Changes in pulse-oximetry perfusion index induced by tidal volume challenge versus fluid volume challenge to detect preload responsiveness in mechanically ventilated patients with low tidal volume: A prospective observational study

Protocol of Thesis Submitted for Fulfillment of

PhD degree in Critical Care Medicine By

Salwa Abbas Awad Eltahawy
MB.B.Ch, MSc, Critical Care Medicine

Under supervision of:

Prof. Ahmed Mostafa Abd El-Hamid
Professor and Head of Critical Care Medicine Department
Faculty of Medicine, Benha University

Dr. Samar Rafik Mohamed Amin
Assistant Professor of Anesthesia and Intensive Care
Faculty of Medicine, Benha University

Dr. Mona Sobhy Emara
Lecturer of Anesthesia and Intensive Care
Faculty of Medicine, Benha University

Faculty of Medicine, Benha University
2024

Initial Approval Date: 02/08/2024

Introduction:

Fluid resuscitation is a critical component in the management of severely ill patients, aimed at optimizing cardiac output and improving tissue perfusion. However, determining the correct fluid volume can be complex, as both insufficient and excessive resuscitation can lead to serious complications. Fluid responsiveness, which refers to the ability of cardiac output to rise following a fluid bolus, is a key component in directing fluid therapy for both spontaneously breathing and mechanically ventilated patients. This approach helps tailor treatment to individual patient needs, enhancing outcomes and minimizing risks associated with fluid administration. [1]

Positive pressure ventilation, which is a common practice in critical care settings, can reduce cardiac preload by increasing the pressure in the pleural cavity during the inspiratory phase of mechanical ventilation. This increase in pleural pressure leads to reductions in both cardiac preload and stroke volume. The variations in stroke volume that occur between the inspiratory and expiratory phases of positive pressure ventilation are known as stroke volume variation (SVV). In human critical care medicine, SVV is regarded as a reliable indicator of fluid responsiveness. [2]

However, patients with atrial fibrillation exhibit variations in pulse pressure, deeming it inappropriate to reliably assess their fluid responsiveness by SVV [3]. Moreover, when changes in pleural pressure are minimal during a single respiratory cycle, alterations in cardiac preload will also be minor to cause change in stroke volume. Small fluctuations in pleural pressure can occur in patients who breathe spontaneously, those receiving mechanical ventilation with low tidal volumes (such as 6 ml/kg), or in patients with increased chest compliance, like

those with an open chest [4]. Therefore, it is important to be cautious before assuming that a patient is not fluid responsive simply because SVV is low, as this could lead to a false-negative result.

Among such conditions, tidal volume (Vt) must be ≥ 8 mL/kg of predicted body weight (PBW), as lower Vt values create false negatives. To overcome this limitation, the Vt challenge has been described in mechanically ventilated patients. It consists in transiently increasing Vt from 6 to 8 mL/kg PBW, and looking for a significant increase in PPV, reflecting that the slope of the cardiac function curve is steep [5]. However, the Vt challenge has two limitations. First, although it has been validated by several studies, the diagnostic threshold they reported is variable. Second, it requires an arterial pressure curve, which is usually plotted by using an arterial catheter [6]

The plethysmographic perfusion index (PI) is a valuable parameter in medical practice with various emerging applications. PI represents the ratio between pulsatile and non-pulsatile components of peripheral circulation, primarily influenced by cardiac output and the balance between sympathetic and parasympathetic nervous systems. When sympathetic predominance and/or low cardiac output occur, PI decreases, making it a useful, non-invasive tool for hemodynamic monitoring as well as predicting patient outcomes in anaesthesiology, perioperative and critical care. [7]

Several studies investigated the use of PI as an alternative to traditional dynamic measures in assessing fluid responsiveness. Some demonstrated that PI was a reliable surrogate of cardiac index, pulse pressure variation and SVV [8], while others were inconclusive [9]. Whether the use of PI in resuscitation algorithms would improve patient outcomes is yet to be explored.

