

# Effect of hypercapnia on pleth variability index during stable propofol: Remifentanil anesthesia

Wesam Farid Mousa

Department of Anesthesia and Surgical ICU, College of Medicine, University of Dammam, Al-Khobar, Saudi Arabia

## Address for correspondence:

Dr. Wesam Farid Mousa,  
Dammam University, P.O. Box 40081,  
Post Code 31952, Al-Khobar,  
Saudi Arabia.  
E-mail: wesammousa@hotmail.com

## ABSTRACT

**Background:** The pleth variability index (PVI), which is calculated from respiratory variations in the perfusion index (PI), has been shown to predict fluid responsiveness in mechanically ventilated patients; however, vasomotor tone changes induced by hypercapnia can affect PI and hence may slim down the accuracy of PVI. This study was designed to find out the impact of mild hypercapnia on PVI. **Methods:** A total of 30 patients were randomized after induction of general anesthesia with target controlled infusion propofol and remifentanil to either hypercapnia, (etCO<sub>2</sub> = 45 mmHg), (group 1, 15 patients) or normocapnia (etCO<sub>2</sub> = 35 mmHg) (group 2, 15 patients). After a stabilization period of 10 min, patients were crossed over to the other intentional level of etCO<sub>2</sub>. Heart rate (HR), mean arterial pressure (MAP), PI, PVI were collected at the end of each stabilization period. **Results:** Patient characteristics and baseline values of HR, MAP, PI and PVI were comparable between the groups. Carryover effect was statistically excluded. Hypercapnia significantly increased PI and decreased PVI with significant negative correlation. **Conclusion:** Hypercapnia retracts back PVI values compared with normocapnia. Precise judgment of fluid responsiveness as indicated by PVI necessitates its comparison against similar etCO<sub>2</sub> levels.

**Key words:** Hypercarpna, perfusion index, pleth variability index

## INTRODUCTION

Pleth variability index (PVI) indicates the cyclic changes in the plethysmographic waveform and has the prospective to provide the useful information for appropriate hydration defined as significant a fall in PVI in response to increased cardiac output after fluid administration.<sup>[1,2]</sup>

Carbon dioxide directly dilates peripheral arterioles while centrally stimulates sympathetic nervous system.<sup>[3,4]</sup> Therefore, changes in CO<sub>2</sub> can affect PI and consequently PVI. The purpose of this study was to evaluate the effect of mild hypercapnia on PI and PVI during the stable propofol and remifentanil anesthesia and before skin incision.

## METHODS

This crossover study was undertaken in Dammam University Hospital, Saudi Arabia. After obtaining approval from institutional Ethics Committee, we included 30 American Society of Anesthesiologists (ASA) Score I or II patients aged 20-45 years scheduled for elective surgery. Written informed consent was obtained from all patients. Exclusion criteria included a history of intracranial disease, lung disease, systemic hypertension and ischemic heart disease. All patients had nothing per orem 6-8 h before surgery, during which time Ringer's lactate infusion at the rate of 2 ml/kg/h was maintained. Intraoperatively, patients were monitored with an electrocardiogram, pulse oximetry, etCO<sub>2</sub> and automated noninvasive blood pressure (Ultima anesthesia gas monitor; Datex, Helsinki, Finland).

In addition, another pulse oximeter probe (LNOP\_ Adt; Masimo Corp., Irvine, CA, USA) was attached to the index finger and connected to a Masimo Radical 7 monitor with PVI software (version 7.3.1.1 and shielded to prevent outside light from interfering with the signal). Arterial pressure measurements were recorded every 3 min until 21 min after endotracheal intubation, then every 5 min until the end of surgery. Baseline values

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of heart rate (HR) and mean arterial pressure (MAP) were determined 5 min before anesthesia. We induced anesthesia with target-controlled infusions of propofol and remifentanyl (Master TCI®, Fresenius Kabi, Bad Homburg; model of Marsh) (ASENA PK TCI® pump, Cardinal Health Alaris Products, Basingstoke, UK; model of Minto). An effect-site concentration of propofol was set at 3 µg/mL then adapted in steps of 0.5 µg/mL every 2 min to maintain the state entropy within the 40-60 range while the estimated effect-site remifentanyl concentration was set at 4 ng/mL during induction then adapted in steps of 1 ng/mL every 2 min according to hemodynamics. After 3 minutes, the target concentrations were achieved; patients received 0.6 mg/kg rocuronium to facilitate tracheal intubation.

