Venous-Arterial PCO_2 Difference as an Early Predictor of Organ Dysfunction in Critically Ill Septic Patient

Thesis

Submitted for fulfillment of the master degree in Critical care medicine

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Faculty of medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

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Dedication

This work is dedicated to the individuals who have given meaning to my life;

To *my mother and my father*, who helped me in every step of my life.

To *my wife* ,who encouraged me to complete this work

To *my brother and sister*, who supported me in my life

To *my daughter, Lama*, who made my days to shine

To *my colleges and all my friends*, who helped me

Mohamed Gamal

Acknowledgement

Praise and thanks to ALLAH for all countless gifts ,I have been offered, one of these gifts is accomplishing this research work.

I am very grateful to *Prof. Dr. Hesham Mohammed Elazzazi*, Prof. of anesthesiology, intensive care and pain management, Faculty of Medicine, Ain Shams University, for his sincere co-operation, unlimited help and continuous guidance during this work.

I am so grateful to *Dr. Ashraf Ahmad Abd El-Hamid Abou Slemah,* Lecturer of anesthesiology, intensive care and Pain Management Faculty of Medicine, Ain Shams University, For his valuable help and guidance in the course of this research. His sincere efforts will never be forgotten.

Really and from my heart, I am deeply grateful to *Dr. Eeman Aboubakr ElSiddik Ahmed Bayoumi,* Lecturer of anesthesiology, intensive care and Pain Management, faculty of medicine, Ain Shams University, for her valuable efforts and advices in all steps of this work

Finally, my best regards to all my *family* for their endless encouragement, help and support.

Mohamed Gamal

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List of Abbreviations

(CO2t: Carbon dioxide tension

(VC-A PCO2) : Central venous-arterial PCO2

ABG: Arterial blood gases

ALT: Alanine transaminase

APCO2: Delta PCO2

APS: Acute Physiology Score

AST: Aspartate transaminase

avPCO2: Arterio-venous difference in CO2 pressure

AVpн: Arterio-venous pH

BSA: Body surface area

BUN: Blood Urea Nitrogen

CaCO2: Arterial CO2 content

CaO2: arterial 02 Content

Carbon dioxide

CBC: Complete blood count

CD02 : Critical Oxygen delivery

CKD: Chronic Kidney disease.

CLD: Chronic lung disease.

CNS: Central Nervous System

CO2: Carbon dioxide

CPR: Cardiopulmonary Resuscitation

CvO2: mixed venous 02 Content

CVS: Cardiovascular System

DBP: Diastolic blood pressure

DM: Diabetes mellitus

DNA: Deoxyribonucleic acid

DO2: oxygen delivery

FiO2: Fraction of Inspired Oxygen

GCS: Glasgow coma score

GDT: Goal-directed therapy

GIT: Gastrointestinal Tract

gm/1: Gram per liter

List of Abbreviations *(Cont..)*

H+: Hydrogen ions

Hb: haemoglobin

Hco3: Bicarbonate

Hct %: Hematocrite Percent

HR: Heart rate

Hs: Hours

HTN : Hypertension

ICU: Intensive Care Unit

INR: International normalized ratio

K : potassium

KV: Mass transfer coefficient

LOS: Length of stay

mmHg: Millimeter mercury

MODS: Multiple Organ Dysfunction Syndrome

MPM: Mortality Probability Model

MV: Mechanical Ventilation

Na: Sodium

NIRS: Near infrared spectroscopy,

NRTIs: Nucleoside reverse transcriptase inhibitors

OER: oxygen extraction ratio

P (cv-a) Co2: Central venous -arterial PCO2

PA02: alveolar PO2

Pa02: Partial Oxygen Tension In Arterial Blood

Paco2: Pressure of carbon dioxide in arterial blood

Pco2: Partial Pressure of Carbon Dioxide

PE02: mixed expired PO2

PECO2: mixed expired PCO2

Pi02: Pressure of inspired oxygen

PLT: Platelets

PO2: Oxygen partial pressure (kPa)

