FEASIBILITY OF PLETHYSMOGRAPHY VARIABILITY INDEX (PVI) IN DETERMINING INTRAVASCULAR VOLUME IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY

A Pilot Study

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Later Belakang: Penilaian status hidrasi pesakit kritikal yang mengalami kegagalan fungsi ginjal akut secara tepat adalah rumit dan mencabar. Teknik menilai status hidrasi dibahagikan kepada dua kategori iaitu dinamik dan statik. Kajian rintis ini mengkaji korelasi teknik dinamik **Plethysmography variability index (PVI)** dengan teknik statik seperti tekanan pusat vena (CVP) dan index pengembangan 'inferior vena cava' (dIVC), dan teknik dinamik seperti tekanan darah arteri sistoli (IASBP) dan variasi tekanan nadi (PPV) dalam penilaian status hidrasi pesakit kritikal yang menghidapi kegagalan fungsi ginjal akut.

Metodologi: Kajian rintis ini adalah 'prospective observational cross sectional study' dengan 'convenient sampling'. Seramai 30 orang pesakit yang dimasukkan ke unit rawatan rapi, diintubasi dan didiagnosa kegagalan fungsi ginjal akut (menurut kriteria AKIN) serta memenuhi kriteria kajian setelah direkrut apabila mendapat kebenaran bertulis dari waris. PVI, CVP, IASBP, PPV dan dIVC dicatatkan sebanyak 3 kali (setiap lapan jam)dalam tempoh 24 jam. Data berangka dinyatakan dalam kekerapan dan peratusan dan data berkategori dinyatakan dalam purata and sisihan piawai. Nilai $p<0.05$ dianggap signifikan secara statistik.

Keputusan : Purata umur pesakit adalah 50 ± 19 tahun. ‘PVI’ menunjukkan korelasi positif dengan dIVC dan PPV (p=<0.001). CVP and IASBP tidak menunjukkan sebarang korelasi dengan PVI (CVP, p = 0.499 and MAP, p value = 0.605).

Kesimpulan : Kajian rintis ini menunjukkan korelasi positif antara ‘PVI’ dengan ‘dIVC’ dan ‘PPV’, tetapi tiada korelasi dengan ‘CVP’ atau IASBP dalam penilaian status hidrasi pesakit kritikal yang menghidapi kegagalan fungsi ginjal akut.

ABSTRACT

Title: Feasibility of Plethysmography Variability Index (PVI) In Determining Intravascular Volume In critically Ill Patients with acute kidney injury : A Pilot Study

Background: Accurate and timely assessment of intravascular volume status in critically ill patients presenting with acute kidney injury remains a challenge despite the availability of various measurement modalities. Technically, these modalities are divided into two groups; dynamic and static modalities.-This pilot study aims to investigate the correlation of plethysmographic variability index (PVI), a dynamic monitoring device with static modalities of central venous pressure (CVP) and inferior vena cava distensibility index (dIVC), and dynamic modalities of intra-arterial systolic pressure (IASBP) and pulse pressure variation (PPV) in the assessment intravascular volume status in critically ill patients with acute kidney injury.

Methods: This was a prospective observational cross-sectional ~~pilot~~ study using convenient sampling.Total of 30 patients who were admitted to critical care facilities, intubated and diagnosed with acute kidney injury based on AKIN (full name) criteria and fulfilled study criteria were recruited in this study after consented by the legal guardian. The PVI, IASBP, CVP, dIVC and PPV values were collected at 8-hour interval for a period of 24 hours. Categorical variables were expressed in frequency and percentage while numerical variables were expressed in mean and standard deviation; statistical analysis was carried by SPSS version 22.0. p value of < 0.05 is considered statistically significant.

Results: The mean age for patients included this study was 50 ± 19. PVI showed a statistically significant positive correlation with both static measurement dIVC and dynamic measurement PPV (p=<0.001). There were no correlation between PVI and CVP or IASBP.(CVP, p = 0.499 and IASBP, p value = 0.605).

