# ROLE OF EARLY CONTINUOUS VENO-VENOUS HEMODIAFILTERATION IN SEPTIC SHOCK AND MULTI-ORGAN FAILURE

Thesis Submitted by

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In Partial Fulfillment of Master Degree in Critical Care medicine

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2009

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## ACKNOWLEDGEMENT

#### Above all, I thank and praise ALLAH.

Thanks to **Prof. Dr. Sherif Mokhtar**, our Master & the founder of our department, we always owe him much. He offered us not only facilities to complete our work but also the spirit of being eager to gain more experience and skills. Words are not sufficient to express my deep gratitude for him.

I would like to start by sending my deepest gratitude and sincere thanks to **Prof. Dr. Hassan Khaled,** Professor & Head of Critical Care Medicine Department, Cairo University for his great encouragement & unlimited support from my starting years of work till now.

I would like to thank **Prof. Dr. Alia Abd El-Fattah** Professor of Critical Care Medicine Department, Cairo University, for supporting me and helping my work to be completed, she didn't save any effort in solving all the difficulties I had faced upon starting my work.

Special thanks to **Prof. Dr. Ahmed El Sherif**, Assist. Prof. of Critical Care Medicine, Cairo University, for his continous help and support. I am extremely grateful to him for his generous advice and for his guidance and assistance throughout the whole work. I owe him great deal of refining & revising this work through the long time & patience he offered me.

I am very grateful to **Dr. Hossam Sherif**, lecturer of Critical Care Medicine, Cairo University, for his contribution in this work by providing me the ideas & methods of how to perform high quality research.

Many thanks to **Dr. Ahmed battah**, lecturer of Critical Care Medicine, Cairo University, for his guidance. He teached me how to approach matters in a scientific and displined way. I am extremely thankful to him for actively participating in refining & revising this work for a long time.

Also I'd like to thank engineers Mohamed Ghonim & Akram Khedr for supporting me in dealing with the machine & all technical problems during my work, also many thanks to Dr. Dalia Ahmed assistant professor of community medicine & statistics for her generous help & support in performing statistical analysis of this work

Finally, I must thank all my colleagues, nursing staff & everyone who gave me help & support throughout my work. I do ask **ALLAH** to forgive me for any faults or forgets in this study

Mohamed Soliman

#### **ABSTRACT**

**INTRODUCTION:** We conducted a prospective observational study from august 2007 to august 2008 to evaluate early continuous veno-venous haemodiafiltration (**CVVHDF**), in patients with refractory septic shock and multi-organ failure upon mortality & morbidity in the ICU.

Methods: CVVHDF was implemented at less than 6–12 hours of maximal haemodynamic support. Metabolic acidosis, serum lactate & serum procalcitonin level (PCT) before & after CVVHDF at day 5 were the monitoring used to evaluate the improvement achieved.40 patients included in the study were chosen randomly, 20 underwent CVVHDF (group I) & 20 were control group (group II) treated using traditional guidelines. APACHE II & Delta-SOFA scoring systems were used before & after CVVHDF at day 5.

RESULTS: Compared to group II, pts of group I had lower mortality (55% vs 70%). Group I patients showed a non significant delta SOFA (5.95±4.39 vs 6.2±3.3 in group I & II respectively & P=0.66), regarding APACHE II scores, group I also showed statistically non-significant lower figures than group II (on admission APACHE II scores were 39.35±10.65 vs 41.85±10 in group I & II respectively & P=0.45) while on day 5 APACHE II scores were (34.8±10.6 vs 36.1±10.9 in group I & II respectively & P=0.41). Group I patients showed lower PCT on admission & day 5 than group II patients (on admission PCT level was 0.64±0.18 vs 0.68±0.17 in group I & II respectively & P=0.5) while day 5 PCT level was (0.51±0.15 vs 0.52±0.17 in group I & II respectively & P=0.83). Indicators of improvement showed statistically significant difference between survivors & non-survivors regarding Serum lactate level at day 5 (P<0.001), while other indicators as Fever, Renal profile, WBC count, Metabolic acidosis, Serum lactate level on admission & Platlets count were statistically insignificant (on admission P-value=0.2, 0.55, 0.45, 0.41, 0.65, 0.55 for each indicator respectively & on day 5 P-value=0.37, 0.94, 0.71, 0.5, <0.001, 0.88 for each indicator respectively).

