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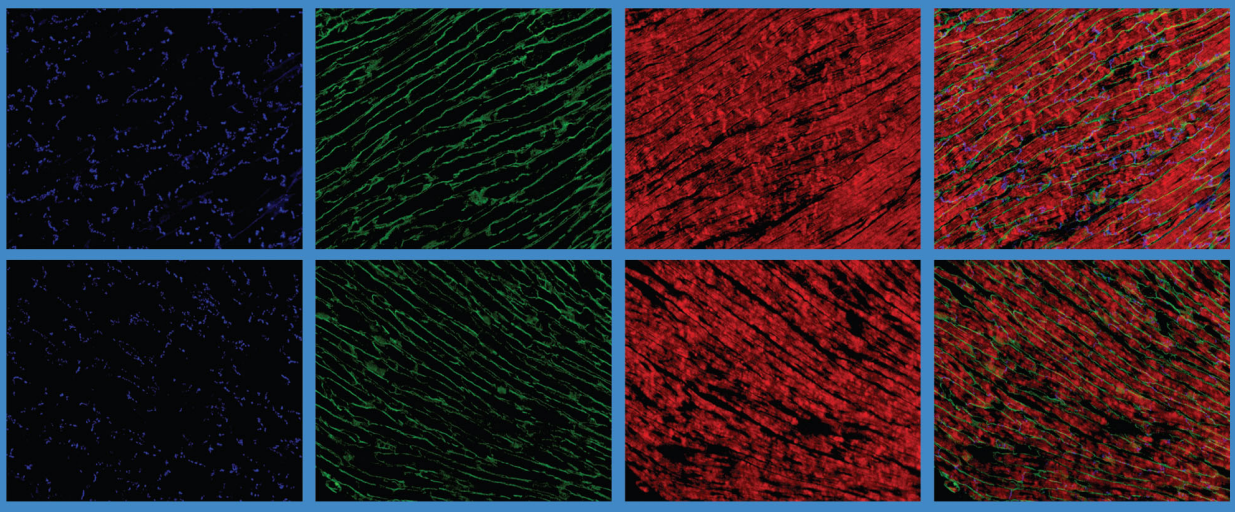
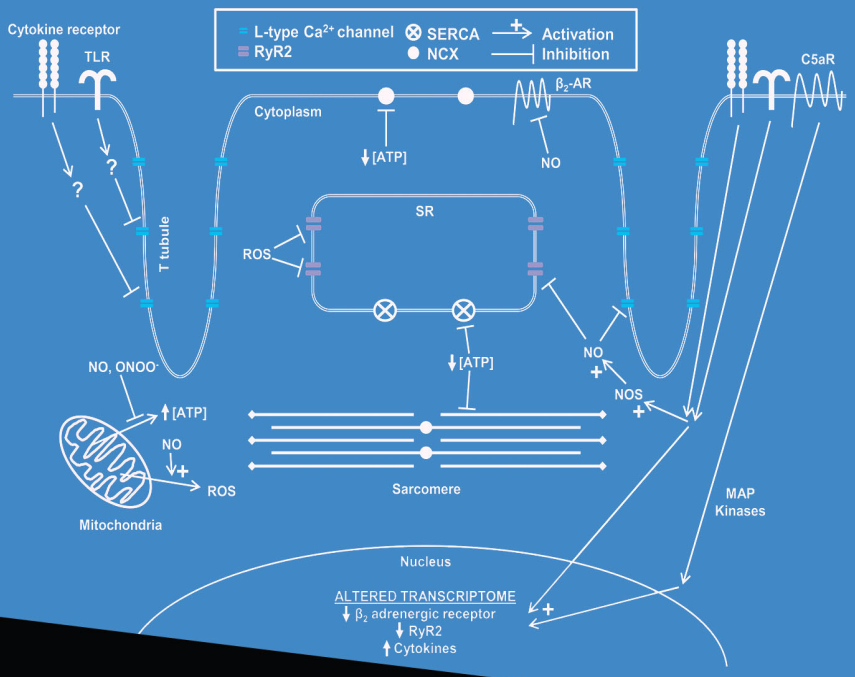
FRONTIERS IN MYOCARDIA

SEPTIC CARDIOMYOPATHY

FROM BENCH-TO-BEDSIDE

Volume 1





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FRONTIERS IN MYOCARDIA

(Volume 1)

'SEPTIC CARDIOMYOPATHY FROM BENCH-TO-BEDSIDE'

Edited By

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FOREWORD

Sepsis is a systematic process that involves all cells and at all levels from intracellular genomic expression, subcellular organelle especially mitochondrial function, cell signaling and organ function. It would be amazing if sepsis did not also alter myocardial function. However, unlike simple ischemic heart disease, the mechanisms and expression of septic cardiomyopathy is more complex and often confusing. This new eBook addresses the various aspects of these processes in a single volume. The authors are all leaders in this field and their insights offer a clear pathway toward understanding the field as it is now and where it is going. I recommend this volume to any acute care physician and scientist whose focus is critical illness and whose goal is to improve the care of the critically ill septic patient.

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PREFACE

Severe sepsis and septic shock are the most common scenarios that a caring physician may deal with, when he is treating a critically ill patient in the Intensive Care Unit (ICU). Moreover, early signs of severe infection associated with organ dysfunction might appear when a patient is treated in a medical or surgical ward, within a hospital. Thus, early diagnosis and prompt treatment are of paramount importance for improving survival of these patients.