Conclusion: This pilot study demonstrates statistically significant correlation of PVI with dIVC and PPV but not with CVP or IASBP.

LIST OF ABBREVIATION

AKI	Acute kidney injury
BP	Blood pressure
CI	Cardiac index
CVP	Central venous pressure
CVL	Central venous line
IABP	Intra-arterial blood pressure
IASBP	Intra-arterial systolic blood pressure
dIVC	Inferior vena cava distensibility index
ICU	Intensive care unit
MAP	Mean Arterial Pressure
PI	Perfusion index
PAOP	Pulmonary artery occlusion pressure
PPV	Pulse pressure variability
PVI	Plethysmographic variability index
SPV	Systolic pressure variability
SVV	Stroke volume variability

CHAPTER 1: INTRODUCTION

1.1 Introduction

Fluid management in patient under critical care medicine has always poses a great challenge to the intensivist and anesthetist, particularly in patient complicated with acute kidney injury. Optimum fluid management is crucial to avoid potential deleterious effects of volume expansion or inadequate fluid resuscitation. Inadequate intravascular volume with subsequent impaired renal perfusion is recognized as an important risk factor of acute kidney failure(1).

On the other hand, many studies have concluded that fluid overload is an independent risk for morbidity and mortality among patients with acute kidney injury (2) (3) (4). Thus, optimization of intravascular volume status is of paramount important to increase the chance of survival among these patients (1) (5).

The aims of this present study is to assess the correlations of PVI with central venous pressure and intra-arterial blood pressure in critical care medicine setting who are diagnosed to have acute kidney injury

1.2 Problem Statement

The difficulty of accurately assessing the intravascular volume status is complicated by the fact that many patients remain normotensive due to an increased circulating level of angiotensin secondary to acute kidney injury. Therefore, blood pressure alone no longer adequate, and often requires other clinical parameters to gauge the intravascular volume (6). Standard Intensive care monitoring often include both invasive and non-invasive devices, each with its own advantages and disadvantages.

The CVP measurement and its trend are commonly used to assess the intravascular volume to guide resuscitation and replacement therapy. However, CVP measurement required CVL placement and removal which poses plenty of risks likes catheter related infection, catheter-induced thrombosis, arrhythmia, vascular injury, pulmonary complications, venous air embolism and bleeding (7). In addition to that, in a meta-analysis of 5 studies, there was a poor correlations between CVP and circulating blood volume and change in cardiac index. Hence, fluid replacement therapy guided by CVP may probably lead to inadequate volume replacement or volume overloaded thus its complications like pulmonary edema and mortality rate of patient. (8)

1.3 Justification

Many recent studies show that PPV which is closely related to SVV and SPV is useful for predicting fluid responsiveness especially in mechanically ventilated patient. (8).

However visual estimation of pulse pressure variation and systolic pressure variation from the arterial pressure waveform is not a reliable indicator in clinical practice. Since PPV is highly correlated to respiratory variations in the ΔPOP waveform amplitude, it has been used to predict fluid responsiveness with high accuracy (9, 10). Nevertheless, both have been found to be impractical in clinical setting because it is not easily calculated from the pulse oximetry display.

More recently, Masimo Corp, Irvine, CA, USA has developed a non-invasive, continuous and easy- to-use commercial device that provides an automatic calculation of the respiratory variation in pulse oximeter waveform amplitude. The data collected through the pulse oximetry sensor were used to formulate physiologic indices, perfusion index (PI) and pleth variability index (PVI). The PVI was found to be correlated with PPV.(11) For PI calculation, the infrared pulsatile signal is indexed against the non-pulsatile infrared signal and expressed as a percentage [PI = (AC/DC) x 100%] reflecting the amplitude of the pulse oximeter waveform. Using PI, PVI is calculated, PVI = [(PImax–PImin)/ PImax] x100% and is displayed continuously. The lower the PVI number the less variability is in PI over a respiratory cycle. The higher the variability, the more likely the patient will respond to fluid infusion with an increase in cardiac output.

