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RESEARCH PROTOCOL

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Use of Near-InfraRed Spectroscopy (NIRS) during Vascular Occlusion Test (VOT) for predicting an increase in oxygen consumption after fluid challenge in circulatory shock patients

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ABSTRACT:

Background: The goal of fluid challenge (FC) is to increase cardiac output (CO) and oxygen delivery (DO_2) (known as fluid responders) to correct tissue hypoxia. To optimize fluid administration, fluid challenge (FC) during dependence of oxygen consumption on oxygen delivery (VO_2/DO_2 dependency) would correct tissue hypoxia confirmed by an increase of oxygen consumption (VO_2) and oxygen delivery (DO_2) after FC (known as VO_2 responders) and get more benefit from a reduction in tissue hypoxia. Markers of anaerobic metabolisms, such as blood lactate concentration or the ratio of venous-arterial CO_2 tension difference ($P_{(cv-a)}CO_2$) over arterial-to-venous oxygen content difference ($C_{(a-cv)}O_2$), can predict VO_2 responders but still have several limitations. Therefore, near-infrared spectroscopy (NIRS) has been developed to evaluate tissue perfusion, presented as tissue oxygen saturation (S_tO_2), at the bedside. Combining S_tO_2 with the vascular occlusive test (VOT) and introducing a short period of forearm ischemia is a non-invasive technique to examine microvascular alterations at the bedside. However, a study validating the ability of these variables to predict VO_2 response has not been conducted.

Methods: We plan to conduct a single-center prospective study on circulatory failure patients. The cardiac index (CI), oxygen delivery (DO_2), oxygen consumption (VO_2), arterial lactate, central venous oxygen saturation ($S_{cv}O_2$), ratio of venous-arterial carbon dioxide tension to arterial-to-central venous oxygen content difference ($P_{(cv-a)}CO_2$/ $C_{(a-cv)}O_2$), and tissue oxygen saturation measured by near-infrared spectroscopy (NIRS) probe during vascular occlusion test variables (NIRS-VOT variables) will be collected before and after the fluid challenge.

Hypothesis: We hypothesize that markers of reactive hyperemia by NIRs will predict an increase in VO_2 after FC in patients with circulatory shock.

Ethics: The study protocol has been approved by the ethics committee of the faculty of medicine, Ramathibodi Hospital, Mahidol University (COA. MURA2022/80).

Keywords: Circulatory failure, Fluid challenge, Fluid responder, Oxygen consumption responder, Near-infrared spectroscopy, Vascular occlusion test

INTRODUCTION

The ultimate goal of fluid challenge (FC) is to increase cardiac output (CO) and oxygen delivery (DO_2) to correct tissue hypoxia. Despite the return to the baseline of systemic hemodynamic parameters, microcirculatory function and tissue perfusion remained altered. Their persistence is related to the development of new organ dysfunctions and high mortality [1]. Nevertheless, excessive fluid administration causes tissue edema, which has been linked to increased organ-support days and mortality. Conversely, inadequate fluid infusion leads to tissue hypoxia or microcirculatory dysfunction.

In the pathology of shock, typically, oxygen extraction increases to maintain oxygen consumption (VO_2) when oxygen delivery (DO_2) decreases. If DO_2 continues to decline, there will be a point at which VO_2 decreases proportionally to the decline of DO_2. This point is referred to as "VO_2/DO_2 dependency", and beyond this point, anaerobic metabolism occurs. VO_2/DO_2 dependency indicates that the cell switches from aerobic metabolism to anaerobic metabolism, leading to elevated lactate levels [2] and tissue hypoxia [3]. Interventions such as fluid challenge (FC) in this state can reduce tissue hypoxia or microcirculatory dysfunction, as confirmed by an increase in VO_2 and DO_2 after FC (known as VO_2 responders)[4].

Optimizing fluid administration is challenging, and several strategies such as fluid challenge (FC), passive leg raising test (PLR), or pulse pressure variation (PPV)[5] have been applied at the bedside to detect patients who would benefit from fluid infusion by increasing their cardiac output (fluid responders). Moreover, Monnet et al. [6] and Mallet et al. [7] observed that patients who experienced an increase in VO_2 and DO_2 (VO_2 responders) after FC had greater reduction in tissue hypoxia. This condition was observed in approximately 25% of patients with circulatory shock.