One of the most significant complications of sepsis is the cardiovascular compromise, mostly due to a vasoplegia induced by different cytokines that are produced during systemic inflammation. In addition, both left and right systolic and diastolic dysfunction has been proven to occur in the course of severe sepsis. This cardiomyopathy, as has been shown from Parrillo and Parker in the 80' using portable radionuclide cardiac imaging and thermodilution cardiac output measurements, is usually reversible within 7-10 days, whereas different echocardiographic studies by Jardin and Baron since the 90' have confirmed left and right systolic dysfunction. In these cases, conventional estimators of ventricular function, such as cardiac output and ejection fraction (EF), lack both sensitivity and specificity for accurate assessment of heart performance, either due to significant afterload reduction or due to severe pulmonary hypertension and alterations in left ventricular compliance.

There is a lot of debate in the literature regarding potential pathogenetic mechanisms of septic cardiomyopathy, such as membrane ionic current remodeling, cardiomyocyte apoptosis, different circulating depressive factors or autonomic nervous system (ANS) output effects. In any case, both animal experiments and human echocardiographic studies reveal that intrinsic mechanisms can be adaptative, leading to a sort of myocardial hibernation, or maladaptative, producing severe cellular stress with associated necrosis or apoptosis. Current treatment of septic shock other than antimicrobial treatment include fluid load, vasopressors and/or positive inotropic agents, which might induce calcium overload and deteriorate cellular stress, similar with band necrosis observed in stress-associated cardio-myopathy or the apical ballooning syndrome.

In conclusion, we think that the topic of septic cardiomyopathy remains significantly obscured, since there is a lot but scarred information in the literature concerning molecular or electrophysiological pathophysiological mechanisms, diagnostic and therapeutic interventions, monitoring tools, and specific treatment options.

The aim of this ebook is to gather scientists from different disciplines in order to provide thorough and concise information regarding all aspect of this 'disease', from

electrophysiological and cellular alterations to clinical, laboratory and imaging technological advances. In addition, it will present novel data concerning new promising treatments, in the context of septic shock management in the ICU.

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INTRODUCTION

In 1996, Chapman and Hall published the first book on septic cardiomyopathy, entitled: 'Cytokines and the Heart: Molecular Mechanisms of Septic Cardiomyopathy', edited by the couple of Karl Werdan and Ursula Müller-Werdan, from Gemany. This book was the first of its kind in the international literature and proved to be a concise review of basic pathophysiological mechanisms regarding cardiac dysfunction during severe sepsis and septic shock.

Today, Bentham's Publishing Group is coming back with a new ebook entitled: 'Septic Cardiomyopathy: from bench-to-bedside', aiming at integrating new and old ideas about molecular mechanisms, histopathological and electrophysiological alterations and at the same time, novel diagnostic and therapeutic perspectives of septic cardiomyopathy.

The evolution of sepsis basic research in the last two decades, along with new concepts and treatment paradigms that have been tested and implemented in the clinical setting of Intensive Care Units around the world, demands an integrative approach towards better understanding the pathophysiology of cardiac dysfunction in septic patients. In this respect, this new ebook is the first of its kind that tries to bridge the gap between basic and clinical scientists and presents novel data on different aspects of cardiac physiology during critical illness. The 12 chapters, written by distinguished scientists and clinicians from around the world, can serve as a guide for both experienced physicians and young scientists, trying to comprehend the enormous complexity of sepsis in relation with the heart and finally, serve better their patients.

We have tried to encompass most of the important topics and we believe that this new ebook will add significant value to every clinician and basic scientist engaged in the fascinating field of critical care medicine.

CHAPTER 1

Potential Pathophysiological Mechanisms in Septic Cardiomyopathy: an Overview

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Abstract: Septic cardiomyopathy can be classified as a secondary form of cardiomyopathy, the heart being involved in the systemic disease "sepsis". The pathophysiology of septic cardiomyopathy is much more complex than the pathophysiology of most of the textbook heart diseases. This complexity is the consequence of the impact of numerous toxins and sepsis mediators on the heart in the course of the disease.

Main trigger substances of septic pump failure are endotoxin, TNF-α, IL-1 and NO, which interfere with receptors, inotropic signal transduction pathways, Ca^{2+} transients and the contractile apparatus of the cardiomyocyte. These inflammatory mediators also impair mitochondrial function of cardiac cells, with the consequence of cytopathic hypoxia and energy depletion, but also increased production of reactive oxygen species and induction of apoptosis in the organ

Cardiac dysfunction is characterized by systolic as well as diastolic dysfunction of the left and the right ventricle and – typically – by reversible dilation of the heart; diastolic dysfunction of the left ventricle seems to be the prognostically most relevant alteration. For compensation of the sepsis-induced vasoplegia resulting in a fall in blood pressure, the diseased heart has to pump even more, to furnish the demands of circulation, which further stresses the organ. Thus "afterload-related cardiac performance" (ACP) characterizes the cardiac pump failure in sepsis much better than isolated measures of systolic or diastolic dysfunction.

Septic cardiomyopathy is not a primary ischemic disease: Coronary macrocirculation seems not impaired, while coronary microcirculation probably is. Drastic alterations are seen in cardiac metabolism, with a strong reduction of free fatty acids fuelling, with cytopathic hypoxia and some form of myocardial hibernation.