Aim of the study:

The primary goal of this study was to assess the ability of PI changes induced by a Vt challenge or fluid challenge test to detect preload responsiveness in critically ill adult patients on mechanical ventilation with low-tidal volume.

The secondary aims were (i) to compare the changes in PI with VTI during a Vt challenge test (ii) to compare the changes in VTI and PI during a volume expansion challenge test, (iii) to compare the Vt-induced changes in PI to changes induced by fluid challenge test, (iv) to compare the Vt-induced changes in VTI to changes induced by fluid challenge test.

Patients and methods

I-Technical design:

1. Study design: A prospective observational study
2. Study setting: The study will be carried out in the department of critical care medicine, Benha university hospitals.
3. Study time: The study time is set to a period of six months from September 2024 to February 2025.
4. Study population:

   The study will be conducted on 75 mechanically ventilated patients with circulatory failure.

5. ***Inclusion criteria:***

- Patients of both genders aged 18 years or older
- Invasive mechanical ventilation in assist controlled mode with a Vt of 6 mL/kg PBW,
- Patients with circulatory failure
- Decision by the clinicians in charge to assess preload responsiveness through a Vt Challenge and a Fluid Challenge test.
- Patients in sinus rhythm

6. ***Exclusion criteria:***

- Open chest
- Pulmonary hypertension
- Poor lung compliance (Crs <30 ml/cmH_2O)
- Obesity (BMI≥35)
- Pregnancy

- Intraabdominal hypertension
- Prone position
- Atrial fibrillation

II -Operational design:

Methods:

Primarily, a tidal volume challenge (VtC) will be performed. The tidal volume will be initially set at 6 ml/kg PBW. Once stability of hemodynamic parameters is established, the tidal volume will be increased transiently from 6 ml/kg PBW to 8 ml/kg PBW for 1 min. Thereafter, the tidal volume will be reduced back to 6 ml/kg PBW.

Once hemodynamic parameters have reached their baseline values, a fluid challenge (FC) will be performed by administering 4ml/kg crystalloid solution over 10 minutes.

Left ventricular outflow tract (LVOT) velocity time index (VTI) as well as the plethysmographic perfusion index (PI) will be determined in all patients at the baseline, after VtC and after a FC via transthoracic echocardiography (GE 3Sc-RS phased array transducer connected to GE LOGIQ F8 Expert R2 ultrasound machine) and a pulse oximeter (ChoiceMMed MD300CN310, Beijing Choice Electronic technology Co., Ltd.) respectively.

The patient will be considered a fluid responder if the VTI increased by 10% after completion of the fluid bolus.

The change in VTI (ΔVTI) will be calculated as follows:

1. ΔVTI (%)= (post-VtC VTI – pre-VtC VTI)/pre-VtC VTI.

2. ΔVTI (%)= (post-FC VTI − pre-FC VTI)/pre-FC VTI.

Study measurements:

Primary outcome:

The ability of changes in PI (ΔPI) to detect fluid responsiveness.

$$\Delta PI = \{(PI \text{ after VtC or FC} - PI \text{ at baseline})/PI \text{ at baseline}\} \times 100$$

Secondary outcomes:

- Hemodynamic variables: heart rate, mean arterial pressure, central venous pressure, and VTI (measured at the baseline, after VtC and 300 mL fluid boluses).
- Perfusion indices: Serum lactate, central venous oxygen saturation (ScVO2), and central venous-arterial CO2 gap (CO2 gap), (measured at the baseline, after TVC and 300 mL fluid boluses).
- The use of vasopressors and inotropic agents.
- Baseline laboratory investigations: hemoglobin level, urea, creatinine, and electrolytes.
- Patient characteristics, including age, sex, source of infection, and the severity of the disease [using Acute physiology and chronic health evaluation (APACHE II)].

III- Administrative and Ethical design:

An approval from Research Ethics Committee of Benha faculty of medicine will be obtained.

An informed written consent will be obtained from all patients or first-degree relatives before participation. It will include data about aim of the work, study design, site, time, subject and methods, confidentiality.

