Septic cardiomyopathy in critically ill patients

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Abdellatif siam.

To my parents, my sisters, my god father
and my fiancée.

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Abbreviations

ACTH: Adrenocorticotropic hormone.
APC: Activated protein C.
APCs: Antigen presenting cells.
ARF: Acute renal failure.
ATP: Adenosine triphosphate.
CARS: Compensatory anti-inflammatory response.
CD: Cluster of differentiation.
CK: Creatin kinase.
CMK: Chloromethyl ketone.
cNOs: Constitutive nitric oxide synthase.
CRH: Corticotropin releasing hormone.
CRP: C reactive protein.
CRRT: Continous renal replacement therapy.
CTLs: Cytotoxic T lymphocytes.
DCs: Dendritic cells.
ECs: Endothelial cells.
FMK: Floromethyl ketone.
GALT: Gut associated lymphoid tissue.
GHSR: Growth hormone secretagogue receptor.
GSH: Glutathione.
GTP: Guanosine triphosphate.
HF: Hemofiltration.
HLA: Human leukocyte antigen.
HPA: Hypothalamic-pituitary-adrenal axis.
HSP: Heat shock protein.
HSS: Hypertonic saline solution.
IELs: Intestinal intra-epithelial lymphocytes.
IG: Immunoglobulin.
IL: Interleukin.
INF: Interferon.
iNOs: Inducible nitric oxide synthase.
LMWH: Low molecular weight heparin.
LPs: Lipopolysaccharides.

MALT: Mucosa associated lymphoid tissue.
MAP: Mean arterial pressure.
MCP: Monocyte chemoattractant protein.
MPs: Microparticles.
NF: Nuclear factor.
NK: Natural killer cells.
NO: Nitric oxide.
PMNs: Polymorphonuclear cells.
nNOs: Neuronal nitric oxide synthase.
PAI: Plasminogen activator inhibitor.
PG: Prostaglandin.
ROIs: Reactive oxygen intermediates.
SGC: Soluble guanylate cyclase.
SIRS: Systemic inflammatory response syndrome.
SLE: Systemic lupus erythematosis.
TCR: T cell receptor.
TF: Tissue factor.
TGF: Tissue growth factor.
TH: T helper lymphocytes.
TLR: Toll-like receptor.
TNF: Tumor necrosis factor.
tPA: Tissue plasminogen activator.
UFH: Unfractionated heparin.
uPA: Urokinase plasminogen activator.
VCAM: Vascular cell adhesion molecule.
vWF: Von willebrand factor.

Introduction

Sepsis is the leading cause of death in critically ill patients. The yearly incidence of severe sepsis is increasing and has recently been reported as 132 per 100,000 population, with a mortality approaching 50%.The incidence of sepsis is disproportionately increased in the elderly, and age is an independent predictor of survival. Sepsis is a complex disease and is the manifestation of the immune and inflammatory response to infection. Severe sepsis is defined as sepsis with organ dysfunction, while septic shock is sepsis with hypotension that persists despite resuscitation with intravenous (IV) fluids **(J. D. Hunter and M. Doddi.,2010).**

Myocardial impairment resulting from systemic sepsis has been recognized for more than a quarter of a century yet much about the phenomenon remains a mystery. The incidence of myocardial depression in the critically ill patient with sepsis is uncertain because of the imprecision with which myocardial depression is
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earlier studies included variable populations of patients and relied on radionuclide or pulmonary artery catheter methods, whereas techniques such as tissue Doppler imaging have been around for only the last decade. Depression of myocardial function in septic patients is likely to be more common than previous thought because echocardiography is now more readily available and used by critical care physicians experienced in using it. Weng and colleagues in measuring echocardiographic, clinical, and laboratory variables in 61 patients with septic shock, found that left ventricular tissue Doppler parameters demonstrated potentially useful prognostic information.In particular, the peak systolic velocity measured at the mitral annulus, a measure of the long axis systolic motion of the left ventricle, was significantly lower in survivors than non survivors. Using a cut off value of 9 cm/second predicted 90 day mortality with a sensitivity and a specificity of 75% and 86%, respectively. Left ventricular ejection fraction measurements between survivors and non survivors were not significantly different **(Weng L etal.,2012).**

This work is the latest in a series of studies examining the pathophysiology of sepsis induced cardiomyopathy and, more specifically, its prognostic significance. Earlier work usingradionuclide and pulmonary artery catheter studies indicated that dilatation of the left ventricle was associated with a lower mortality in patients with sepsis. Later studies using echo Doppler techniques did not confirm the relationship between left ventricular dilatation and improved outcome from sepsis but did confirm the relationship between left ventricular dysfunction and outcome. Vieillard Baron and colleagues found that 60% of their patients with sepsis

experienced underlying left ventricular dysfunction as a result of sepsis when evaluated by transesophageal echocardiographic examination. The assumption that septic cardiomyopathy is somehow beneficial and indicates a better patient outcome should be treated with caution. This is an attractive hypothesis, but the focus may be incorrect **(Vieillard Baron A etal.,2008).**