Volume controlled ventilation (Datex, Ohmeda, Bromma, Sweden) was started using an oxygen-air mixture (FiO<sub>2</sub> 40%) with respiratory rate 10 beats per minute and the tidal volume (TV) was adjusted to achieve either normocapnia (etCO<sub>2</sub> 35 mmHg=N group *n*=15) or hypercapnia (etCO<sub>2</sub> 45 mmHg=H group *n*=15) according to a computer generated randomization schedule and then maintained for 10 min after which the 1<sup>st</sup> set of measurements were taken. TV was then manipulated to achieve the 2<sup>nd</sup> objective point of etCO<sub>2</sub> and a 2<sup>nd</sup> set of measurement were taken after a stabilization period of 10 min. Most of that time was utilized by the surgeon to accomplish preparation and sterilization of the surgical site. Data collected included PVI, perfusion index (PI), TV, MAP and HR. All data among Normocapnia were collected in a new Group: N. Similarly, all data among Hypercapnia were collected in group H.

Data are expressed as mean ± SD. Statistical analysis was performed between group 1 and 2 (*n*=15) using the independent *t*-test for the demographic data, baseline HR, MAP, PI and PVI and to exclude the possibility of the carryover effect in the aforementioned variables. Given that there was no such effect, data in Group A (*n*=30) and Group B (*n*=30) regardless of the sequence of the etCO<sub>2</sub> applied first were analyzed using paired *t*-test. Data analysis was performed using SPSS, version 16 (IBM, Somers, NY, USA). A probability level of 0.05 was considered significant. We chose to test the null hypothesis that hypercapnia “etCO<sub>2</sub>=45” has no effect on PVI; this was chosen as the primary outcome measure. Secondary outcomes were PI, MAP and HR. A minimum of 26 patients were needed to enter this two-treatment crossover study. The probability is 90% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 2.0 units. This is based on the assumption that the within-patient standard deviation of the response variable is 2.1. This was derived from a

pilot study that was conducted on 10 patients (who were not later included in this study).

## RESULTS

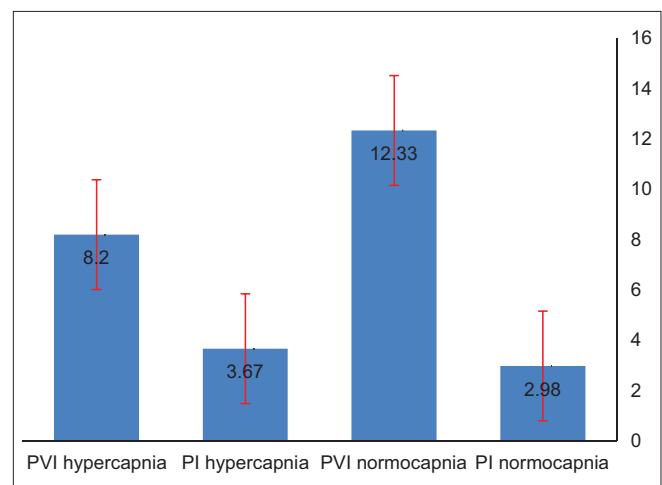
A total of 30 patients were enrolled in the study with no patient excluded for any reason. No significant differences were detected between group 1 and group 2 (No=15) as regards patient characteristics and baseline of MAP, HR, PVI and PI [Table 1]. Absence of the carryover effect of treatment from the previous time period on the response at the second time period was excluded [Table 2].

No statistical differences were detected between group H and group N regarding MAP and HR. During hypercapnia, the PI was significantly increased while PVI was significantly decreased compared with normocapnia (*P*=0.000 for each). A significant negative correlation was observed between PI and PVI during the normocapnia (*P*=0.014, Pearson correlation coefficients (*r*<sup>2</sup>=−0.45) and hypercapnia (*P*=0.00, *r*<sup>2</sup>=0.81) [Table 3], [Figure 1].