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Also chronotropic and bathmotropic dysregulation characterizes septic cardiomyopathy: resting heart rate is high and heart rate variability is reduced. This is the result of cardiac autonomic dysfunction with a strongly depressed vagal as well as sympathetic regulation in sepsis. Moreover, endotoxin interacts with the HCN channels of the pacemaker current in sinus node, thereby contributing to the intrinsic impairment of heart rate regulation.

The pathophysiology of septic cardiomyopathy is complex, the cardiac alterations can be reversible and the impairments of heart function contribute to the unfavorable prognosis of septic patients.

Keywords: ACP, Afterload-related cardiac performance, Apoptosis, Autonomic dysfunction, Cardiac index, Cardiac output, Cardiomyopathy septic, Coronary circulation, Cytopathic hypoxia, Diastolic dysfunction, Echocardiography, HCN channels, Heart rate, Heart rate variability, I_f, Inotropy, Interleukin, Mitochondria, Pacemaker current, Respiratory chain, Septic cardiomyopathy, Systemic vascular resistance, Systolic dysfunction, TNF-α, Ventricular dilation.

1. SEPTIC CARDIOMYOPATHY: A PROGNOSTICALLY RELEVANT COMPONENT OF SEPTIC SHOCK

In patients with septic shock, the "warm septic shock" with low blood pressure, vascular leakage and vasoplegia (low SVR) dominate the clinical picture. And indeed, dramatic damage can be observed both in the macrocirculation as well in the microcirculation of a septic patient and structurally in the tissue itself due to the impaired cellular oxygen utilization named cytopathic hypoxia (Table **1**). Moreover myocardial dysfunction in septic shock – septic cardiomyopathy - contributes considerably to septic shock.

1.1. Some Historical Remarks

Early descriptions of haemodynamic impairment in infectious diseases, especially in septic shock, can be found in publications from R.T.H. Laennec (1830), W. Stokes (1855), E. Romberg & H. Paessler (1899), M.H. Weil (1956) and J. Siegel (1967), with this history having been nicely compiled recently [9, 10]. The first researchers who described the "vascular paralysis" in acute severe infections - the specific aspect of septic shock - were Romberg & Paessler in 1899 [11]. These

authors at that time believed that circulatory collapse associated with severe infections was the result of vascular paralysis rather than heart failure [11].

In the preantibiotic era, "septic acute myocarditis" was a well known clinical entity, characterized by abscess formation in the heart seen in patients with sepsis [12].

However, it is undoubtedly the merit of J. Parrillo and his group having started systematic research about myocardial dysfunction in patients with sepsis and the pathophysiological mechanism behind [13 - 15].

Table 1. Pathophysiological components of septic shock.

MACROCIRCULATION
• Extensive vascular damage and leakage due to endotoxin, TNF-α, NO and other toxins and mediators) • Vasoplegia → afterload ⇓ (systemic vascular resistance (SVR) (⇓)) • Catecholamine refractoriness of the vessels
MICROCIRCULATION
• Impairment of microvascular flow and oxygen delivery due to inflammation and disseminated intravascular coagulation (DIC) (see 4.3.)
CELLULAR OXYGEN UTILISATION
• Cytopathic hypoxia: cellular oxygen utilisation ⇓, due to impairment of mitochondrial respiration by NO, TNF-α, IL-1, ROS (see 4.3. and 5.2.)
SEPTIC CARDIOMYOPATHY LEADING TO IMPAIRMENT OF CARDIAC FUNCTION OF DIFFERENT DEGREE (⇓ - ⇓⇓⇓)[1]
• Systolic dysfunction due to negative inotropic effects and attenuation of positive inotropic cascades by bacterial toxins and sepsis mediators (see 2.) • Diastolic dysfunction (see 2.) • Arrhythmias (foremost: atrial fibrillation) (see 3.) • Alterations in coronary circulation and myocardial oxygen metabolism (see 4.) • Impairment of cardiac metabolism and mitochondrial function (see 5.) • Disturbance of heart rate and heart rate regulation (see 6.)

[1]for reviews see [1 - 8].

The term "Septic Cardiomyopathy" was for the first time proposed in German by H.P. Schuster in our workshop in 1989 [16] and probably first mentioned in the international literature in 1996 [17]. It characterizes myocardial dysfunction in

CHAPTER 2

Cellular and Molecular Mechanisms of Septic Cardiomyopathy

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Abstract: Cardiac dysfunction is a well-known complication of severe sepsis and septic shock. Septic cardiomyopathy is characterized by reduced cardiac output and left ventricular pressures and biventricular dilatation, resulting in systemic hypoperfusion and multi-organ failure. There is emerging evidence suggesting that mediators of septic cardiomyopathy include cardio-depressive cytokines, Toll-like receptor signaling, cardiomyocyte production of reactive oxygen species and nitric oxide, and dysregulated Ca^{2+} homeostasis. This chapter will review the current evidence describing the cellular and molecular mechanisms of septic cardiomyopathy.

Keywords: Ca^{2+}, Cardiomyocyte, Cecal ligation and puncture, Cytokines, Endotoxemia, Heart, Nitric oxide, Reactive oxygen species, Sepsis, Toll-like receptors.