Recent meta- analyses (12) have suggested that plethysmographic indices such as Plethymography variability index are accurate in predicting fluid responsiveness in mechanical ventilated patient.

Majority of these studies were conducted in perioperative setting in patients with a stable hemodynamic condition. Only few studies were carried out in critically ill adult patient (13, 14)

The accuracy of Plethymography variability index to predict volume status of patient in critically ill adult patients who are mechanically ventilated and require vasopressor remains controversial as altered sympathetic tone, induced either by circulatory failure or by vasoactive drugs might affects the accuracy of Plethymography variability index. In this respect, a study found that Plethymography variability index has a poor correlation with fluid responsiveness in patients receiving norepinephrine (15). In contrast, a meta-analysis by (16) found that PVI was a reliable predictor of fluid responsiveness in a population of patients receiving norepinephrine. Addition to that, the different sites of measurement with variable sensitivity and vasomotor tone might influence the accuracy of PVI (17).

Our study aims to investigate the feasibility and reliability of a non- invasive monitoring device utilizing plethysmographic variability index (PVI) in predicting the intravascular volume status as reflected by changes in the index, and correlate this with the parameters obtained from the standard intensive care monitoring devices (CVP and IABP).

CHAPTER 2: OBJECTIVES OF THE STUDY

2.1 GENERAL OBJECTIVES

To investigate and correlate PVI value with standard intensive care monitoring in assessing volume status of critically ill adult patients who is newly diagnosed with acute kidney injury.

2.2 SPECIFIC OBJECTIVES

1. To study the correlations of PVI with central venous pressure in assessing volume status in critically ill patients with acute kidney injury
2. To study the correlations of PVI with mean intra-arterial blood pressure in assessing volume status in critically ill patients with acute kidney injury
3. To study the correlations of PVI with IVC in in assessing volume status in critically ill patients with acute kidney injury
4. To study the correlations of PVI with PPV in assessing volume status in critically ill patients with acute kidney injury

CHAPTER 3: MANUSCRIPT

3.1 Title

Article Title: The pilot study of volume status assessment using Plethysmography variability index (PVI) in critically ill adult patients with newly diagnosed acute kidney injury correlate with central venous pressure and intra-arterial mean arterial pressure**..**

Running Head:

1. To study the correlations of PVI with central venous pressure in assessing volume status in critically ill patients with acute kidney injury
2. To study the correlations of PVI with mean intra-arterial blood pressure in assessing volume status in critically ill patients with acute kidney injury
3. To study the correlations of PVI with IVC in in assessing volume status in critically ill patients with acute kidney injury
4. To study the correlations of PVI with PPV in assessing volume status in critically ill patients with acute kidney injury

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3.2 ABSTRACT

Title: Plethysmography variability index (PVI) significantly correlates with inferior vena cava distensibility index (dIVC) and pulse pressure variation (PPV) in the assessment of intravascular volume status in critically ill patients with acute kidney injury.

Background: Accurate and timely assessment of intravascular volume status in critically ill patients presenting with acute kidney injury remains a challenge despite the availability of various measurement modalities, either invasive or non-invasive. Technically, these modalities are divided into two groups; dynamic and static modalities. This pilot study aims to investigate the correlation of plethysmographic variability index (PVI), a dynamic monitoring device with static modality of inferior vena cava distensibility index (dIVC), and dynamic modality of pulse pressure variation (PPV) in the assessment intravascular volume status in critically ill patients with acute kidney injury.

Methods: This was a prospective observational cross-sectional study using convenient sampling and had been approved by the ethical committee from our institution. Total of 30 patients who were admitted to critical care facilities, intubated and diagnosed with acute kidney injury based on AKIN (full name) criteria and fulfilled study criteria were recruited in this study after consented by the legal guardian. The PVI, dIVC and PPV values were collected at 8-hour interval for a period of 24 hours. Categorical variables were expressed in frequency and percentage while numerical variables were expressed in mean and standard deviation; statistical analysis was carried by SPSS version 22.0. p value of < 0.05 is considered statistically significant.