Markers of anaerobic metabolisms, such as blood lactate concentration or the ratio of the venous-to-arterial CO_2 tension difference over the arterial-to-venous oxygen content difference ($P_{(cv-a)}CO_2/C_{(a-cv)}O_2$), which is surrogate of the respiratory quotient (RQ), are likely to increase in cases of oxygen debt, and these variables can predict VO_2 responders [6,7]. However, several conditions other than anaerobic metabolism cause lactate elevation [8]. $P_{(cv-a)}CO_2/C_{(a-cv)}O_2$ is generally confounded by hemoglobin level and is limited by low repeatability[9]. Therefore, new non-invasive technologies such as near-infrared spectroscopy (NIRS) or laser doppler have been developed to evaluate tissue perfusion, presented as tissue oxygen saturation (S_tO_2), at the bedside. Combining S_tO_2 with the vascular occlusive test (VOT), which involves a short period of forearm ischemia [10-12] is a non-invasive technique to examine microvascular alterations at the bedside within 5 minutes. Reactive hyperemia after VOT represents the ability to increase flow in previously blocked capillaries and recruit additional capillaries [12]. We hypothesize that markers of reactive hyperemia measured by NIRs will predict an increase in VO_2 after FC in patients with circulatory shock.

KEY MESSAGE:

- Predict VO_2 responder in fluid responder after a fluid challenge by NIRS-VOT variables.

OBJECTIVES

Primary objective

- To assess the ability of NIRS-VOT variables to predict VO_2 responders in circulatory shock patients.

Secondary objective

- To observe changes in NIRS-VOT variables after fluid challenge (FC).
- To evaluate the ability of $S_{cv}O_2$, lactate, CO_2 and O_2 derived parameters to predict VO_2 responders in circulatory shock patients

MATERIALS AND METHODS

Research design

Prospective single-center observational study.

Population

Adult patients with circulatory failure who needed a fluid challenge.

Eligibility criteria

Inclusion criteria

- Adults aged 19 years or older.
- Circulatory failure is defined as systolic blood pressure (SBP) less than 90 mmHg, mean arterial pressure (MAP) less than 65 mmHg, or use of a vasopressor to maintain MAP equal to or greater than 65 mmHg, along with at least one of the following signs: urinary output of 0.5 ml/kg/h or less for two or more hours, heart rate equal to or greater than 100 beats per minute, skin mottling, or lactate level greater than 2 mmol/L.
- Require an intravenous fluid challenge as determined by the attending physician.
- Presence of a central venous catheter inserted into the internal jugular vein.
- Presence of an arterial catheter for hemodynamic monitoring, connected to a Flotrac® system.
- Willingness to provide informed consent to participate in the study.

Exclusion criteria

- Pregnancy
- Moribund condition
- High risk of pulmonary edema from fluid loading based on the clinical judgment of the attending physicians.
- Declining participation in the study or withdrawing their consent at any point after initially agreeing to participate.

Research site

The study will be conducted at the Intensive care unit of Ramathibodi Hospital.

Duration of data collection

The data collection will span from February 2022 to July 2023, fora total duration of 2 years. It is planned to renew the ethical committee's permission annually to ensure the continuation of the study.

Method

After obtaining informed consent from the patient's direct relatives, the researcher will record the demographic data and severity scores of patients upon ICU admission and at the time of inclusion. Hemodynamic variables (heart rate, mean arterial pressure, and cardiac output), O_2 and CO_2-derived parameters, vasopressor doses, the presence of mechanical ventilators and renal replacement therapy, arterial lactate concentration, and NIRS-VOT variables will be obtained before and after FC. Continuous pulse contour analysis using Flotrac® will be utilized to measure CO. Blood samples will be collected for the analysis of O_2 and CO_2-derived variables calculated from arterial and central venous blood gas results using the following formulas:

- $DO_2 = CI \times C_aO_2 \times 10$
- $C_aO_2 = (Hb \times 1.34 \times S_aO_2) + (P_aO_2 \times 0.003)$
- $C_vO_2 = (Hb \times 1.34 \times S_aO_2) + (P_{cv}O_2 \times 0.003)$
- $VO_2 = CI \times (C_aO_2 - C_{cv}O_2)$
- $O_2ER = (C_aO_2 - C_{cv}O_2)/C_aO_2$
- $P_{(cv-a)}CO_2 = P_{cv}CO_2 - P_aCO_2$
- $P_{(cv-a)}CO_2/C_{(a-cv)}O_2 = (P_{cv}O_2 - P_aCO_2)/(C_aO_2 - C_vO_2)$

Note: $P_{cv}O_2$ – partial pressure of oxygen in central venous blood, $P_{cv}CO_2$ – partial pressure of carbon dioxide in central venous blood, C_aO_2 – arterial oxygen content, C_vO_2 – venous oxygen content, O_2ER – oxygen extraction ration, S_aO_2 – oxygen saturation of arterial blood, $S_{cv}O_2$ – oxygen saturation of central venous blood, Hb – hemoglobin, CI – cardiac index (cardiac output divided by body surface area). Arterial blood gas analysis will be performed using the STAT PROFILE® pHOx® Ultra™ Analyzer System.

Near-infrared spectroscopy (NIRS)

The FORE-SIGHT ELITE® 15 mm-spacing tissue spectrometer will be used to measure tissue oxygenation by detecting the backscattered light from four wavelengths (680 nm, 720 nm, 760 nm, and 800 nm), with a focus on two wavelengths (720 nm and 760 nm). This device is widely used in clinical studies [13], and no reported side effects have been documented [13].

Vascular occlusion test (VOT) [13]

A NIRS probe will be positioned on the skin of the thenar eminence to measure thenar S_tO_2 during the VOT. The hand and forearm will be maintained at heart level in a supine position. Baseline arterial pressure will be measured using arterial catheterization, and baseline S_tO_2 will be assessed following a 3-minute stabilization period. Subsequently, a pneumatic cuff will be rapidly inflated around the arm to 50 mmHg above systolic blood pressure for 3 minutes and then promptly deflated. S_tO_2 measurements will continue for up to 5 minutes.

S_tO_2 curve characteristics and Variables (NIRS-VOT variables) [13]

S_tO_2 data will be continuously recorded on a HemoSphere® monitor, with a value recorded every 20 seconds. The collected data will be retrospectively analyzed using HemoSphere® software. The NIRS-VOT variables, including baseline S_tO_2 (%), S_tO_2 downslope (%/min), minimum S_tO_2 (%), rise time (min), S_tO_2 upslope (%/min), peak S_tO_2 (%), and area under the hyperemic curve (% x min), will be analyzed.

Fluid challenge [14]

In this study, fluid challenge (FC) is defined as the administration of 250 mL of crystalloid or colloid solution intravenously within a 15-minute period. It is important to note that the decision to perform FC is made by the intensivist team , which is not involved in this research.

Protocol flow chart

(Figure 1)