IV- Data management and statistical analysis:

The clinical data will be collected, verified, edited, and then analyzed using SPSS (statistical program for social science) as follows:

- Quantitative data will be presented as mean and standard deviation
- Qualitative data will be presented as numbers and percentages.
- Comparisons between patients with positive and negative fluid responders will performed by two-tailed Student t or Wilcoxon tests. We will compare the percent relative changes of SVV to those of PI by linear regression analysis. Correlations will be assessed by the Spearman coefficient.
- Receiver operating characteristic (ROC) curves will be constructed to predict fluid responsiveness. Sensitivities, specificity, positive predictive values (PPV), negative predictive values (NPV) and accuracy by area under the curve (AUC).

- P Value < 0.05 will be considered statistically significant.
- P Value < 0.01 will be considered statistically highly significant.

Sample Size:

The sample size was calculated using the MedCalc Software version 18 (MedCalc Software bvba, Ostend, Belgium) based on the assumption that ΔPPI could determine fluid responsiveness at an AUC of 0.70, corresponding to a good discriminative ability for the diagnostic test, whilst the null hypothesis was assumed to be AUC =0.5, and the risk of alpha error at 5% and beta error at 20% were accounted for. According to Yang, the ratio of non-responders cases to responder cases was supposed to be about 0.7 [10]. The minimum number of calculated patients was 63 patients with at least 37 responders and 26 non-responders. The estimated sample size was corrected to 75 participants in consideration of at least a 15% drop-out rate.

References:

1. Luigi La Via, Francesco Vasile, Francesco Perna, Mateusz Zawadka, Prediction of fluid responsiveness in critical care: Current evidence and future perspective,Trends in Anaesthesia and Critical Care, Volume 54, 2024,101316, ISSN 2210-8440, https://doi.org/10.1016/j.tacc.2023.101316.
2. Endo Y, Tamura J, Ishizuka T, et al. Stroke volume variation (SVV) and pulse pressure variation (PPV) as indicators of fluid responsiveness in sevoflurane anesthetized mechanically ventilated euvolemic dogs. J Vet Med Sci. 2017;79(8):1437-1445. doi:10.1292/jvms.16-0287
3. Dynamic filling parameters in patients with atrial fibrillation: differentiating rhythm induced from ventilation-induced variations in pulse pressure Piet A. H. Wyffels, Frederic Van Heuverswyn, Stefan De Hert, and Patrick F. Wouters American Journal of Physiology-Heart and Circulatory Physiology 2016 310:9, H1194-H1200
4. Frédéric Michard, Volume Management in Critically Ill Patients, European Cardiology 2008;4(1):99–100 https://doi.org/10.15420/ecr.2008.4.1.99
5. Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The Changes in Pulse Pressure Variation or Stroke Volume Variation After a "Tidal Volume Challenge" Reliably Predict Fluid Responsiveness During Low Tidal Volume Ventilation. Crit Care Med. 2017 Mar;45(3):415-421.
6. Wang X, Liu S, Gao J, Zhang Y, Huang T. Does tidal volume challenge improve the feasibility of pulse pressure variation in patients mechanically ventilated at low tidal volumes? A systematic review and meta-analysis. Crit Care. 2023 Feb 2;27(1):45.

7. Elshal MM, Hasanin AM, Mostafa M, Gamal RM. Plethysmographic Peripheral Perfusion Index: Could It Be a New Vital Sign?. Front Med (Lausanne). 2021;8:651909.
8. Beurton A, Gavelli F, Teboul JL, De Vita N, Monnet X. Changes in the Plethysmographic Perfusion Index During an End-Expiratory Occlusion Detect a Positive Passive Leg Raising Test. *Crit Care Med*. 2021;49(2):e151-e160. doi:10.1097/CCM.0000000000004768
9. Hasanin A, Karam N, Mukhtar AM, Habib SF. The ability of pulse oximetry-derived peripheral perfusion index to detect fluid responsiveness in patients with septic shock. *J Anesth*. 2021;35(2):254-261. doi:10.1007/s00540-021-02908-w
10. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care. 2014;18(6):650.