFSM) and diagnosed with CEH-P, without history of other associated-comorbidities, with one or more organic dysfunction - based on SOFA assessment criteria - were included in the study.

The animals were randomly split into two groups (G1 - ovariohysterectomy (OVH) + clinical therapy, and G2 – OVH + clinical therapy + HO). Each group held 4 models. Only animals in G2 were subjected to three HO sessions after OVH as adjuvant therapy, based on guidelines suggested by Memar *et al.* (2019) for both number of sessions and their duration.

The following examinations were carried out: physical examination, blood count, biochemical analysis (albumin, alanine aminotransferase, creatinine, alkaline phosphatase, total proteins and urea) and, subsequently, central venous blood gas analysis with samples collected with the aid of central venous catheter. Patients who presented at least one organic dysfunction, based on SOFA assessment criteria, were taken into consideration.

The post-operative treatment was standardized to both groups. Either G1 or G2 were treated with conventional clinical therapy: antibiotic (ceftriaxone 30 mg/kg, BID, associated with metronidazole 15 mg/kg, BID), non-steroidal anti-inflammatory (meloxicam 0.1 mg/kg, SID), antiemetic (ondansetron 0.2 mg/kg, BID), opioid analgesia (methadone 0.2 mg/kg, TID) and fluid therapy (lactated Ringer at the rate of 2.5 mL/kg/h). However, three HO sessions at 2 ATA (75 minutes long with 24-h time interval between them) were associated with conventional clinical therapy in G2.

All animals included in the study were individually assessed by evaluation triage based on SOFA score for organic dysfunction quantification and sepsis frame diagnosis, as recommended by the *Third International Consensus Definition for Sepsis and Shock* (*Sepsis-3*).

SOFA score was recorded and computed for 4-day hospitalization period, according to criteria available in the literature (Ripanti *et al.*, 2012; Singer *et al.*, 2016). Laboratory data necessary to calculate SOFA scores were measured once a day, at 24-h time interval between collection sessions, and it totaled four SOFA scores for each animal in both groups.

The first sample collection for SOFA scoring took place at the time the patient was admitted for surgery (D0), and it was followed by new sample collections 24 hours after the previous one (D1 – 24 h after D0; D2 – 48 h after D0; D3 – 72 hours after D0).

Six (6) systems were assessed, in total, namely: respiratory, cardiovascular, hepatic, renal, neurological and coagulation systems, and each one of them was assessed and scored from 0 to 4 – score equal to, or higher than, 2 confirmed organic dysfunction. Whenever 2 or more systems recorded scores equal to, or higher than 2, it would feature organs' multiple dysfunction.

The partial oxygen pressure/inspired oxygen fraction ratio (PaO2:FiO2), recording 0.21 FiO2 standardization in both groups, was used for respiratory system assessment.

Systolic blood pressure (SBP) measured through the non-invasive method with Vascular Doppler in the right radial artery, was adopted for cardiovascular system assessment. Hepatic system assessment was carried out by measuring serum creatinine. Neurological assessment was performed by following the modified Glasgow Coma Scale and coagulation evaluation was conducted by measuring the platelets, as shown in Table 1.

$SvcO_2$ was used to assess and monitor tissue hypoperfusion in order to quantify tissue hypoxia severity, to follow-up responses to standard clinical treatment and to HO as post-operative adjuvant method. $SvcO_2$ was assessed at the following moments: D0, D1, D2 and D3, and it totaled 4 measurements during patients' hospitalization time. All $SvcO_2$ assessments took place before the HO session.

All collected samples regarded central venous blood, and collections were conducted by introducing the central venous catheter and fixing it in the left external jugular vein until reaching the third intercostal space – catheter tip had to be placed between the cranial vena cava and caudal vena cava bifurcation. Each sample counted on 1 mL central venous blood and $SvcO_2$ value was found through blood gas analysis (Cobas® b 121 system, Roche-Switzerland, Basel).

Animals in G2 were subjected to HO sessions at the post-operative period, throughout hospitalization time. Four sessions at 2 ATA were carried out at 24-h time interval between sessions, which lasted 75 minutes, each. Monoplace hyperbaric chamber (HVM®, HVM-H1- USA, Florida), for exclusive veterinary-medicine use, was herein adopted (Figure 1).

Physical parameters and lack of HO contraindications were analyzed before placing the patient in the hyperbaric chamber. The first HO session (D0) was carried out in the same day of the OVH surgical procedure. In order to do so, patients were subjected to post-anesthesia monitoring for 1 hour to make sure about their full recovery before the HO session. The other sessions took place 24 hours (D1), 48 hours (D2) and 72 hours (D3) after anesthesia recovery – the same time schedule was followed in all sessions.