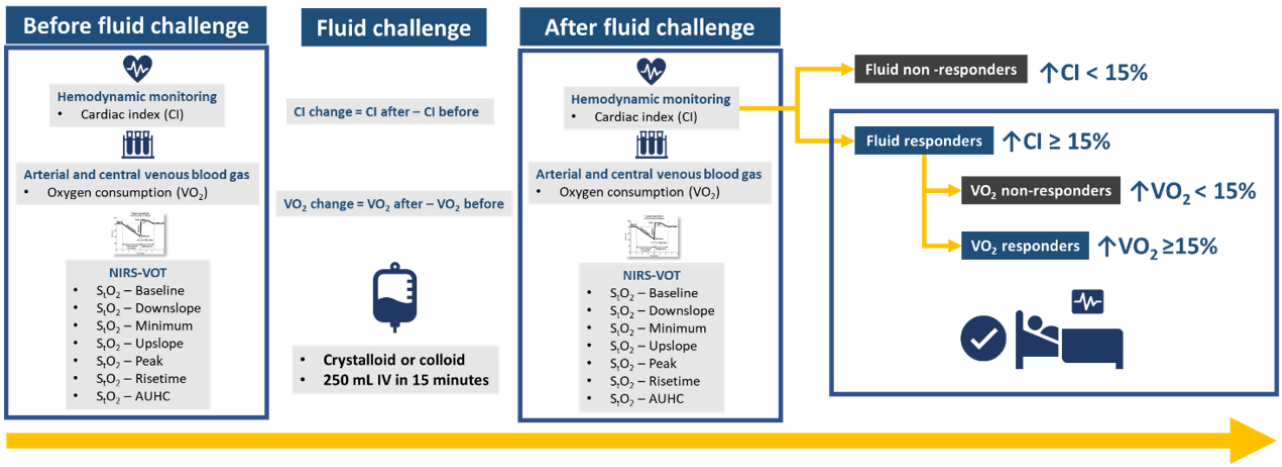

Figure 1. Flow chart.

DATA MANAGEMENT AND DATA MONITORING

Sample size

Based on a previous study [6], where the baseline central venous oxygen saturation had an area under the receiver operating characteristics curve of 0.68 for predicting a fluid-induced increase in oxygen consumption greater than or equal to 15%, a sample size estimation was conducted. The analysis determined that at least a minimum of 88 patients would be required to detect a difference of 0.20 between the areas under the receiver operating characteristics curves of NIRS-VOT and central venous oxygen saturation areas under the receiver operating characteristics curves (two-tailed type I error at 5%, power equal to 90%). The ratio of sample sizes in the negative and positive groups was assumed to be 1:3.

The sample size calculation was performed using MedCalc®[15]. Considering a proportion of 25% VO_2 responders among all patients, a minimum of 18 fluid-responder patients are required to achieve a power of 90% and an alpha risk of 0.05. Assuming a proportion of fluid responders close to 50%, approximately 88 patients would be necessary.

Statistical analysis

The patients who demonstrated a 15% or greater increase in cardiac output (CO) after fluid challenge were defined as fluid responders. while those with a rise in CO below this threshold were classified as fluid non-responders. Within the fluid responders group, patients were further categorized as VO_2 responders if their oxygen consumption (VO_2) increased by 15% or greater [6]; otherwise, they were considered VO_2 non-responders.

All data were presented as mean ±SD for normally distributed variables or as median with 25^{th} and 75^{th} percentiles for non-normally distributed variables. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. A two-tailed Student's t-test, or Mann-Whitney U test, was employed to compare values between different patient groups, depending on the nature of the data. Paired Student's t-test or Wilcoxon's sign-rank test was used for pairwise comparisons between different study time points, as appropriate. Linear correlations were assessed using the Pearson or Spearman tests. To account for changes in variables over time, an analysis of covariance (ANCOVA) was performed, with the absolute differences in variables as dependent variables, the patient group as a factor, and the baseline value as a covariate.

Receiver operating characteristics (ROC) curves were constructed to evaluate the predictive ability of NIRS-VOT and tissue oxygenation variables at baseline for identifying a 15 % or greater increase in oxygen consumption (VO_2) following the fluid challenge in the fluid responders' group. The areas under the ROC curves (AUCs) were compared using the nonparametric technique described by DeLong et al. The best cutoff of a ROC curve was chosen with the highest Youden index.

Statistical analysis was conducted using MedCalc® and STATA® software. A p-value of less than 0.05 was considered statistically significant, and all reported p-values were two-sided.

OUTCOME ANALYSIS PLAN

Input data and monitoring method

- Baseline characteristics variables (Table 1)
- Hemodynamic and tissue oxygenation parameters before and after administering 250 mL of volume expansion based on the response of VO_2 in fluid-responder patients (Table 2)
- Diagnostic ability of baseline values of arterial lactate, central venous oxygen saturation, the ratio of venous-arterial carbon dioxide tension difference to arterial-to-central venous oxygen content difference, and tissue oxygen saturation during the vascular occlusion test variables in predicting fluid-induced outcomes (Table 3)