P-Value: Probability value

PVCO2: Pressure of carbon dioxide in venous blood

List of Abbreviations *(Cont..)*

Qt: cardiac output

RBS: Random blood sugar

RR: Respiratory rate

Sa02: arterial so2

SAPS: Simplified Acute Physiology score

SBP: Systolic blood pressure

SCCM: Society of Critical Care Medicine

SD: Standard Deviation

SGOT: Serum glutamic oxalacetic transaminase

SGPT: Serum glutamic pyruvic transaminase

SO2: (%) oxygen saturation

SOFA: Sepsis-Related (sequential) organ Failure

SPSS: Social scientific software program

SV: Stroke or systolic volume

Sv02: Mixed venous S02

Svc02: Central venous so2

TLC: Total leucocytic count

USA: United states of America

VAPCO2(V-a PCO2) : Mixed Venous or venous-arterial PCO2

vCo2: CO2 production

VO2: oxygen consumption

WBC: White Blood Cells

APACHE: Acute Physiology And Chronic Health

ACCP: American College of Chest Physician

ATP: Adenosine triphphosphate

MABP: Mean arterial blood pressure

CI: Cardiac index

CO: Cardiac output

Abstract

Introduction: The early identification and scrupulous monitoring of tissue dysoxia can improve the management of critically-ill patients. In this light, the final product of aerobe and anaerobe metabolism (that is, carbon dioxide) can provide useful information on adequacy of tissue perfusion and metabolism. ***The aim of our study*** was to evaluate whether the venous-arterial PCO_2 gradient provides useful information on tissue dysfunction in patients admitted to the ICU**.** ***Methods:*** We prospectively studied 50 patients admitted to ICU in 2017/2018 with length of stay (LOS) >24 hours. A sample of arterial and venous blood was taken for gas analysis at admission. Venous-arterial PCO_2 gradient (ΔPCO_2), organ dysfunction in the first 24 hours and ICU mortality were collected. Organ dysfunction was defined as a SOFA score ≥ 2 for each organ. The patients were subdivided and compared on the basis of ***Δ*** PCO_2 value: $\Delta PCO_2 \geq 6$ mmHg (*Higher* group) and $\Delta PCO_2 < 6$ mmHg (*Normal* group). ***Results:*** Twenty-nine patients (58%) showed a $\Delta PCO_2 \geq 6$ mmHg (*Higher* group) and twenty-one patients (42%) showed a $\Delta PCO_2 \leq 6$ mmHg (*Normal* group).The *higher* group showed a larger rate (34%) of cardiovascular dysfunction than the *Normal* group (8**%**)**(*P value*< 0.05).** Respiratory dysfunction was observed in 54% of the patients of the High group and only in 32% of the Normal group. Similarly, renal dysfunction was also slightly larger in the Higher group (26%) than in the Normal group (20%) **(*P* value> 0.05).** As expected, patients of *higher* group showed more complications (52%) than *Normal* group (32%) **(*P value* > 0.05)** and ICU mortality (40%) three times larger than *Normal* group (12%) **(*P* value< 0.05).** ***Conclusions &Recommendations:*** Despite its limitations, The above data support the hypothesis that ΔPCO_2 can provide useful information on the tissue perfusion and metabolism in ICU patients and can be used as a reliable biomarker for early prediction of organ dysfunction and outcome in critically-ill patients. But, further studies on a larger number of patients are needed to confirm its reliability. ***Limitations :*** Our study was done on a small sample size and based on a pre-defined set of study parameters, which might not have reflected the true nature of general changes observed in sepsis.

Key words: Dysoxia - Shock - Delta PCO_2 - Haemodynamics - Scoring systems - Organ dysfunction - Clinical outcome.

Introduction And Aim of Work

Introduction

The identi cations of tissue hypoxia and hypoperfusion play important roles in the management of critically ill patients during early resuscitation. Global metabolism measurements that are derived from blood gas analyses are the frequently practical methods for assessing global anaerobic metabolism (**Cuschieri *et al*., 2005).**

Resuscitation may be guided by indicators of tissue hypoxia, such as central venous oxygen saturation, which re ects important changes in the relationship between delivery and consumption of oxygen (DO_2/VO_2). Signi cant uctuations in $ScvO_2$ (central venous oxygen saturation) may occur during sepsis, and high $ScvO_2$ values do not necessarily re ect changes intracellular oxygen utilization and perfusion of the microcirculation. Persistent tissue hypoperfusion caused by microcirculatory and mitochondrial failure may occur in the presence of normal or increased $ScvO_2$ (**Huai *et al*., 2016).**