Results: The mean age for patients included this study was 50 ± 19. PVI showed a statistically significant positive correlation with both static measurement dIVC and dynamic measurement PPV (p=<0.001).

Conclusion: This pilot study demonstrates statistically significant correlation of PVI with dIVC and PPV assessing intravascular volume status in critically ill patients with acute kidney injury.

3.3 Introduction

Intravenous fluid management has evolved significantly over past few years. Many efforts has been put to estimate the adequacy of fluid administration to critically ill patient as the harmful effects of fluid overloading or under volume in the critically ill patient are very well demonstrated (1), (2), (3).

Generally, hemodynamic monitoring can be divided into static and dynamic hemodynamic monitoring. The use of static hemodynamic monitoring for example CVP and PAOP based on the assumption that intravascular volume in great vessel is a reflection of right atrial pressure and thus reliable indicator of right ventricular preload. And as right ventricular preload approximate left ventricular filling, CVP is assumed to correlate with left ventricular preload. Recent trend of dynamic hemodynamic monitoring such as SVV, PPV, SPV and PVI by using continuous automatic measurement of dynamic change in perfusion index, arterial waveform or stroke volume with standard multiparametric monitor has been shown to be more accurate in predicting intravascular volume.

For decade, our standard static hemodynamic monitoring in intensive care setting would be the Central venous pressure. However, CVP measurement requires CVL placement and removal which subjects patient to numerous risks likes catheter related infection, catheter-induced thrombosis, arrhythmia, vascular injury, pulmonary complications, venous air embolism and bleeding (7). In addition to that, in a meta-analysis of 5 studies, there was a poor correlation between CVP and circulating blood volume and changes in cardiac index (19, 20). Hence, fluid replacement therapy guided by CVP may lead to inadequate volume replacement or volume overloaded resulting in complications such as pulmonary edema and increase in the mortality rate of patient.

Optimum fluid therapy is particularly important especially in patient at risk or has established acute kidney injury which has impaired free water and solute excretion and easily lead to electrolyte imbalance and fluid accumulation. More importantly acute kidney injury could be prevented or reversed with adequate and accurate fluid resuscitation(1),(18).

The difficulty of accurately assessing the intravascular volume status is complicated by the fact that many patients remain normotensive due to an increased circulating level of angiotensin secondary to acute kidney injury and often modified by the use of sympatomimetic drugs. Mortality could be improved by expanding one's hemodynamic goal via accurate fluid monitoring beyond simply maintaining adequate blood pressure (6).

Latest concept in the intravenous fluid management in the critically ill patients uses dynamic indexes to assess patient hydration status. Our tool of study, PVI provides us with a non- invasive, dynamic monitoring to assess patient's fluid status and guide the fluid administration from time to time according to patient's body demand (12). Nevertheless, majority of these studies were conducted in perioperative settings in patients with a stable hemodynamic condition. Its clinical value in intensive care unit remain undetermined. However, current evidences from available studies possibly favored its use in Intensive care setting (13, 14).

Our study aims to investigate the feasibility and reliability of a non- invasive monitoring device utilizing plethysmographic variability index (PVI) in predicting the intravascular volume status as reflected by changes in the index, and correlate this with the parameters obtained from the standard intensive care monitoring devices (CVP value and mean IABP). The outcome of the study could probably provide a more rational way to manage fluid administration in intensive care setting as well as being translatable to clinical practice in other settings.

3.4 Methodology

<u>Study Design</u>:

A single –center, observational, cross-sectional, single-arm, non-randomized, interrupted interval studies

<u>Study Sample</u>:

All adult patients admitted to the ICUs at Hospital Universiti Sains Malaysia between Jan 2016 until June 2017 who met the inclusion criteria were recruited to participate in this study. The sampling framework consisted of a time period of 24 consecutive hours and the inclusion criteria.

<u>Inclusion Criteria</u>:

All adult ICU patient with newly diagnosed acute kidney injury according to AKIN criteria within 48 hours of established diagnosis.