As soon as the hyperbaric chamber door was closed, one could observe patients' behavior for 5 minutes. The chamber's compression phase would start if the animal remained stable, and it was done by opening the oxygen valve and increasing pressure to 1 psi per minute. Gradual environment pressurization was activated every 15 minutes until reaching the desired pressure: 2 ATA, since it would provide patients with 100%-oxygen environment.

The treatment phase would start after chamber pressure reached 2 ATA and oxygen concentration reached 100%, and it was done by maintaining the 2 ATA pressure for 45 minutes. Finally, the chamber decomposition phase would start by both closing the oxygen valve and slow decompression at 1 psi per minute for 15 minutes. Chamber opening was carried out and patients were removed from it whenever pressure reached 0 psi. Patients were subjected to physical examination after it was taken out of the chamber, before referring it to the hospitalization sector.

It is important pointing out that the patient was continuously monitored in the hyperbaric chamber throughout

Source: The author's inventory

Figure 1 . Monoplace Hyperbaric Chamber (HVM®) of UFSM University Veterinary Hospital.

Table 1 . SOFA Score's organic dysfunction assessment criteria - *Sequential [Sepsis-Related] Organ Failure Assessment*. Adapted from Singer et al., 2016.

Sequential Organ Failure Assessment Score (SOFA)						
Systems	**Variable**	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Score 4**
Respiratory	PaO_2/FiO_2 (mmHg)	> 512	< 512	< 357	< 214	< 89
Cardiovascular	PAS (mmHg)	> 100	85 - 99	< 85	Norep. 0.1 – 0.5 ug/kg/min	Norep. > 0.5 ug/kg/min
Neurological	Modified Glasgow	> 16	15	14	12 – 13	< 11
Hepatic	Albumin (mg/dL)	> 3.0	2.6 – 2.9	2.2 – 2.5	1.8 – 2.1	< 1.7
Kidney	Creatinine (md/dL)	< 1.2	1.3 – 1.9	2.0 – 3.4	3.5 – 4.9	> 5.0
Coagulation	Platelets ($x10^3$/uL)	> 150.00	< 150.00	< 100,000	< 50,000	< 20,000

PaO2 – partial oxygen pressure; FiO2 – inspiratory fraction of oxygen

the session, so that it could be stopped and assistance would be provided to the model in case of any sign of serious side effect such as seizures, syncope or barotrauma. All HO sessions in the present study were followed and inspected by the same vet (in charge), who was trained by HVM® (*Hyperbaric Veterinary Medicine*) for chamber functioning and animal management. There was no complication requiring immediate therapy canceling.

Data were subjected to Shapiro-Wilk test for group homogeneity assessment - sets of values were parametric at p>0.05. Parametric data were subjected to analysis of variance followed by Newman-Keuls post-hoc test. Non-parametric data were analyzed through Mann-Whitney and/or Kruskal-Wallis test. $SvcO_2$ data were assessed through Analysis of Variance followed by Newman-Keuls post-hoc test, SOFA data were assessed through non-parametric statistics, based on Kruskal-Wallis test, whenever data recorded for the same treatment were compared to each other, at different time intervals. Mann-Whitney test was used to compare groups within the same time interval.

RESULTS AND DISCUSSION

Based on SOFA score, all animals presented at least one organic dysfunction caused by sepsis at hospital admission day (T0). The median recorded for the SOFA score of animals in G1 reached 3.5 points at day one (T0) and 2.5 at day 4 (T3). The mean SOFA score recorded for animals in G2 was 8.5 at T0 and 4.2 at T3 (Table 2). Mann-Whitney test showed significant difference between control groups and HO at D0 (p=0.014), but there was no statistical difference at D3 (p=0.10).

Conventional clinical therapy led to 29% reduction in the initial SOFA scores recorded for animals in G1. On the other hand, those in G2, who were subjected to hyperbaric oxygen therapy sessions, recorded the best clinical conditions and reduction by 51% in initial scoring (Figure 2).

Based on the Mann-Whitney test, there was significant difference between the control and HO groups at times D0 (p=0.014), D1 (p=0.014) and D2 (p=0.042), but there was no statistical difference in D3 (p=0.10). The Kruskal-Wallis test did not show statistical difference in the long run, either in the control (p=0.09) or HO group (p=0.018).

Consequently, based on the raffle criterion, animals in G2 were those presenting the worst conditions, and it was proven by its SOFA score, which was higher than that recorded for G1. However, there was significantly higher improvement and remarkable SOFA score reduction in patients subjected to HO associated with conventional clinical therapy, since it led to greater organic dysfunction reduction in patients subjected to it.