Which may therefore limit the usefulness of ScvO2 in clinical practice. Normalization of systemic hemodynamic and oxygen metabolism variables does not ensure an adequate tissue perfusion and does not prevent progression to multiorgan dysfunction and death **(Lamia *et al*., 2006).**

Central or mixed venous–arterial carbon dioxide partial pressure difference (ΔPCO_2) has also been used to guide the treatment of shock **(Marit *et al*., 2015).**

$\Delta\ PCO_2$ is the difference between the partial pressure of CO2 in mixed venous blood or central venous blood ($PvCO_2$ or $PcvCO_2$) and the partial pressure of CO_2 in arterial blood ($PaCO_2$): $\Delta\ PCO_2 = PvCO_2 - PaCO_2$. $PaCO_2$ and $PvCO_2$ represent only a fraction of arterial CO_2 content

($CaCO_2$) and central venous CO_2 content ($CvCO_2$), respectively, but as the relationship between partial pressure and content of CO_2 is almost linear under normal physiological conditions, PCO_2 can be taken as a measure of CCO_2. At the cellular level, CO_2 is a normal terminal product of oxidative metabolism. Thus, in the absence of a shunt, CCO_2 in the ef uent venous blood must be higher than in the afferent arterial blood. Therefore, the difference between central venous blood and arterial blood PCO_2 (ΔPCO_2) may be considered as a marker of the global hemodynamic status **(Monnet *et al*., 2013).**

The Fick equation applied to CO_2 indicates that the CO_2 excretion (equivalent to CO_2 production in a steady state) equals the product of cardiac output (CO) and the difference between the PCO_2 content in mixed venous blood ($CvCO_2$) and in arterial blood ($CaCO_2$): $VCO_2 = CO \times (CvCO_2 - CaCO_2)$. In the equation $\Delta PCO_2 = VCO_2 \times k/CO$, k is assumed to be constant, and ΔPCO_2 is linearly related to CO2 production and inversely related to CO .Therefore, if cardiac output is low than normal, ΔPCO_2 is expected to be abnormally high i.e. More than 6mmHg (**Puskarich *et al*., 2011).**

A reverse correlation have been found between [$P(cv\text{-}a)CO_2$] and cardiac index with a central venous blood sample and so, a sample of central venous blood could be used instead of blood from the pulmonary artery for this purpose **(Vallee *et al*., 2008).**

Global indices of tissue perfusion include lactate and central venous oxygen saturation ($SvcO_2$). But, the mixed $V\text{-}APCO_2$ difference cannot serve as a marker of tissue hypoxia. But, it can be considered as a marker of the adequacy of venous blood flow (i.e. cardiac output) to remove the total CO_2 produced by the peripheral tissues. In this regard, the knowledge

of Delta PCO_2 should help the clinicians for the decision of giving therapy aimed at increasing cardiac output **(Vallet *et al*., 2000).**

Elevated V-a PCO_2 has also been described in patients with sepsis, cardiogenic shock, acute myocardial infarction, and congestive heart failure, as well as cardiac arrest following cardiopulmonary resuscitation (CPR) and heart surgery **(Victor *et al*., 2009).**

Interestingly, central venous-arterial PCO_2 (Pcv-aCO_2), has recently been proposed as a useful tool for goal directed therapy (GDT) in ICU-septic patients to identify persistent hypoperfusion when saturation of central venous oxygen ($ScvO_2$) > 70% has been reached Although oxygen delivery (DO_2) in septic shock can be elevated, oxygen consumption (VO_2) is impaired as a consequence of mitochondrial dysfunction in sepsis **(Wei *et al*., 2013).**

The venoarterial CO_2 gradient (V-a PCO_2) is influenced by two other factors: the dissociative curve of CO_2 and tissue blood flow. The curve of CO_2 dissociation from hemoglobin follows the so-called **Haldane's effect**, in which oxygen and its bonding with hemoglobin allows easier release of CO_2 in lungs. Experimental models have shown that in toxemia, venous hypercapnia is a more significant contributor to the increase in the venoarterial CO_2 gradient than arterial CO_2 values **(Antonelli *et al*., 2007).**