Adult patient aged between 18 to 65 years old

Requiring mechanical ventilation with Synchronize Intermittent Mechanical Ventilation without significant spontaneous breathing effort (spontaneous breathing rate <10% of prescribed mechanical breath)

<u>Exclusion Criteria</u>:

Extreme age of less than 18 or more than 65 years old

Patients with cardiac arrhythmias

Patient with intracardiac shunts

Patients who are pregnant

Patients who require higher mechanical ventilation setting with positive end- expiratory pressure >10 cmH20

Patient with increase intra-abdominal pressure eg. Intestinal obstruction

Patient with condition affecting placement of forehead probe excluded from study (eg, facial burn/skin trauma, tumor)

Study Centre:

ICU Hospital Universiti Sains Malaysia (tertiary care hospital)

Sample Size

The sample size of this pilot study was based on the sample size of (13, 17)
The power of study will be calculated from the study during analysis.

The power of 80% was accepted as level of significance.

Study Flow:

The patients will be screened according to the inclusion and exclusion criteria as listed during selection of candidate of study.

Informed consent to be obtained from immediate family member or caregiver

The patients are placed with standard intensive care monitoring in local hospital setting.

Data collection (3 measurements in each parameter within 1 hour) in 8 - hour intervals for a period of 24 hours:

a) PVI
b) PI

c) Intra-arterial SBP

d) Intra-arterial SBP

e) Intra-arterial DBP

f) Heart rate

g) Respiratory rate

h) CVP

i) Cumulative I/O Balance

j) Temperature

k) Lactate

Statistical analysis would be carried out with SPSS version 22.0.

Descriptive statistics would be used to describe the demographic variables. Normality of the numerical variables will be checked using the Histogram. Numerical variables will be described using mean and standard deviation. Categorical variables will be described using frequency and percentage

The results would be expressed as mean (+/- standard deviation), mean [95% confidence intervals] or number (percentage). The level of significance will be determined as $p < 0.05$.

3.5 Results

Overall demographic data of study participants are shown in Table 1. A total of 30 subjects consented to participate in the present study. The average age of the subjects was 50±19 years old in which the minimum and the maximum ages were 16 and 76 years old. Majority of the study subjects were male 27/30 (90%), while female subjects only constituted 10% of the total number of recruited subjects. Mean SOFA value of the study subjects was 8.1±3.1 wherein the minimum and maximum SOFA values were 2 and 13, respectively. Mean AKIN value of the study subjects was 1.67±0.81 wherein the minimum and maximum SOFA values were 1 and 4, respectively

There was a significant correlation of PVI and dIVC and PPV ($p<0.001$) as shown in Table 4. The correlation of PVI between patients with or without diuretic are shown in Table 5. Further analysis found that PVI showed significant association with dIVC in patients without diuretic ($p=0.002$) but–has no significant association with dIVC in patients with diuretic ($p=0.089$). There were no association between PVI and dIVC in patients with vasopressor ($p=0.062$) or without vasopressor ($p=0.846$).

PVI also showed significant correlation with PPV in patients administered with vasopressor ($p<0.001$). There was no demonstrable association between PVI and PPV in patients without vasopressor ($p=0.292$). Additionally, PVI showed significant association with PPV in patient who did not received diuretic ($p<0.001$), but showed no correlation with PPV in patients receiving diuretic ($p=0.064$)

3.6 Discussion

PVI is a non-invasive, continuous and automated dynamic measurement of the changes in perfusion index during a respiratory cycle. It is a convenient tool, with easy application to any patient. Automatic calculation based on validated algorithm abolish the discrepancy of operator dependent measurement in other hemodynamic tool like IVC distensibility measurement.