Figure

- Figure 2 Flow chart showing the original 88 patients separated according to their response to volume expansion in terms of cardiac index, fluid responsiveness, and oxygen consumption (VO_2)
- Figure 3 Receiver operating characteristic (ROC) curves showing the ability of baseline arterial lactate, central venous oxygen saturation, the ratio of venous-arterial carbon dioxide tension difference over arterial-to-central venous oxygen content difference, tissue oxygen saturation during vascular occlusion test variables to predict an increase in oxygen consumption of ≥15% induced by volume expansion

DISCUSSION

Fluid management plays a crucial role in the care of patients with circulatory shock. Achieving optimal tissue oxygenation while avoiding overload is a delicate balance. This research protocol addresses the need to identify patients who are likely to respond favorably to fluid challenge based on their VO_2 responsiveness. The study focuses on the use of NIRS-VOT variables as potential predictors of VO_2 responders as well as assessing other established markers such as $S_{cv}O_2$, lactate, and O_2 and CO_2-derived parameters.

By incorporating non-invasive techniques such as NIRS and the VOT, this study aims to provide valuable insights into microcirculatory function and tissue perfusion. The results may contribute to improved fluid management strategies, allowing for targeted interventions and potentially reducing morbidity and mortality associated with circulatory shock.

Strengths

(1) Our study aims to be the first to investigate the ability to predict oxygen consumption responsiveness of fluid responders in patients with circulatory failure by analyzing NIR-VOT variables.

(2) The utilization of an automated tourniquet machine for conducting a vascular occlusion test offers a reliable and consistent ischemic challenge.

Limitations

(1) The study was conducted at a single center, which may limit the generalizability of the findings to other settings or patient populations.

Table 1. Baseline characteristics of the patients (n= 88).

Characteristics	Collection method
Age [years]	Chart review
Gender (male) %	Chart review
BMI [kg/m^2]	Chart review, manual calculation
Comorbidities • DM [n (%)] • Metformin (mg/day) [n (%)] • HT [n (%)] • Chronic lung disease [n (%)] • Cirrhosis [n (%)] • Other [n (%)]	Chart review
Reason for admission • Medical [n (%)] • Surgical [n (%)]	Chart review
Main type of shock • Sepsis [n (%)] • Cardiogenic [n (%)] • Hemorrhagic [n (%)] • Hypovolemic [n (%)] • Obstructive [n (%)] • Anaphylaxis [n (%)]	Chart review
Source of infection [n (%)]	Chart review
Time between diagnosis and inclusion [hours]	Chart review

Characteristics	Shock diagnosis	Inclusion	Collection method
Criteria of shock • Hypotension [n (%)] • Oliguria [n (%)] • Alteration of consciousness [n (%)] • Lactate ≥2 mmol/L [n (%)] • Lactate level [mmol/L] • CRT at finger [sec] • Mottling score [points] • Cold skin [n (%)]			Chart review
Severity • SAP II score [points] • APACHE II score [points] • SOFA score [points]			Chart review
Patients receiving norepinepgrine [n (%)]			Chart review
Norepinephrine dose [mch/kg/min]			Chart review
Patients receiving dobutamine [n (%)]			Chart review
Dobutamine dose [mcg/kg/min]			Chart review
Hemodynamic variables • SBP [mmHg] • DBP [mmHg] • MAP [mmHg] • HR [mmHg] • CVP [mmHg]			Chart review
Ventilation type • Mechanical ventilation [n (%)] • NIV [n (%)] • HFNC [n (%)] • Oxygen mask with bag [n (%)] • Oxygen cannula [n (%)] • Room air [n (%)] • Minute ventilation (L/min)			Chart review
• FiO_2 • PF ratio			Chart review

Table 1. (Continued) Baseline characteristics of the patients (n= 88).

Characteristics	Shock diagnosis	Inclusion	Collection method
• ECMO [n (%)]			Chart review
Sedative and paralytic drugs • Propofol (mg/kg/h) • Midazolam (mg/kg/h) • Dexmedetomidine (mcg/kg/h) • Cisatracurium (mcg/kg/min)			Chart review
RRT [n (%)]			Chart review
Fluid accumulation (mL)			Chart review
ICU mortality [n (%)]			Chart review
ICU LOS [days]			Chart review

Definition of abbreviations: BMI: body mass index; DM: diabetes mellitus; HT: hypertension; CRT: capillary refill time; SAP: simplified acute physiology; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; FiO_2: fractional of inspired oxygen; PF ratio: ratio of arterial oxygen tension to fractional of inspired oxygen; ECMO: extracorporeal membrane oxygenation; RRT: renal replacement therapy; ICU LOS: intensive length of stay.

