Myocardial Dysfunction Post-Sepsis in critical ICU patients

Essay

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Abstract

Introduction: Sepsis has been defined by consensus as a systemic inflammatory response syndrome (SIRS) to infection. It is generally viewed as being aggravated by an inappropriate immune response, and it occasionally leads to multiple organ failure and shock. The pathophysiology of septic shock is thought to involve complex interactions between pathogens and a host immune system. Russel and colleague. (2011) have shown that the host immune system recognizes infection through recognition of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), lipoteichoic acid, flagellin and DNA in bacteria, mannan in fungi, and single- or double stranded RNA in viruses. These mediators bind to pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs) that are expressed on the surface of host cells.

Aim of the Work: The aim is to describe some important features of septic myocardial dysfunction, assess the underlying mechanisms of cardiac dysfunction in sepsis, and briefly outline current therapeutic strategies and potential future approaches.

Summary: Sepsis is generally viewed as a disease aggravated by an inappropriate immune response encountered in the afflicted individual. As an important organ system frequently compromised by sepsis and always affected by septic shock, the cardiovascular system and its dysfunction during sepsis have been studied in clinical and basic research for more than 5 decades.

Goals and principles of treatment: The treatment of patients with septic shock has the following major goals: Start adequate antibiotic therapy (proper dosage and spectrum) as early as possible. Resuscitate the patient, using supportive measures to correct hypoxia, hypotension, and impaired tissue oxygenation (hypoperfusion).

Keywords: Myocardial Dysfunction, Post-Sepsis, Critical ICU Patients

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Contents

List of Abbreviations

AC	: Adenylate Cyclase.
ACCCM	: American College Of Critical Care Medicine
ACCP	; American College Of Chest Physician
ACEP	: American College Of Emergency Physician
ADH	: Anti Diuretic Hormone.
AIS	: American Thoracic Society
ALI	: Acute Lung Injury
APACHE	: Acute Physiology And Chronic Health Evaluation
appt	: Activated Partial Thromboplastin Time
ARISE	: Australasian Resuscitation In Sepsis Evaluation.
ATP	: Adenosine Tri Phosphate.
AUC	: Area Under the Curve.
B-AR	: Beta-Adrenergic Receptor.
BCSH	: Brittish Committee For Standard In Heamstology
BNP	: B-type Natriuretic Peptide.
CA _MRSA	: Community Acquired MRSA
CaMK11	: Ca2+ l Calmodulin-dependent protein Kinase.
cAMP	: Cyclic Adenosine Monophosphate.
CIRCI	: Critical Illness Related Corticosteroid Insufficiency
CM	: Calmodulin.
CMK	: Calmodulin Kinase.
CN	: Calcineurin .
cNOS	: Constitutive Nitric Oxide Synthase.
CNS	:Central Nervous System.
CORTICUS	: Corticosteroid Therapy Of Septic Shock
COX-2	: Cyclooxygenase-2.
cTn1	: Troponin 1.
CTNT	: Cardiac Troponin T.
CVP	: Central Venous Pressure.
Cyt C	: Cytochrome C.
DAD	: Diffuse Alveolar Damage
DAMPs	: Damage-Associated Molecular Patterns.

DIC	: Disseminated Intravascular Coagulopathy.
DVT	: Deep Venous Thrombosis
EAU	: European Association Of Urology.
ED	: Emergency Department.
EF	: Ejection Fraction.
EGDT	: Early Goal-directed Therapy.
ELBW	: Extremely Low Birth Weight.
eNOS	: Endothelial Nitric Oxide Synthase.
ERK1l2	: Extracellular signal Regulated Kinases.
ESBL	: Extended-Spectrum Beta-Lactamase.
ESICM	: European Society Of Intensive Care Medicine
ET-1	: Endothelin-1.
FFP	: Fresh Frozen Plasma.
FIO2	: Fraction Of Inspired Oxygen
GCS	: Graduated Compression Stocking
GDT	: Goal- Directed Therapy.
GI	: Gastrointestinal.
Gs	: G-proteins
HMGB1	: High Mobility Group Box 1.
HPA	: Hypothalamic Pituitery Adrenal Axis
HR	: Heart Rate.
ICDs	: Intermittent Compression Devices
ICU	: Intensive Care Unit.
IDSA	: Infection Disease Society of AMERICA
IFN-Y	: Gamma Interferon
IL-1B	: Interleukin-1-Beta.
iNOS	: Induced Nitric Oxide Synthase.
IRAK1	: Interleukin-1 Receptor Associated kinase 1
IV	: Intra Venous.
L	: L-type voltage calcium channels
LMWH	: Low Molecular Weight Heparin
L-NMMA	: NG-Monomethyl-L-Arginine
LPs	: Lipopolysaccharides.
LV	: Left Ventricle.
LVEDV	: Left Ventricular End-diastolic Volume.