The PVI correlates closely with the respiratory induced variation in the plethysmographic and arterial pressure waveforms and can predict fluid responsiveness non-invasively in mechanically ventilated patients.(9, 12). The dynamic changes of the plethysmographic waveform with positive pressure ventilation have shown a significant correlation and good agreement with the PPV, and has accurately predicted fluid responsiveness in both the operating room and ICU setting (9), (12), (21). In our study, we included stable mechanical ventilated patient without significant breathing effort and low peep requirement with adequate sedation to reduce the effects of sympathetic tone on PVI readings. However, patients with vasopressor were not excluded. Although some studies has shown that correlation between PVI and PPV are altered by changes in vasomotor tone due to vasopressor in critically ill patient(14), our results are not in accordance with it. PVI demonstrated significant association between PVI and PPV in patients with vasopressor support. Thus, we believed that PVI can still possibly been used for patient with vasopressor support if the vasomotor tone is affected in modest degree.

This association between PVI and PPV, SPV and PPV under the effect of vasopressor is likely due to various possibilities which determine the degree of vasomotor tone in patient, such as vasopressor given in therapeutic range just enough to improve or restore vasomotor tone to maintain adequate cerebral perfusion may not overly affect the peripheral vasomotor tone, and, patient with different pathology such as brain injury and septic shock with different vasomotor tone may respond in different manner towards vasopressor, effective intravascular volume (normovolemia or hypovolemia), arterial compliance and acute circulatory failure or stages of recovering from circulatory failure. Thus the role of PVI in critically ill patient should be emphasized and further evaluation needed to determine the group of patient with variable vasomotor tone which are suitable for using PVI as hemodynamic monitor.

A number of studies has shown that inferior vena cava (dIVC) distensibility index has been used as a reliable indicator of volume status in mechanically ventilated patient. (25). Measurement of IVC diameter gives an indirect measurement of right atrial pressure and cardiac preload as IVC is directly connected to right atrium without venous valve. IVC distensibility index is calculated as a ratio of IVC diameter during inspiration and expiration(23). In hypovolemic patient, the variation of IVC diameter is higher as it operate on the steep portion of the Frank-starling curve(24). Positive pressure ventilation with relatively larger tidal volume (8ml/kg) on volume controlled ventilation may generates higher amplitude of changes. A dIVC value above 16% in mechanical ventilated patient allowed prediction of the efficacy of volume expansion with 70.59% sensitivity and 100% specificity(26). In our study, dIVC measurement in patient without diuretic is associated with a change in PVI. This finding reinforced the potential beneficial role of PVI as a hemodynamic monitor in critical care.

By virtue of its simplicity and accuracy, PVI as a continuous non- invasive dynamic monitoring appear to be the valuable ideal modern hemodynamic monitoring tool for guiding fluid management in mechanical ventilated patient in context of the patients' clinical conditions and parameters eg. urine output, renal function and chest radiograph.

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3.8 Tables and Figures

Table 1 Demographic Data

Variable	N (%)	Mean (SD)
Age, year old		50 (19)
Minimum		16
Maximum		76
Gender		
Male	27 (90)	
Female	3 (10)	
SOFA		8.1 (3.1)
2	1 (3.3)	
3	2 (6.7)	
4	3 (10.0)	
5	2 (6.7)	
6	6 (20.0)	
7	1 (3.3)	
9	1 (3.3)	
10	8 (26.7)	
11	2 (6.7)	
12	2 (6.7)	
13	2 (6.7)	
AKIN		1.67 (0.81)
1	16 (53.3)	
2	10 (33.3)	
3	3 (10.0)	
4	1 (3.3)	

*SOFA: Sequential Organ Failure Assessment, AKIN: Acute Kidney Injury Network Classification

Table 2 Haemodynamic Profile Of Patients

Parameters	Mean	95% CI
SPO2	99.71	(99.52, 99.90)
HR	96.36	(92.72, 100.00)
PVI	12.97	(11.54, 14.40)
PI	2.09	(1.62, 2.57)
IASBP	127.28	(122.98, 131.59)
IAMAP	82.55	(79.84, 85.27)
IADBP	61.51	(58.92, 64.10)
PPV	7.09	(6.30, 7.89)
CVP	9.15	(8.14, 10.15)
IVC	15.07	(11.05, 19.09)
TEMP	36.84	(36.06, 37.62)
CIOB	759.96	(509.94, 1009.97)
UO	650.85	(523.71, 777.99)