**Table 1: Patient characteristics and baseline plethysmographic and hemodynamic data**

Variable	Group (1) normocapnia first ( <i>n</i> =15)	Group (2) hypercapnia first ( <i>n</i> =15)	<i>P</i> level
Male/female	7/8	8/7	
Age	33.87±5.263	31.80±4.81	0.978
Weight	74.20±9.45	75.27±8.67	0.871
Height	159.47±7.17	160.80±6.93	0.723
BMI	29.39±4.84	29.15±5.16	0.799
Baseline MAP	77.13±5.78	73.87±6.15	0.703
Baseline HR	76.00±4.78	74.87±5.34	0.923
Baseline PVI	25.13±2.59	26.07±2.63	0.924
Baseline PI	1.89±0.58	2.08±0.57	0.964

BMI – Body mass index; MAP – Mean arterial pressure; HR – Heart rate; PVI – Pleth variability index; PI – Perfusion index (*n*=15)



**Figure 1:** PI and PVI during normocapnia and hypercapnia. The error bar represents the standard error. The number represents the mean

**Table 2: Plethysmographic and hemodynamic data**

Variable	Group (1) normocapnia first (n=15)	Group (2) hypercapnia first (n=15)	P level
PI (normocapnia)	2.75±0.63	3.21±0.62	0.625
PI (hypercapnia)	3.59±0.66	3.746±0.61	0.360
PVI (normocapnia)	12.20±2.27	12.467±2.34	0.903
PVI (hypercapnia)	8.07±1.16	8.33±1.11	0.944
MAP (normocapnia)	68.80±3.67	69.33±3.85	0.911
MAP (hypercapnia)	69.87±3.96	69.00±3.89	0.861
HR (normocapnia)	66.80±3.88	69.00±3.66	0.851
HR (hypercapnia)	66.79±2.78	68.27±2.92	0.622

MAP – Mean arterial pressure; HR – Heart rate; PVI – Pleth variability index;  
PI – Perfusion index (n=15)

**Table 3: Plethysmographic and hemodynamic data**

Variable	Group N (n=30)	Group H (n=30)	P level
PI	2.98±0.66	3.67±0.63	0.001*
PVI	12.33±2.28	8.20±1.13	0.000*
MAP	69.07±3.70	69.43±3.88	0.645
HR	68.10±3.82	67.53±2.90	0.217

\* (P<0.05); MAP – Mean arterial pressure; HR – Heart rate; PVI – Pleth variability index; PI – Perfusion index (n=30) N – Normocapnia; H – hypercapnia

## DISCUSSION

Our results demonstrated that mild hypercapnia significantly increased PI and decreased PVI with a significant negative correlation observed between them during stable remifentanyl and propofol anesthesia. Parallel to our results, skin incision was shown in a previous study<sup>[5]</sup> to decrease PI and increase PVI with significant negative correlation that was demonstrated to be owing to sympathetic stimulation with peripheral arteriolar vasoconstriction rather than stroke volume variability. Furthermore, PVI was shown in another study<sup>[6]</sup> to be less reliable in patients receiving norepinephrine and might not be a useful predictor of fluid responsiveness due the vasopressor effect of norepinephrine that dampen the plethysmographic signal.

PI is the ratio of non-pulsatile to pulsatile blood flow through the peripheral capillary bed. The non-pulsatile component of the photoplethysmographic signal is mostly related to the light absorption of tissues, venous blood and the diastolic volume of the arterial blood and accordingly, its variability is related to changes in the venous blood volume, whereas the pulsatile component is related to the light absorption arising from the pulsating volume of arterial blood and represents the beat-to-beat variation in the photoplethysmographic signal.<sup>[7,8]</sup> PVI is an automatic measure of the dynamic

change in PI that occurs during the respiratory cycle<sup>[2]</sup> while the amplitude of the photoplethysmographic wave has been related to stroke volume changes<sup>[9]</sup> and to local vascular distensibility.<sup>[10]</sup> In this study, however, respiratory variability in PI due to stroke volume changes is implausible to occur due to stability of the circulating blood volume and constancy of the MAP and HR. The reason for the decrease in the PVI during hypercapnia might be owing to the rapid elevation in the PI since the PVI is calculated from the difference between the two extreme PI values recorded during a time interval of at least one complete respiratory cycle.