LVEF : Left Ventricular Ejection Fraction.
MAP : Mean Arterial Pressure.
MDF : Myocardial Dysfunction.
MI : Myocardial Ischemia.
MODS : Multiple Organ Dysfunction Syndrome
MOF : Multiple Organ Failure.
MRSA : Methicillin-Resistant Staph Aureus.
MSSA : Methicillin-Susceptible Staph Aureus
Mt DNA : Mitochondrial DNA.
MVO2 :Maximal Venaous Oxygen.
NETs : Neutrophil Extracellular Traps.
NF-kB : Nuclear Factor-kB.
NICU : Neonatal Intensive Care Unit.
NIH : National Institute Of Health.
NO : Nitric Oxide.
NOS3KO : Nitric Oxide Synthase3 Knock Out.
NPV : Negative Predictive Value.
O2- : Super Oxide Anion.
PAMPs : Pathogen Associated Molecular Patterns.
PAOP : Pulmonary Artery Occlusion Pressure.
Pa-vo2 : Arterial to-Central venous Po2 gradient.
PAWP : Pulmonary Arterial Wedge pressure.
PDE : Phosphodiesterase.
PEEP : Positive End Expiratory Pressure
PH : Phospholamban.
PKG : Protein Kinase G
PPV : Positive Predictive Value.
PROCESS : Protocolised Care For Early Septic Shock.
ProMISe : Protocolised Management In Sepsis.
PRRs : Pattern-Recognition Receptors.
PT : Prothrombin time
PTP : Permeability Transition Pore.
PV-aCo2 : Central Venous-to-Arterial PCo2 gap
RBC : Red Blood Cell
RCOG : Royal College Of Obstetricians And Gynaecologists

RhAPC : Recombinant Activated Protein C.
ROS : Reactive Oxygen Species.
rTM : Recombinant Thrombomodulin.
RYR2 : Ryanodine Receptor 2
SAFE : Saline versus Albumin Fluid Evaluation.
SCCM : Society Of Critical Care Medicine
SCVO2 : Central Venous Oxygen Saturation
Scvo2 : Central venous oxygen saturation
SERCA : SR-Calcium-Adenosine Triphosphatase
SICU : Surgical ICU
SIRS : Systemic Inflammatory Response Syndrome
SIS : Surgical Infection Society
Smvo2 : Mixed venous oxygen saturation.
SOFA : Seqyantial Organ Failure Assessment
SR : Sarcoplasmic Reticulum
SSCG : Surviving Sepsis Campaign Guidelines
SV : Stroke Volume
SVR : Systemic Vascular Resistance
Tc : Troponin c
Ti : Troponin i
TLRs : Toll-Like Receptors
TNF : Tumor Necrosis Factor
UCP : Uncoupling Proteins
UFH : Unfractionated Heparin
UOP : Urine output
VASST : The Vasopressin and Septic Shock Trial
WT : Wild Type

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Introduction

Sepsis has been defined by consensus as a systemic inflammatory response syndrome (SIRS) to infection. It is generally viewed as being aggravated by an inappropriate immune response, and it occasionally leads to multiple organ failure and shock. The pathophysiology of septic shock is thought to involve complex interactions between pathogens and a host immune system **(Annane et al., 2006).**

Russel and colleague. (2011) have shown that the host immune system recognizes infection through recognition of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), lipoteichoic acid, flagellin and DNA in bacteria, mannan in fungi, and single- or double stranded RNA in viruses. These mediators bind to pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs) that are expressed on the surface of host cells. These PRRs are essential for initiating host immune defenses against invading pathogens and mediating PAMP recognition. They also serve as receptors for endogenous danger signals by identifying various damage-associated molecular patterns (DAMPs) as potent activators of the innate immune system.