<u>Conclusion:</u> Early CVVHDF may improve the prognosis of sepsis-related multiple organ failure, Failure to correct metabolic acidosis rapidly during CVVHDF is a strong predictor of mortality as it was more evident in non-survivors. Continous rising of serum lactate level despite CVVHDF is associated with increased mortality rate. Of all scoring systems used SOFA maximum, Delta-SOFA and APACHE II day 5 were the most accurate prognostic indicators for mortality. More than 4 organs failure showed 100% mortality, while less than 4 organs failure showed no mortality in our study. PCT level was higher in non-survivors but with insignificant statistical difference between the 2 groups.

**KEYWORDS**: continuous veno-venous hemodiafiltration, lactate, procalcitonin, delta-sofa, APACHE II

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## Abbreviations

ABP	Arterial Blood Pressure
APACHE II	Acute Physiology and Chronic Health Evaluation II
APACHE III	Acute Physiology and Chronic Health Evaluation III
aPTT	Activated Partial Thromboplastin Time
ARDS	Adult Respiratory Distress Syndrome
ARF	Acute Renal Failure
AT	Anti-Thrombin
BAL	Bronco-Alveolar Lavage
Bcl-2 gene	B-cell Leukemia/lymphoma-2 genes
C3a	Activated Complement 3
CD 46,256	Cell of Differentiation 46,256
CHFD	Continuous High-Flux Dialysis
CO	Cardiac Output
CPFA	Continuous Plasma Filtration Adsorption
CRP	C-Reactive Protein
CRRT	Continuous Renal Replacement Therapies
CVP	Central Venous Pressure
CVVH	Continuous Veno-Venous Hemofiltration
CVVHDF	Continuous Veno-Venous Hemodiafiltration
DIC	Disseminated Intravascular Coagulation
DNA	Deoxyribo Nucleic acid
DO2	Oxygen Delivery
ED	<b>Emergency Department</b>
EGDT	Early Goal-Directed Therapy
ESKD	End Stage Kidney Disease
FIO2	Fraction of Inspired Oxygen
FISH	Fluorescent Insitu Hybridization
FIX	Factor 9
FVa	activated Factor 5
FVIIa	activated factor 7
FVIIIa	activated factor 8
FX	factor 10
FXa	activated factor 10
GCS	Glasgow Coma Scoring
G-CSF	Granulocyte Colony-Stimulating Factor
HLA-DR	Human Leukocytic Antigen- type DR
HR	Heart Rate
HVHF	High Volume Hemo-Filtration
ICU	Intensive Care Unit
IFN-g	Interferon-Gamma

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IHD	Intermittent Hemodialysis
IL-1,2,4,6,8,10	Interleukin-1,2,4,6,8,10
INR	International Normalized Ratio
LPS	Lipopolysaccharide
MAP	Mean Arterial blood Pressure
mHLA-DR	Monocyte Human Leukocytic Antigen type DR
MODS	Multi-Organ Dysfunction Syndrome
MOF	Multi-Organ Failure
mRNA	Messenger Ribonucleic Acid
MRSA	Methicillin Resistant Staphylococcus Aureus
NFkB	Nuclear Factor- Kappa B
NO	Nitric Oxide
PACO2	Partial Pressure of Carbon Dioxide in the Arterial blood
PAI-1	Plasminogen Activator Inhibitor-1
PAO2	Partial Pressure of Oxygen in the Arterial blood
PARs	Protease Activated Receptors
PCR	Polymerase Chain Reaction
PCT	Pro-calcitonin
RCT	Randomized Controlled Trials
RNA	RiboNucleic Acid
RR	Respiratory Rate
rRNA	Ribosomal Ribonucleic Acid
SBP	Systolic Blood Pressure
SC tissue	Subcutaneous Tissue
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
sPLA2	Secretory Phospholipase A2
ScVo2	Central venous oxygen saturation
SVO2	Mixed Venous Oxygen Saturation
T-cells	Thymus Cells
TF- VIIa	Activated Tissue Factor 7
TFPI	Tissue Factor Pathway Inhibitor
TGF-b	Transforming Growth Factor-b
Th1	Type 1T-helper cells
Th2	Type 2 T-helper cells
TLC	Total Leukocytic Count
TNF-a	Tumor Necrotic Factor alpha
VO2	Oxygen Consumption
WBC	White Blood Cell