Table 2. Hemodynamic and tissue oxygenation parameters before and after 250 mL of volume expansion according to the response of VO_2 in fluid-responder patients.

	VO_2 change ≥15%		VO_2 change <15%		Collection method
	Before fluid challenge	After fluid challenge	Before fluid challenge	After fluid challenge	
HR (beats/min)					Hemosphere® data review
MAP (mmHg)					Hemosphere® data review
PPV (%)					Hemosphere® data review
SVV (%)					Hemosphere® data review
SVR (dynes/sec/cm^{-5})					Hemosphere® data review
SV (mL/beat)					Hemosphere® data review
CI (L/min/m^2)					Hemosphere® data review
CVP (mmHg)					Hemosphere® data review
Arterial pH					Arterial blood gas review
PaO_2 (mmHg)					Arterial blood gas review
$PaCO_2$ (mmHg)					Arterial blood gas review
Ca					Blood chemistry review
Arterial lactate (mmol/L)					Arterial blood gas review
Hba (g/dL)					Arterial blood gas review
SaO_2 (%)					Arterial blood gas review
Central venous lactate (mmol/L)					Central blood gas review
Central venous pH					Central blood gas review
PvO_2 (mmHg)					Central blood gas review
$PvCO_2$ (mmHg)					Central blood gas review
$vHCO_3$					Central blood gas review
Hbv (g/dL)					Central blood gas review
$ScvO_2$ (%)					Central blood gas review
ΔPCO_2 (mmHg)					Calculated from blood gas result
DO_2 (mL/min/m^2)					Calculated from blood gas result
VO_2 (mL/min/m^2)					Calculated from blood gas result
CaO_2 (mL)					Calculated from blood gas result

Table 2. (Continued) Hemodynamic and tissue oxygenation parameters before and after 250 mL of volume expansion according to the response of VO_2 in fluid-responder patients.

	VO_2 change ≥15%		VO_2 change <15%		Collection method
	Before fluid challenge	After fluid challenge	Before fluid challenge	After fluid challenge	
CvO_2 (mL)					Calculated from blood gas result
$\Delta CavO_2$ (mL)					Calculated from blood gas result
$\Delta PCO_2/\Delta CavO_2$					Calculated from blood gas result
PI (%)					Review from Hemosphere®
CRT (msec)					Bedside test using slide
Baseline S_tO_2 (%)					Review NIRS-VOT result from Hemosphere®
Downslope (%/min)					Review NIRS-VOT result from Hemosphere®
Minimum S_tO_2 (%)					Review NIRS-VOT result from Hemosphere®
Upslope (%/min)					Review NIRS-VOT result from Hemosphere®
Peak S_tO_2 (%)					Review NIRS-VOT result from Hemosphere®
Rise time (sec)					Review NIRS-VOT result from Hemosphere®
AUC (% • min)					Review NIRS-VOT result from Hemosphere®

Definition of abbreviations: HR: heart rate; MAP: mean arterial pressure; PPV: pulse pressure variation; SVV: stroke volume variation; SVR: systemic vascular resistance; CI: cardiac index; CVP: central venous pressure; PaO_2 : arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; Ca: serum calcium level; Hb: hemoglobin; SaO_2: arterial oxygen saturation; $ScvO_2$: central venous oxygen saturation; ΔPCO_2: venous-arterial carbondioxide tension difference; DO_2: oxygen delivery; VO_2: oxygen consumption; CaO_2: arterial oxygen content; $CcvO_2$: central venous oxygen content; $\Delta CavO_2$: arterial-to-central venous oxygen content difference; PI: perfusion index; CRT: capillary refill time; S_tO_2: tissue oxygen saturation; AUC: area under hyperemic curve.