The proinflammatory response induced by infection is normally balanced by anti-inflammatory cytokines. However, the normally effective inflammatory response to infection becomes systemically dysregulated during sepsis due to significantly imbalanced cytokine responses referred to as a cytokine storm.

The production of excess antimicrobial products and inflammatory mediators elicits the generation of reactive oxygen and nitrogen species, superoxide anion (O), and nitric oxide (NO), causing adjacent tissue damage and an amplified inflammatory reaction **(Soriano et al., 2011)**.

A major mechanism of direct cardiac depression in sepsis is the attenuation of the adrenergic response at the cardiomyocyte level due to down-regulation signaling pathways. These changes seem to be mediated by many substances , such as cytokines and nitric oxide.

Another mechanism of direct cardiac depression in sepsis is cardiomyocyte injury or death, which can by induced by toxins, complements, DAMPS, and as-yet unidentified myocardial depressants **(Kakihana et al., 2016)**.

Early control of the source and monitoring hemocultures in conjunction with early adequate antibiotic care is important to decrease PAMPs arising from invasive

microorganisms. Moreover, aggressive fluid replacement guided by monitoring fluid response parameters appears to be a rational strategy to remedy hypovolemia. While early and sufficient fluid administration is likely to be beneficial, excessive volume loading is harmful. The risk of pulmonary edema formation is particularly elevated due to increased permeability of the pulmonary microcirculation and LV diastolic dysfunction. Supportive therapy encompasses early and goal-directed , vasopressor and inotropic therapy, red blood cell transfusion, mechanical ventilation, and renal support when indicated. Goal-directed therapy (GDT) appears to significantly reduce overall mortality in patients with sepsis, especially when implemented within the first 6 h of admission; this is called early GDT (EGDT) **(Rivers et al., 2001)**.

Aim of the Work

The aim is to describe some important features of septic myocardial dysfunction, assess the underlying mechanisms of cardiac dysfunction in sepsis, and briefly outline current therapeutic strategies and potential future approaches.

Pathophysiology of Myocardial Dysfunction Postsepsis

Sepsis remains one of the leading causes of mortality in critically ill patients in the ICU. Over the last decade there has been a demonstrable significant reduction in mortality from severe sepsis and septic shock through the use of performance metrics and collaborative quality improvement efforts that facilitate the incorporation of the latest scientific and clinical advancements into bedside practice. As scientific knowledge and clinical expertise continue to grow as to the treatment of patients with sepsis, and new innovative technologies and approaches are developed, continued efforts must be made to translate this into improved patient care **(Levision et al., 2011)**.

Sepsis or serious infection within the first four weeks of life kills greater than one million newborns globally every year. The attack rate for neonatal sepsis is variable (from < 1% to > 35% of live births) based on gestational age and time of onset [early (72 hours after birth) or late (> 72 hours after birth)]. Neonates with sepsis may present in or progress to septic shock, exemplified initially by cardiovascular dysfunction requiring fluid resuscitation or inotropic support. If the progression of infection cannot be stopped, end organ damage and death become much more

likely. While the true incidence is not known, septic shock was found in 1.3% of neonates admitted to the NICU over a 6-year period with an associated mortality peaking at 71% for Extremely Low Birth Weight (ELBW) neonates < 1000 gm **(Wynn et al., 2010)**.

Septic shock is sepsis with cardiovascular System dysfunction, despite the administration of ≥ 40 ml/kg of isotonic fluid in one hour. Shock is an acute syndrome characterized by body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Patients in shock have insufficient oxygen at the tissue level to support normal aerobic cellular metabolits, resulting in a shift to less efficient anerobic metabolism. The Increase in tissue oxygen extraction is unable to compensate for this deficiency in oxygen delivery, leading to progressive lactic acidosis and possible clinical deterioration. If inadequat tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen the physiologic instability **(Turner and Cheifetz, 2012)**.

Compensation for inadequate oxygen delivery invovles a complex set of responses that attempt to preserve oxygenation of the vital organs (i.e. brain, heart, kidneys and liver) at the expense of other organs (i.e. skin,