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# INTRODUCTION & AIM OF WORK

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#### INTRODUCTION

Sepsis constitutes a significant consumption of intensive care resources and remains an ever-present problem in the intensive care unit. It has been estimated that between 400,000 and 500,000 patients are so affected each year in both the **USA** and Europe. Morbidity and mortality have remained high despite improvements in both supportive and antimicrobial therapies. Mortality rates vary from 40% for uncomplicated sepsis to 80% in those suffering from septic shock and multi-organ dysfunction. <sup>(1)</sup>

Severe sepsis and septic shock are common, accounting for about 2.9% of hospital admissions and 10% of admissions into the intensive care unit (**ICU**). The mortality rates for these 2 conditions exceed 30 %. (2) Patients admitted and treated for sepsis in the **ICU** are often transferred from general medical/surgical practice units, operating rooms, Emergency Departments, long-term care facilities and other hospitals. The diagnosis and treatment of these patients may be sub-optimal, even among those who were admitted to general medical or surgical practice units or the **ICU**. (3)

Delays in the identification, transfer and management of critically ill patients during the first 6 hours after **ICU** admission have been associated with higher mortality rates<sup>(4)</sup> and increased utilization of hospital resources.<sup>(2)</sup> Within the last 5 years, advances in the treatment of severe sepsis and septic shock have provided new therapies to treat this disease.

Although these studies were **ICU**-based, the timelines of treatment became a more important issue when Rivers and colleagues <sup>(5)</sup> were able

to show a significant mortality benefit when hemodynamic optimization was provided within the first few hours of disease presentation.

This "*golden hour*" and "*silver day*" perspective of early resuscitation, which traditionally has been applied to trauma, can now be applied to severe sepsis and septic shock. Early diagnosis and rapid intervention became synonymous with improved outcomes for trauma patients, which inspired the concept of the "golden hour." (7)

In turn, the "silver day" represented the first day's remaining hours, during which aggressive correction of shock and organ dysfunction was found to decrease health-care resource utilization <sup>(8)</sup> and improve outcomes, these ideals have been incorporated into the Surviving Sepsis Campaign, a multinational initiative, which recommends a 24-hour sepsis pathway that includes a critical 6-hour course of action. <sup>(9)</sup>

The conventional treatment in septic shock is the use of antibiotics, and fluid replacement. Once they do not respond promptly to fluid replacement to prevent development of septic shock, the patient is worsening into a more severe condition, necessitating intensive care treatment, including vasopressor support, besides respiratory aid and dialysis. (10, 11)

Septic shock is usually accompanied by acute renal injury, heralded by a drop in diuresis. However, when standard intermittent hemodialysis (**IHD**) is used to treat renal failure, the initiation of renal replacement therapy is often delayed by concerns about haemodynamic tolerance. With the availability of continuous veno-venous hemofiltration (**CVVHF**), a safe procedure in haemodynamically unstable patients <sup>(12)</sup>, there is no reason to delay renal replacement therapy <sup>(13)</sup>.

Hemofiltration has been reported to improve cardio-pulmonary function in septic patients, even if they are not oliguric <sup>(14)</sup>. In hemodynamically stable patients with acute renal failure, continuous veno-venous hemofiltration and intermittent hemodialysis are equally effective. In hemodynamically unstable patients, continuous hemofiltration provides easier management of fluid balance. <sup>(15)</sup>

The incidence of renal failure requiring dialysis is low in sepsis patients (<5%); however, the risk of mortality in sepsis patients with acute renal failure (**ARF**) exceeds 50% <sup>(9)</sup>. Renal replacement therapies in critically ill patients are primarily limited to intermittent renal replacement therapy (**IRRT**) and continuous renal replacement therapy (**CRRT**). Considerable debate surrounds the management of **ARF** patients and whether or not the more costly **CRRT** should be adopted. A recent meta-analysis suggested that **CRRT** was associated with a significant mortality reduction when adjustments were made for study quality and severity of illness <sup>(16)</sup>.

#### **AIM OF THE WORK**

The aim of the presented study is to:

- ➤ Evaluation of the effect of early continuous veno-venous hemodiafiltration therapy in septic shock regarding mortality & morbidity in **ICU**.
- Evaluating **Delta-SOFA** & **APACHE II** scoring systems in critically ill patients due to septic shock.
- > Evaluating **PCT** level in association to mortality