1. INTRODUCTION

Myocardial dysfunction following sepsis, often called "septic cardiomyopathy", is characterized by depressed ventricular myocardial function and biventricular dilatation which is refractive to fluid supplementation. Clinically, sepsis consists of an early "hyperdynamic phase", associated with amplified cardiac output, tachycardia, and increased tissue perfusion. This phase often devolves into a "hypodynamic phase" with contrary hemodynamics (septic cardiomyopathy) [1, 2]. Septic cardiomyopathy is common, and is estimated to affect 40-60% of patients with severe sepsis/septic shock [3, 4]. The development of septic cardiomyopathy and accompanying hemodynamic changes (septic shock) results

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in poor systemic perfusion and multiple organ failure (MOF) [5], and the severity of cardiac dysfunction is associated with a worse prognosis [6]. It is still not known exactly what cellular and molecular events drive septic cardiomyopathy. The aim of this chapter is to present current evidence for several distinct and overlapping cellular and molecular mechanisms of cardiac dysfunction during sepsis.

2. BASIC MOLECULAR MECHANISMS OF NORMAL CARDIOMYOCYTE (CM) FUNCTION

In normal CMs, contraction and relaxation is mediated by interactions between the contractile apparatus (actin and myosin filaments), regulatory proteins (*e.g.*, troponin, calcium regulatory proteins), and Ca^{2+}. In the relaxed state, tropomyosin inhibits actin-myosin interactions while troponin inhibits the actin-myosin ATPase. During the action potential, Ca^{2+} enters the cell through the L-type Ca^{2+} channels, the result of which triggers stored intracellular Ca^{2+} release into the cytoplasm from the sarcoplasmic reticulum (SR) *via* ryanodine receptors (RyR).

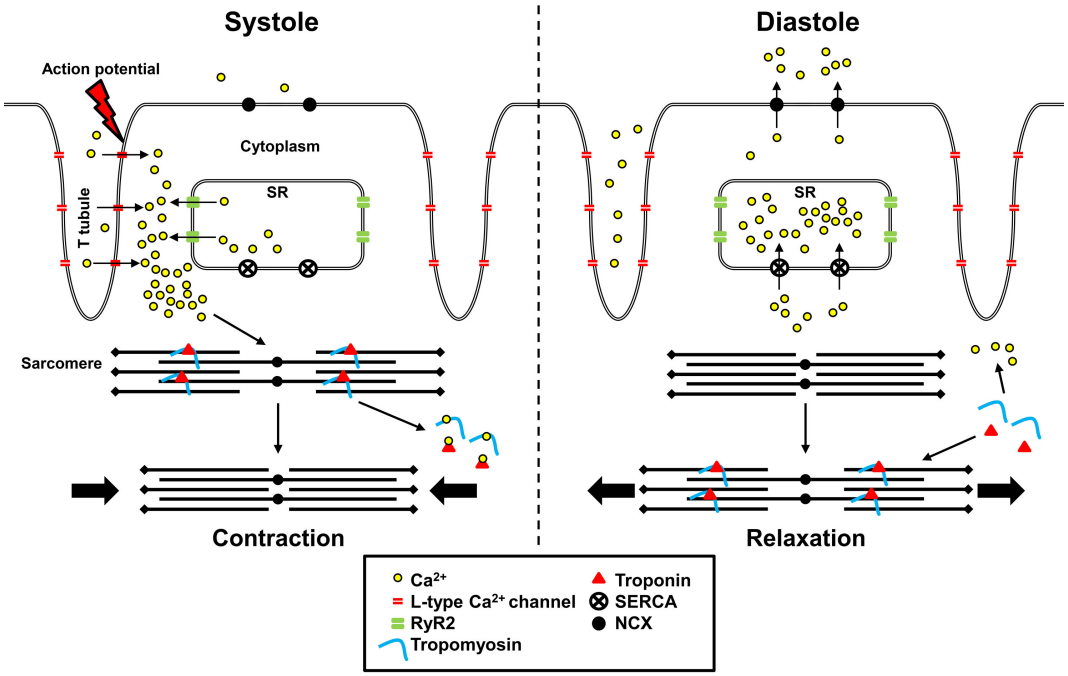

Fig. (1). Basic molecular mechanisms of CM function.

RyR2 is the major RyR in CMs. Elevation of the intracellular Ca^{2+} levels causes Ca^{2+} binding to troponin, leading to conformational changes which reverses troponin and tropomyosin inhibition, leaving actin and myosin free to interact and contract *via* ATP hydrolysis. Contraction is relieved by closing of the Ca^{2+} channels and transport of cytoplasmic Ca^{2+} back into the SR (*via* the SR Ca^{2+} ATPase (SERCA)) or into the extracellular space (*via* the sodium-calcium exchanger (NCX) and plasma membrane Ca^{2+} pump). This reduction in intracellular Ca^{2+} levels allows troponin and tropomyosin to reassume their inhibitory functions, leading to myocardial relaxation. The basic molecular mechanisms of CM function are summarized in Fig. (**1**). As is evident, the complex events that are triggered by endogenous electrical signals in the heart occur very rapidly (millisecond scale for cellular events). As described in subsequent sections, sepsis alters most aspects of CM function on a molecular level.