$$\left( PVI = \frac{PI_{\text{maximum}} - PI_{\text{minimum}}}{PI_{\text{maximum}}} \right)^{[11]}$$

Hypercapnia affects peripheral arterioles either by vasoconstriction, through sympathoadrenal excitation<sup>[12]</sup> that results from activation of central<sup>[13]</sup> and peripheral<sup>[14]</sup> chemoreceptors or by vasodilatation through direct, locally-mediated effect.<sup>[2,14]</sup> The elevation in systemic vascular resistance induced by sympathetic vasoconstriction, especially the splanchnic blood vessels, might cancel the effect of peripheral vasodilatation on venous return.<sup>[15]</sup> This could give explanation to our results where hemodynamic stability was maintained despite hypercapnia in the form of comparable MAP and HR between groups. Furthermore, we chose TCI anesthesia technique with remifentanyl and propofol because it is more accurate and reliable to provide steady anesthesia with stable hemodynamics since it uses patient's weight and age to calculate the rate of infusion required to achieve a constant plasma (and brain) concentration.<sup>[16]</sup>

In healthy individuals, etCO<sub>2</sub> is about 2-5 mmHg lower than arterial PaCO<sub>2</sub>, which reflects the alveolar dead space and was shown to be a reliable measure of PaCO<sub>2</sub> that can obviate the need for repeated arterial blood gas determination.<sup>[17,18]</sup> Mild Tobacco smokers (10-15 cigarette/day)<sup>[19]</sup> were accepted to come into this study as it was shown previously<sup>[20]</sup> that preoperative PaCO<sub>2</sub> values were not significantly different between smokers and non-smokers. Moreover, smokers were requested in the pre anesthesia clinic to cease smoking 2 weeks before the surgery. Smokers with apparent lung disease were excluded from the study.

We favored the crossover design for our study as it yields a more efficient comparison of treatments than a parallel design: Patients are on their own controls with patient variability is eliminated. Furthermore, the increased power with greater precision to estimate the treatment differences reduces the sample size. Potential carryover effect was not statistically found with suitable stabilization time granted.<sup>[21]</sup>

This study is not without limitations. Hypercapnia lowered the PVI value, but the weather this value reflects an interaction of hypercapnia with the assessment itself (i.e., the PVI value is changed and the preload-dependency is the same) or due to a cardiovascular change (i.e., the value remains correct but the preload-dependency has been changed) is not known. Moreover, our parameters were not evaluated using gold-standard methods: Cardiac output was not measured using the thermodilution method and the PVI was not compared with the respiratory variation in the arterial pulse pressure, which is considered to be the most accurate predictor of fluid responsiveness.<sup>[22,23]</sup> Therefore, the effect of hypercapnia on the stroke volume remains uncertain.

For our knowledge, this is the first study to evaluate the effect of hypercapnia on PVI. Clinically, the reduction in PVI after hypercapnia would have betrayed the ability of the PVI to precisely evaluate fluid responsiveness. Hence, we recommend comparing PVI readings under similar  $\text{etCO}_2$  values. Furthermore, the PI and PVI were recorded at the finger, which is more sensitive to sympathetic stimulation than the ear.<sup>[24]</sup> Further studies are needed to evaluate whether the PVI recorded at the ear is less affected by hypercapnia.

In conclusion, Hypercapnia decreases PVI in mechanically ventilated patients during stable propofol-remifentanyl anesthesia; thus, it is crucial to pay attention to PVI variability in response to  $\text{etCO}_2$  level when it is used as an indicator for fluid responsiveness by comparing its values alongside similar  $\text{etCO}_2$  levels.

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