The contrary emphasis could be that the hyperkinetic state present in many patients with sepsis indicates profound vasoplegia and this is responsible for the increased mortality in this group. Also, the clinician needs to consider more than left ventricular systolic function as left ventricular diastolic function and right heart function can also be affected in sepsis, either independently or collectively. Even when the more recent sophisticated echo Doppler techniques are applied, there is disagree ment regarding the prognostic or potentially protective value of cardiac depression. In a study of only 21 patients, E/Ea (early diastolic transmitral velocity/early mitral annular diastolic velocity ratio), but not Sa, was an independent predictor of mortality in septic shock. In a larger and more recent study involving 262 patients with severe sepsis, the presence of systolic dysfunction, diastolic dysfunction, or both was associated with a higher mortality **(Vieillard Baron A etal.,2011).**

The actual cause of the cardiac dysfunction found in many patients with severe sepsis is still uncertain and multiple etiologies are proposed. Cytokines have been favorite candidates over the years; a circulating myocardial depressant factor was first postulated by Wiggers in 1947 and was advanced further by Parillo and colleagues in 1985. Complement molecules, nitric oxide, cellular adhesion molecules, disordered intra cellular energetics, and abnormalities in intracellular calcium fluxes are some of the more recently postulated causes **(Flynn A etal.,2010).**

Considerable uncertainty still surrounds the incidence, etiology, assessment, and prognostic significance of septic cardiomyopathy, and the findings by Weng and colleagues should be observed in this light. It is unlikely that a single measurement such as Sa will prove to be a robust prognostic marker, particularly since the range for this parameter in the healthy population is so broad. It may be that recently developed echo Doppler techniques will provide a more accurate set of methods of evaluating cardiac dysfunction in severe sepsis. Recent developments, including velocity vector tracking and four dimensional echocardiography, open a window on ventricular rotation during systole, a significant contributor to cardiac output. In the past, echo Doppler techniques which, a part from magnetic resonance imaging, are the best tools

available for assessing ventricular function have not taken into account the contribution of twisting and torsion of the ventricle, estimated to account for 40% of cardiac output. Tissue Doppler imaging has enhanced our understanding of left ventricular function, and the finding that may be an important prognostic marker in septic cardiomyopathy is a stimulus to more closely examine myocardial reaction to the insult. The cardiac sequelae of severe sepsis can be severe, and bedside echocardiographic assessment is essential to the further understanding of this most intriguing condition **(Chahal NS,.2010).**

The best treatment for myocardial dysfunction is the proper management of sepsis. The early collection of hemocultures in conjunction with adequate antibiotic care is the gold standard. Moreover, aggressive fluid replacement to remedy hypovolemia, guided by the examination of fluid responsiveness parameters, appears to be a rational strategy. This approach aims to provide adequate perfusion, as evaluated by central venous saturation (SvcO) optimization and lactate clearance. Keeping arterial pressure stable is very important for reestablishing organ perfusion pressure, which helps maintain blood flow to tissues. Norepinephrine is the vasopressor of choice when a patient is nonresponsive to fluids **(Constantino Jose Fernandes Jr.and Murillo Santucci Cesar de Assuncao 2012).**

Only 10 to 20% of patients who have myocardial depression will need to receive inotropic drugs to obtain adequate tissue perfusion. Most patients will benefit from administration fluid infusion. However, when inotropes are indicated to optimize flow and cardiac output and improve hemodynamics, dobutamine is the first choice. Patients may have a poor response to β-adrenergics due to myocardial depression. In this situation, an alternative is levosimendan, a calcium sensitizer, which in some clinical and experimental studies has improved perfusion**(Constantino Jose Fernandes Jr.and Murillo Santucci Cesar de Assuncao 2012).**

Sepsis : definitions and pathophysiology

Introduction:

Sepsis is among the most common reasons for admission to intensive care units (ICUs) throughout the world. During the past two decades, the incidence of sepsis in the United States has tripled and is now the tenth leading cause of death. In the United States alone, approximately750,000 cases of sepsis occur each year, at least 225,000 of which are fatal. Septic patients are generally hospitalized for extended periods, rarely leaving the ICU before 2-3 weeks. Despite the use of antimicrobial agents and advanced life support. The case fatality rate for patients with sepsis has remained between 20% and 30% during the past 2 decades **(paul E Mirk.,2011).**

The concept of sepsis syndrome originated during the time of Hippocrates. But it was not until the nineteenth century when Sir William Osler recognized that except on few occasions, the patient appears to die from the body's response to infection rather than to the infection. During a long period of time great confusion existed as to the description of systemic inflammatory response to infection and several terms were used interchangeably: septicemia, sepsis, sepsis syndrome and septic shock. In clinical practice sepsis is the most confusing term used to describe the body's systemic response to infection and to many clinicians sepsis implies a life threatening state **(Hodgkin KE ,Moss M.,2008).**