3. FUNCTIONAL *VS*. ANATOMIC ABNORMALITIES

The progression of sepsis includes vascular endothelial cell damage, leading to increased vascular permeability. The loss of endothelial integrity results in "third-space" loss of fluids, as water and electrolytes enter the interstitial space, resulting in reduction of blood volume. In addition, vascular tone is diminished. These changes result in systemic hypotension and hypothermia. Reduced circulatory function may place CMs at risk of energetic failure (ATP depletion), leading to cell dysfunction and death. However, patients with septic shock have demonstrated normal or even elevated levels of coronary blood flow [7]. In addition, postmortem studies in sepsis patients revealed little, if any, myocyte necrosis or apoptosis, in contrast to changes in other organs [8 - 12]. This finding has been largely mirrored in animal studies [13, 14]. Therefore, it is likely that septic cardiomyopathy is mediated primarily by functional and reversible abnormalities in CMs, and not by CM death. This conclusion is bolstered by the reversible nature of septic cardiomyopathy. In patients who survive sepsis, the early cardiac failure gives way to cardiac function that was present before the onset of sepsis.

CHAPTER 3

Cellular Electrophysiological Mechanisms in Septic Cardiomyopathy

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Abstract: Excitability and contractility of the heart rely on proper functioning of cardiac ion channels. Ion channels are transmembrane proteins enabling ions to cross the cell membrane and thereby changing membrane potential. Multiple studies have shown that remodelling of ion channel function occurs in various heart diseases (*e.g.* atrial fibrillation, heart failure) and there is growing evidence that alterations in ion channel activity play an important role in septic cardiomyopathy. The purpose of this chapter is to review sepsis-induced ion channel dysfunction. Particular emphasis is placed on the L-type calcium and the pacemaker channel. The L-type calcium channel is a key nexus linking cellular excitation and contraction and sepsis-induced channel impairment very likely contributes to the pathogenesis of myocardial depression. A reduction of heart rate variability is a further characteristic of cardiac dysfunction in sepsis probably attributable to autonomic dysfunction and/or a reduced responsiveness of the sinus node to autonomic stimuli. The pacemaker channel comprises an important final common pathway for autonomic heart rate regulation and is directly impaired by endotoxin. These facts strongly imply a major contribution of the pacemaker channel to the sepsis-induced reduction of heart rate variability.

Keywords: Action potential, Autonomic nervous system, Beat-to-beat variability, Ca^{2+} homeostasis, Heart rate, Heart-rate variability, Ion channels, Ivabradine, LPS, L-type calcium current $I_{Ca,L}$, Myocardial depression, Na^+/Ca^{2+}-exchanger I_{NCX}, Na^+/K^+-ATPase, Pacemaker current I_f, Patch-clamp, Sepsis, Sinoatrial pacemaking.

1. INTRODUCTION

During a normal human lifetime, the heart may beat over 2 billion times, ensuring

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systemic and pulmonary circulation. The excitability of the cardiac myocyte, the functional core element of the heart, plays a central role in cardiac (patho) physiology (Fig. **1b**). The cardiac myocyte belongs to a class of highly differentiated cells specialised in tasks of impulse formation/conduction (sinus node/conductive tissue) or excitation-contraction coupling (working myocardium). In the process of cardiac conduction electrical signals (action potentials) originating in the sinoatrial node (right atrium) spread over the atria, and the atrioventricular node and are propagated *via* the specialised His-Purkinje conduction system to the ventricles (Fig. **1a**). This cellular electrical activation (depolarisation) is translated into myocyte contraction (excitation-contraction coupling) and is electrochemically coordinated by communication structures of adjacent myocytes (gap junctions) enabling the heart to contract in synchrony. The heart is an important target in sepsis. The main proposed mechanisms underlying the pathophysiology of myocardial dysfunction (depression) in sepsis support a prominent role of functional alterations including electrophysiological changes in ion channel activity. In a first step, basic concepts of cardiac cellular electrophysiology will be briefly introduced (for more details see [1, 2]) in order to facilitate the understanding of the cellular electrophy-siological mechanisms in septic cardiomyopathy.

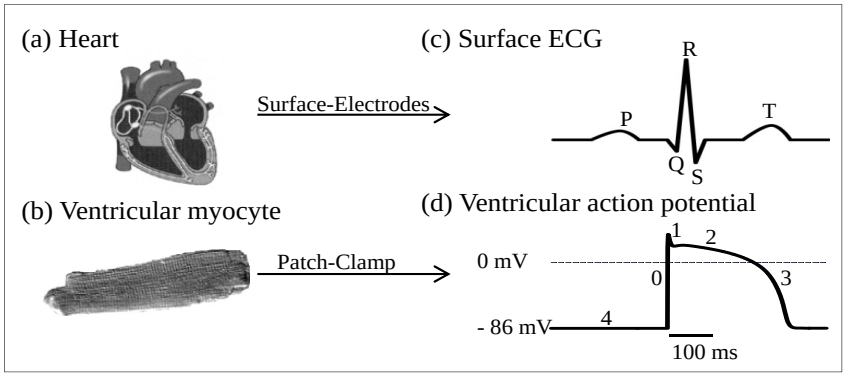

Fig. (1). Electrical signals from organ and cell level. The electrical activity of the whole heart (**a**) and of the cardiac myocyte (**b**) can be recorded as body surface ECG (**c**) and as action potential (**d**), respectively. The ECG represents a summation signal generated by the action potentials of the cardiomyocytes. Approximate temporal relationship between surface ECG and a representative ventricular action potential is shown in (**c**) and (**d**). In the ECG, the P wave describes depolarisation of the atria, while the QRS complex represents depolarisation of the ventricles and the T wave summarises repolarisation of the ventricles. In the time course of the action potential 5 phases can be distinguished: resting (4), upstroke (0), early repolarisation (1), plateau (2) and final repolarisation (3).