Two patients in G2 were hospitalized with septic shock conditions and multiple organic dysfunctions, so they scored higher SOFA (11 and 10 points) and scores higher than those recorded for animals in other studies. Both animals presented high blood pressure (PAS < 85 mmHg), stupor only responsive to nociceptive (Glasgow 14) and hypoalbuminemic (albumin < 2.2 mg/dL) stimuli, with renal function loss (creatinine 7.0 and 3.5 mg/dL) and thrombocytopenia (132,000 and 108,000). These two animals were normotensive, with alert consciousness level and without neurological deficits, normoalbuminemia, normal platelet activity. One of the animals showed reestablished renal function, and the other one presented creatinine increase (3.0 mg/dL).

Clinical changes in the other animals, in both groups, at admission time, were similar to each other, each of them showed one or two organic dysfunctions, mainly high blood pressure and hypoalbuminemia, due to sepsis. Either the conventional clinical therapy or HO associated with conventional clinical therapy were efficient in stabilizing animals' health conditions in these cases, since there were no statistical differences at the 4th hospitalization day (T3).

According to Ripanti *et al.* (2012) and Kalogianni *et al.* (2022), using SOFA criteria is good to treat severely ill dogs, mainly those with sepsis, since they can be adopted to quantify organic dysfunction degree from their hospital admission to their evolution frame and outcome. The SPFA score is widely used in human medicine, in emergency cases, in internal medicine and in ICU patients, to assess the conditions and prognosis of individuals presenting organic dysfunction or multiple organ failure (Zhang *et al.*, 2019). Furthermore, the

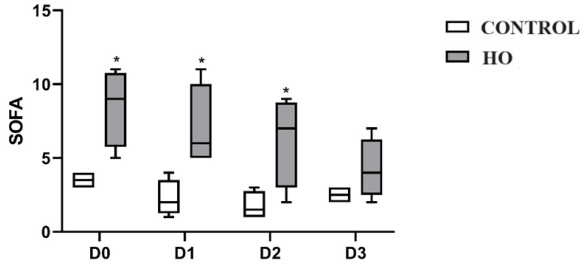

Figure 2 . Statistical representation based on Mann-Whitney and Kruskal-Wallis tests applied to SOFA scores of bitches with sepsis caused by EC-P.

Table 2 . Mean SOFA score recorded for bitches with sepsis caused by CEH-P in the control (G1) and hyperbaric groups (G2)

Groups	T0	T1	T2	T3
G1	3,5 ± 0,5	2,2 ± 1,2	1,7 ± 09	2,5 ± 0,5
G2	8,5 ± 2,5	7,0 ± 2,8	6,2 ± 3,0	4,2± 2,0

Data were expressed as mean ± standard deviation.

SOFA score also works as quantitative index to analyze changes in target-organs' organic function based on oscillations in the score recorded for patients within 24-h time intervals (Liu *et al.*, 2022).

As for guidelines by Singer *et al.* (2016), nowadays sepsis is classified as organic dysfunction posing risk to life due to the body's exaggerated and exacerbated response to infection processes. This inflammatory response accounts for inducing the organism to develop macro and microcirculatory dysfunctions caused by tissue oxygen shortage. This process leads to hypoperfusion and systemic hypoxia in several tissues and viscera (Caraballo & Jaimes, 2019).

Thus, dysfunction and organic failures are changes often observed in sepsis or septic shock frames, and it turns the SOFA system into a valuable tool to detect such changes, as well as to quantify and assess disease severity degree, or to anticipate likely complications caused by sepsis, itself (Grooth *et al.*, 2017; Caraballo & Jaimes, 2019; Kalogianni *et al.*, 2022).

The option for using the SOFA score in the present study allowed identifying CEH-P animals also presenting sepsis, and quantifying the number of organic dysfunctions, the affected systems and sepsis evolution.

According to Poff *et al.* (2016), HO increases the levels of oxygen diluted in the plasma, and it increases PaO2, which accounts for supplementing oxygen availability to tissues, mainly to the hypoperfused ones. This process improves cell metabolism. Based on Rossignol *et al.* (2007), using HO as adjuvant therapy in patients with Systemic Inflammatory Response Syndrome (SIRS) – nowadays classified as sepsis – is beneficial to reduce inflammatory processes by reducing the production of pro-inflammatory cytokines and by releasing the tumor necrosis factor.

Tissue cells demand approximately 60 mL oxygen per 1L of blood for physiological respiration cell maintenance. Oxygen concentration in the blood reaches approximately 3 mL/L (0.0031 mL/dL of blood per mmHg of arterial oxygen tension) whenever these cells reach 1 ATA (equivalent to that at sea level) (Leach *et al.*, 1998; Piantadosi, 1999). Oxygen dissolved in blood plasma reaches concentration of 60 mL/L when these cells are subjected to pressure of 3 ATA. It makes the aerobic cell metabolism more efficient and is enough to fulfil physiological tissues' demand, without the need of oxygen linked to, and carried by, hemoglobin – this process is called transient hyperoxia (Leach *et al.*, 1998).