After numerous unsuccessful trials of anti inflammatory agents in patients with sepsis investigators doubted that mortality could be decreased. Advances in unraveling the pathophysiology and genetic basis for the host response to sepsis have changed the prevailing understanding of the syndrome and several therapies have demonstrated surprising efficacy **(Richard S etal.,2003).**

Definitions:

Sepsis is defined as the combination of pathologic infection and physiological changes known collectively as the systemic inflammatory response syndrome. This response results in physiological alterations that occur at the capillary endothelial level. In the early stages, the clinical manifestations of this process are unspecific and it is often underappreciated in clinical practice. However, early recognition of this syndrome is vital to reducing mortality in sepsis **(Martin GS etal., 2006).**

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine convened a Consensus Conference and the definitions of sepsis syndromes were published in order to clarify the terminology used to describe the body's systemic responses to infection .These definitions are easy to use based on clinical data of the patients, and describe a clinical continuum response to infection. these definitions have not only been widely used in practice and clinical trials of therapeutic interventions but they have greatly contributed to the recognition of these syndromes. The definitions of bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock are shown in table 1-1, and the relationships between infection, systemic inflammatory response syndrome (SIRS) and septic syndromes are shown in figure 1-1 **(Artero A etal.,2012).**

Bacteremia	The presence of viable bacteria in the blood
SIRS	The systemic inflammatory response to a variety of severe clinical insults which is manifested by two or more of the following conditions: (1) temperature >38C or <36C (2) heart rate >90 beats per minute (3) respiratory rate >20 breaths per

	minute or PaCO2 <32 mm Hg (4) white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.
Sepsis	The systemic inflammatory response (SIRS) as a result of Infection.
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Septic Shock	Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Table 1-1 Definition of Bacteremia, SIRS, sepsis, severe sepsis and septic shock(**Artero A etal.,2012).**

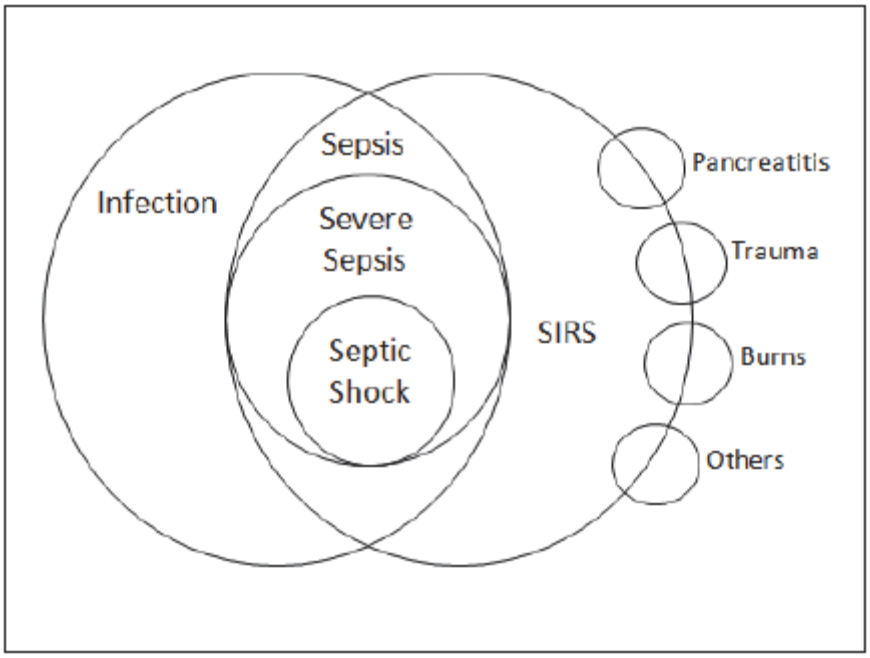

Fig 1-1 The relationship between infection, systemic inflammatory response syndrome (SIRS) and sepsis syndromes**(Artero A etal.,2012).**

In 2001, an International Sepsis Definitions Conference (Levy, 2003; Dunne, 2003) was sponsored by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS) to revisit the sepsis guidelines. Based on this conference a consensus document was developed, concluding that there was not enough evidence to support a change to the previous definitions. This document expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience. Besides, the document developed a classification scheme for sepsis, called PIRO (Predisposition, Insult infection, Response, Organ dysfunction), that will stratify patients on the basis of their predisposing conditions, the nature and extent of the insult (in the case of sepsis, infection), the nature and magnitude of the host response, and the degree of concomitant organ dysfunction. This has provided a basis for introducing PIRO as a hypothesis-generating model for future research .This conference gave priority to the