1.1. Basic Concepts

1.1.1. Bioelectricity

As shown in Fig. (**1d**) cardiac myocytes are capable of producing active signals, so called action potentials (APs), the fundamental electrical signals of the heart. The sum of all cellular cardiac activities is reflected in the ECG, *e.g.* the average duration of the ventricular AP corresponds to the QT interval in the ECG (Fig. **1c**, **d**). An AP represents a transient, regenerative and self-propagating change in the membrane potential of excitable cells, like cardiac myocytes and neurons. The membrane potential, the difference in electrical potentials across the cell membrane, is negative (inside with respect to outside) in unexcited cells: *e.g.* the resting membrane potential (Fig. **1d**, phase 4) amounts to approximately -85 mV in ventricular myocytes. Terminologically, a change of the resting membrane potential towards more positive or negative values is called depolarisation or hyperpolarisation, respectively. When the membrane potential is depolarised during the AP a return to the resting membrane potential is called repolari-sation. The resting membrane potential relies on an unequal distribution of electrically charged ions (outside/inside: > for Na^+ and Ca^{2+}, < for K^+) maintained by the activity of ion pumps like Na^+/K^+-ATPase and the presence of certain open sarcolemmal ion channels (above all special K^+ currents, like the inward rectifier potassium current I_{K1}). Ion channels are pore-forming transmembrane proteins that provide an aqueous path for ions to cross the otherwise due to its oily nature impermeable cell membrane very rapidly ($>10^6$/s).

Many ion channels are highly selective allowing only certain ions to pass through cell membrane while others are excluded. The selective permeability of ion channels to specific ions allows the channels to be categorised, *e.g.* into Na^+, K^+, and Ca^{2+} channels. Besides rapid ion permeation ion channels show the fundamental property of gating: channel conductance is modified in response to specific environmental stimuli. According to the gating mechanism, ion channels can be subclassified in voltage-dependent, ligand-dependent and mechano-sensitive channels. In principle, cardiac AP formation is the result of transmembrane current through over a dozen and mainly voltage-dependent ion channels running *via* a highly sophisticated sequence of opening and closing.

CHAPTER 4

Septic Cardiomyopathy: A Distinct Histopathological Entity

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Abstract: Sepsis is the leading cause of death in critical ill patients in intensive care units around the world. Cardiac dysfunction is one of the major clinical manifestations in septic patients (about 60%), with mortality rate of approximately 80%, while septic patients without cardiovascular impairment present mortality rates around 20%. However, cardiac involvement as an important contributing factor to the multiple organ dysfunction in the sepsis syndrome, has been rejected. Principal mechanisms proposed to explain the cardiac dysfunction in sepsis originates from functional abnormalities, not from structural changes. In spite of the evolution of septic cardiomyopathy concept, the study of structural change as an important component in the development of myocardial dysfunction has been omitted in sepsis. In 2007, morphological analysis of human heart samples obtained by autopsy reported cases of severe sepsis/septic shock condition in patients submitted a longer periods of hospitalization. Septic patients showed structural myocardial alterations classified as "inflammatory cardiomyopathy" probably responsible for the myocardial depression induced by sepsis. Since then, structural changes on cardiac dysfunction in sepsis/septic shock has been object of several studies, experimental and clinical, aiming to improve the diagnosis and treatment of this syndrome. In this chapter, will be presented results of studies conducted in our laboratory analyzing cellular and molecular mechanisms underlying

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sepsis/septic shock, which may result in morphological alterations in the myocardium of mice subjected to CLP-sepsis model.

Keywords: Cardiac structural changes, Dystrophin-glycoprotein complex (DGC), Experimental sepsis model, Myocardial depression, Sepsis, Septic cardiomyopathy.

1. INTRODUCTION

Sepsis, described as a complex clinical syndrome resulting from hyperactivation of the immune response to exposure a deleterious or harmful agents in response to infection. Clinical signs include fever, altered mental status, hypotension, oliguria and coagulation disorders that could develop irresponsible hypotension and organs dysfunction (severe sepsis/septic shock) [1].

In the United States, an estimated 750,000 patients develop severe sepsis with mortality rate around about 230,000 deaths per year and, this condition has been considered as the third most common cause of death in this country after cardiac disease and cancer [2] Additionally, the financial costs associated to this syndrome are approximately $24.3 billion to the healthcare system [3 - 5].

Heart is one of most important organs affected during severe sepsis/septic shock and myocardial dysfunction is observed in approximately 50% of diagnosed patients [6]. The correlation between severe sepsis/septic shock and myocardial dysfunction elevates the patients' susceptibility to death when compared with those without heart dysfunction [7].This chapter discusses the potential mechanisms responsible for the evolution of septic cardiomyopathy highlighting myocardial structural changes in the heart of septic patients and animals subjected to sepsis induced by cecal ligation and puncture (CLP) with a discussion of experimental model.