Therefore, HO plays key role in oxygen diffusion, mainly in ischemic tissues, besides helping post-ischemic tissue oxygenation (Oley *et al.*, 2020). This outcome can be observed through slow improvement in, and reduction of, organic dysfunction, just as they carried out in HO sessions, based on SOFA scoring. It is essential recovering animals in G2, mainly because they showed worse conditions than those in G1.

According to Memar *et al.* (2019) and Gouveia *et al.* (2022), 1.4 ATA is the minimum pressure necessary for achieving HO therapeutic effects, and 3 ATA is the maximum tolerated pressure. The herein observed 2-ATA pressure exerted during the three 75-m sessions was efficient and led to positive outcomes regarding organic dysfunction reduction in these animals. Besides, there were no complications or collateral effects during, and after, the sessions.

Although results were above the aforementioned ones, it was not observed significant change between groups within the same time interval, or between the same group at different time intervals, assessed based on $SvcO_2$ values. Mean $SvcO_2$, at admission moment and four days after treatment, was similar in both groups. This finding shows that hyperbaric oxygen therapy did not significantly interfere with this parameter (Table 3 and Figure 3).

There was no significant difference between groups within the same time interval or in the same group at different assessed time intervals.

Animals with tissue hypoperfusion presenting $SvcO_2$ values lower than 70% were taken into account (Conti-patara *et al.*, 2013; Wittayachamnankul *et al.*, 2020). According to Rivers *et al.* (2001), macrohemodynamic parameters, such as blood pressure and vital signs, are not early markers for hypoxia and systemic hypoperfusion. Therefore, their use as central or mixed venous saturation demands using more sensitive parameters to point out tissue perfusion reduction and to guide treatment based on hemodynamic changes in preload, afterload, contractility and arterial oxygen content.

Based on guidelines by Evans et al., (2021), central venous oxygen saturation or mixed venous oxygen saturation are useful to assess balance between tissue oxygen offer and consumption, mainly in case of critical patients, like those with sepsis (Gutierrez, 2020). It is not possible stating HO's ineffectiveness over these parameters before increasing the number of repetitions in both groups. Furthermore, it is important keeping in mind that the worst situation of animals raffled to form G2 might have had negative influence on this outcome.

Although HO remains widely outspread in veterinary medicine, it is a rising methodology in this field, since it

Table 3 . Mean $SvcO_2$ values recorded for bitches in the control (G1) and hyperbaric groups (G2) with sepsis caused by CEH-P

Groups	T0	T1	T2	T3
G1	72,8 ± 2,4	69,6 ± 3,9	70,7 ± 2,4	71,3 ± 1,8
G2	68,9 ± 7,6	68,3 ± 5,1	70,1 ± 8,3	69,6 ± 6,3

Data were expressed as mean ± standard deviation.

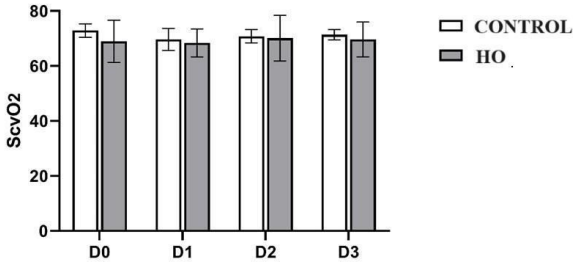

Figure 3 . Statistical representation based on Mann-Whitney and Kruskal-Wallis tests applied to $SvcO_2$ recorded for bitches with sepsis caused by CEH-P

leads to positive outcomes when it comes to improved survival and reduced mortality in patients (experimental models) presenting sepsis and endotoxemia (Halbach *et al.*, 2019; Yang *et al.*, 2020).

Yet, the hyperbaric therapy has some other beneficial therapeutic effects on septic patients, such as angiogenesis stimulation (Muhonen *et al.*, 2004), antioxidant action and oxidative stress reduction (Sureda *et al.*, 2016; Gao *et al.*, 2017), helping immune response through infection suppression and phagocytic leukocyte production (Yamanel *et al.*, 2011; Yang *et al.*, 2020). Although the mentioned effects were not the target of the present study, it was possible observing the clear benefit of associating hyperbaric therapy and conventional HVO treatment, since it resulted in clinical improvement and in hospital discharge.

CONCLUSION

Three sessions of hyperbaric oxygen therapy based on 100% pressurized oxygen at 2 ATA, for 75 minutes (each session), have shown positive effects and efficacy in reducing organic dysfunction in bitches with sepsis caused by CEH-P. However, although there was improvement in central venous saturation, it was not possible highlighting the hyperbaric therapy interference with this parameter in comparison to the conventional clinical therapy.

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