Table 3. Diagnostic ability of baseline values of arterial lactate, central venous oxygen saturation, the ratio of venous-arterial carbon dioxide tension difference over arterial-to-central venous oxygen content difference, tissue oxygen saturation during vascular occlusion test variables to predict a fluid-induced increase in oxygen consumption ≥15% in fluid-responder patients (n= 88).

	Best cutoff value	Se (%) (95%CI)	Sp (%) (95%CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95%CI)	LR- (95% CI)
Arterial lactate							
$ScvO_2$ (%)							
$\Delta PCO_2/\Delta CavO_2$							
Baseline S_tO_2 (%)							
Downslope (%/min)							
Minimum S_tO_2 (%)							
Upslope (%/min)							
Peak S_tO_2 (%)							
Rise time (sec)							
AUC (%•min)							

Definition of abbreviations: $ScvO_2$: central venous oxygen saturation; ΔPCO_2: venous-arteial carbon dioxide tension; $\Delta CavO_2$: arterial-to-central venous oxygen content difference, S_tO_2: tissue oxygen saturation; AUC: area under hyperemic curve.

(2) The study only evaluated the predictive value of a limited number of variables, which may not fully capture the complexity of identifying VO_2 responders in fluid responders.

(3) The optimal method for conducting vascular occlusion testing (VOT) is still a matter of debate. There is controversy regarding the intensity and/or duration of the VOT, with some authors advocating for a time-targeted VOT and others recommending occlusion for a S_tO_2-targeted VOT. In this study, we employed a time-targeted VOT methodology.

CONFIDENTIALITY

Informed consent is obtained within the isolated private room in the ICU by the researchers only. Patients' data are encrypted with the hospital-based healthcare personnel passcode-locking system in the database. After the trial, all data will be eliminated from all computers or physical documents.

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AUTHORS' CONTRIBUTIONS

K.C., S.M., and S.T. contributed to the study design, data collection and interpretation, statistical analysis, and drafting of the manuscript; W.M. contributed to the study design, data interpretation, and critical review of the manuscript; P.T. contributed to the critical evaluation of the manuscript; All authors contributed to the revision of the final manuscript.

SUPPLEMENTARY MATERIALS

None

REFERENCES

1. Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care. 2015;19 Suppl 3:S8.
2. Haupt MT, Gilbert EM, Carlson RW. Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis. 1985;131:912-6.
3. Schumacker PT, Cain SM. The concept of a critical oxygen delivery. Intensive Care Med. 1987;13:223-9.
4. Vallet B. Pathophysiology of VO2/DO2 in Sepsis. In: Pinsky MR, editor. Applied Cardiovascular Physiology. Berlin, Heidelberg: Springer Berlin Heidelberg; 1997. p 185-96.
5. Shi R, Monnet X, Teboul JL. Parameters of fluid responsiveness. Curr Opin Crit Care. 2020;26:319-26.
6. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med. 2013;41:1412-20.
7. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Ann Intensive Care. 2016;6:10.
8. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet. 1999;354:505-8.
9. Mallat J, Lazkani A, Lemyze M, Pepy F, Meddour M, Gasan G, et al. Repeatability of blood gas parameters, PCO2 gap, and PCO2 gap to arterial-to-venous oxygen content difference in critically ill adult patients. Medicine (Baltimore). 2015;94:e415.
10. Creteur J, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL. The prognostic value of muscle StO2 in septic patients. Intensive Care Med. 2007;33:1549-56.
11. Pareznik R, Knezevic R, Voga G, Podbregar M. Changes in muscle tissue oxygenation during stagnant ischemia in septic patients. Intensive Care Med. 2006;32:87-92.
12. Gómez H, Torres A, Polanco P, Kim HK, Zenker S, Puyana JC, et al. Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue O(2) saturation response. Intensive Care Med. 2008;34:1600-7.
13. Bezemer R, Lima A, Myers D, Klijn E, Heger M, Goedhart PT, et al. Assessment of tissue oxygen saturation during a vascular occlusion test using near-infrared spectroscopy: the role of probe spacing and measurement site studied in healthy volunteers. Crit Care. 2009;13 Suppl 5:S4.
14. Vincent J-L, Cecconi M, De Backer D. The fluid challenge. Critical Care. 2020;24:703.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143:29-36.