2. SEPTIC CARDIOMYOPATHY

The concept of septic cardiomyopathy has evolved over the years which imply changes in the myocardium physical composition [8]. The most important mechanisms proposed to explain the pathophysiology of cardiac dysfunction in

severe sepsis give more emphasis on functional changes rather than anatomical abnormalities such as [9]: ***(i) Autonomic deregulation.*** In accordance with some authors, during severe sepsis apoptosis of cardiovascular autonomic centers could lead to autonomic failure that precedes the onset of septic shock [10 - 12]. In the central nervous system, neuronal and glial apoptosis in the cardiovascular modulator centers could be related to inflammatory response, mainly mediated by inducible nitric oxide synthase (iNOS) [13]. Peripherally, increased levels of IL-6 [14], plasma free fatty acids [15], and constant block of the sinus node [16] occurs in addition to uncoupling of cells responsible for heart rate from cholinergic neural control during sepsis [17]; ***(ii) Microvascular dysfunction.*** Severe sepsis is associated with impaired microvascular oxygen transport [18] maldistribution of coronary circulation, increased resistance of coronary vessels with vascular hyporesponsiveness to vasodilators [19], and neutrophil emigration to the interstitial space [20]; ***(iii) Metabolic disorders***. During sepsis, the occurrence of metabolic changes due to accumulation of lipids in cardiomyocytes as well as glycogen in non-survivors [21] has been proposed. One of the clinical signs of sepsis is the hyperlactatemia, hearts of septic patients showed a reduced lactate withdrawal [22] associated with reduced myocardial glucose uptake, free fatty acids and ketone bodies [23]; ***(iv) Mitochondrial dysfunction.*** Alterations in mitochondrial function have been strongly associated with increased mortality rate in septic patients. Multiple mechanisms, including changes in mitochondrial energy metabolism, mitochondrial toxins and triggered caspase activation can result in impaired organ and systemic failure resulting in death [24]; ***(v) Nitric Oxide and peroxynitrite pathways.*** Overproduction of nitric oxide (NO) with subsequent development of local oxidative stress has been proposed to be one of the significant pathophysiological mechanisms for sepsis by exerting a negative inotropic and chronotropic effects on the heart [25]. Increased production of NO, as a result of iNOS induction, by enzymatic ligation causes cell injury by stimulating macrophages and neutrophils along with mitochondrial inhibition by direct or by means of free radicals resulting in the peroxynitrite formation causing further cellular damage [26]. Peroxynitrite generated can exert cardiodepressant effects through the prevention of cardiomyocytes contraction even in the presence of high levels of calcium (Ca^{+2}) [27] leading to mitochondrial respiratory chain dysfunction [28]; ***(vi) Inflammatory cytokines.*** There are many potential

CHAPTER 5

Septic Cariomyopathy: A Distinct Metabolic and Genetic Entity?

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Abstract: During the course of sepsis, myocardial dysfunction occurs in 20-30% of patients. Septic cardiomyopathy has a high mortality and the underlying molecular pathophysiology remains still largely unclear. Sepsis induced cardiac dysfunction (SICD) or septic cardiomyopathy (SC) gathered increasing denotation during the last years since mortality rates are high.

Septic shock is characterized by circulatory compromise, microcirculatory alterations and mitochondrial damage, which all reduce cellular energy production in the myocardium. As the specific underlying molecular causes of septic cardiomyopathy remain largely unclear, characteristic alterations in the organ proteome ("tissue proteomics") and metabolome are of high interest to understand emerging dysfunction and to identify molecular details to establish new treatment approaches.

Thus, it is of outstanding importance to diagnose septic cardiomyopathy effectively being able to treat specifically this entity of a disease.

Keywords: Cardiac dysfunction, Heart, Protein alterations, Protein expression, Proteomics, Sepsis, Septic cardiomyopathy, Septic myocardial dysfunction.

1. INTRODUCTION

Severe sepsis, septic shock, and sepsis-induced multi-organ failure (MOF) are the major causes of mortality and morbidity in critically ill patients [1 - 3]. Although mortality from sepsis has decreased in the recent years with intense sepsis programs, it is still the [4, 5] and remains as high as between 40 - 60% [6].

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Furthermore, the absolute number of sepsis-related deaths has actually increased because the incidence of sepsis also increased during the recent years [7]. Dysfunction of organs [8 - 11] is one of the major criteria of severe sepsis. Incidence and severity vary on a time course with early as well as late [9] changes leading to failure of specific organs as well as to multiple organ failure.

Although there are recommendations for the treatment of sepsis and severe sepsis, the exact patho-physiology [12] and precise mechanisms through which organ dysfunction develops [13, 14] remain largely unknown, as do reasons for its persistence long after cessation of the acute inflammatory response [1].

The heart is an extremely interesting organ during sepsis, since especially its failure may lead to adverse outcomes in the course of sepsis [15]. Therefore, sepsis induced cardiac dysfunction (SICD) or septic cardiomyopathy (SC) gathered increasing denotation during the last years [16]. Septic cardiomyopathy has an incidence of approximately 15% in critically ill patients [17] and is associated with high mortality rates [14]. It has also been shown that sepsis leads to a depression of myocardial function characterized by decreased rates of ventricular relaxation and contraction [18, 19]. However, myocardial depression is a major contributor to mortality and morbidity in patients with sepsis [20]. Sepsis-induced myocardial dysfunction is common, corresponds to the severity of sepsis, and is reversible in survivors [21].

Traditionally, the physiologic disturbances have classically been described in a biphasic spectrum: early hyperdynamic shock characterized by increased cardiac output, decreased systemic vascular resistance (SVR) and warm, perfused skin, followed by cold hypodynamic shock, during which SVR increases to compensate for worsened cardiac output, resulting in tissue hypoperfusion, cool skin and eventual organ failure [20, 22].

2. CLINICAL ASPECTS

Septic cardiomyopathy was first noted during the early 1980s by Parrillo *et al.* using myocardial scintigraphy in critically ill patients to diagnose this entity [16, 23]. At large, sepsis is characterized by a decreased nutritive blood flow despite increased organ blood flow most of which contributes to shunting. Experimental

models of sepsis show clear evidence of myocardial contractile disturbance both *in vivo* and *in vitro* [20]. The reduction in contractile performance during ischemia despite normal or increased blood flow has been previously suggested to follow metabolic changes associated with the loss of creatine phosphate, increased intracellular acidosis, and the accumulation of inorganic phosphate and lactate [14, 24].

Myocardial dysfunction is particularly important in patients with severe septic shock who progress to a hypodynamic pre-terminal phase [25]. Multiple different aspects of this septic inflammatory response contribute to the pathogenesis of decreased ventricular contractility [25].

3. MOLECULAR ASPECTS

Although the exact cellular signalling pathways that are responsible for the negative inotropic effects of the heart are not yet fully understood, it is clear that septic shock is characterized by a circulatory compromise, microcirculatory alterations, and mitochondrial damage, which all reduce cellular energy production [21].

The same applies to the cellular mechanisms underlying cytokine-mediated cardiomyopathy which are also not entirely clear [20]. A careful inspection of presently available data suggests that TNF-α plays a central role and modulates myocardial function through at least two different pathways [20]. On one hand, it can produce immediate negative inotropic effects in myocardial tissue, on the other hand, it exerts delayed effects on myocardial function that appear to be related to uncoupling of the ß-adrenergic receptor from cyclic AMP [26].

Although temporary cytokine response (TNF-α, IL-6, and IL-10) is detectable in peripheral blood of septic animals [9, 27, 28] their specific role is not yet completely understood. In addition, serum levels of TNF-α and IL-6 following coecal ligature and puncture (CLP) in animals seem not to reflect activity of these proteins within the organs [28].

The energetic state of the myocardium is mainly supported by oxidative phosphorylation, in which mitochondrial ATP synthase synthesizes ATP being

CHAPTER 6

Clinical and Molecular Aspect of Septic Cardiomyopathy: Basic Concepts

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Abstract: Cardiomyopathy of sepsis has been described over three decades ago while sporadic description of the phenotype has permeated the literature for two decades prior to the emergence of a coherent description. Although its prevalence is high in severe sepsis and septic shock, its impact on the overall prognosis of patients with sepsis is less clear. The clinical manifestations are varied and the syndrome presents several phenotypes, depending on when observations are made and how severe the underlying sepsis is. The most important concepts underlying the current understanding of the cellular pathophysiology, namely inflammation-driven elevations on various forms of intracellular nitric oxide synthases, their interaction with calcium fluxes, cellular respiration and oxidative stress are reviewed. The links between current concepts of pathophysiology, clinical manifestations and therapeutic options are discussed.

Keywords: Calcium channels, Cardiomyopathy, Dobutamine, Echocardiography, Fluid responsiveness, Levosimendan, Muscle contraction, Nitric oxide, Pulmonary hypertension, Sepsis, Septic shock, Troponin, Ventricular dysfunction.

1. INTRODUCTION AND HISTORICAL PERSPECTIVE

Severe sepsis, the combination of infection and a systemic inflammatory response, is typically associated with a phenotype of high cardiac index and low systemic vascular resistance. Several cases however, present with a clinical phenotype characterized by inappropriately low cardiac output and hypoperfusion [1]. Although decreased intravascular volume contributes to inappropriate cardiac output and oxygen delivery in this phenotype, an acute and reversible primary

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myocardial depression, despite appropriate preload, has been convincingly demonstrated to also contribute to the pathophysiology of hemodynamic compromise in severe sepsis and septic shock. In contradistinction to cardiogenic shock, this impaired contractility is observed despite low to normal filling pressures. Depending on the underlying fluid status and severity of the contractile dysfunction, septic cardiomyopathy may present with a variety of phenotypes. Several excellent reviews of septic cardiomyopathy, its clinical manifestations, proposed pathophysiology, and clinical approach, have been published in recent years [2 - 6]. Clinical reports of sepsis associated cardiomyopathy appeared in the literature as somewhat detailed description of myocardial dysfunction. Based on hemodynamic measurements, observational studies by, Wilson [7], Siegel [8], and Clowes [9] firmly established the existence of sepsis-related decrease in cardiac contractility in the presence of presumably adequate fluid resuscitation. More detailed studies augmenting hemodynamic studies with radionuclide cineangiography by Calvin [10] and later Parker [11] provided a more comprehensive understanding of a syndrome of biventricular decrease in systolic function of rapid onset, yet reversible over a period of 7 to 10 days in survivors. Remarkably, Parker also showed that patients experiencing the highest reduction left ventricular ejection fraction had an improved prognosis compared to patients with persistently elevated cardiac output, suggesting that ventricular dilatation might actually represent a favorable adaptive response of the myocardium to increased circulatory demands associated with sepsis.

2. DEFINITION AND CLINICAL MANIFESTATIONS

Cardiovascular alterations in sepsis consist of hypovolemia, loss of peripheral vascular tone, hypotension, decreased or increased peripheral perfusion, acute left and right ventricular systolic and diastolic dysfunction, and occasionally pulmonary hypertension. Combinations of these contributions can result is a variety of phenotypes ranging from adequately resuscitated hyperdynamic shock, to a clinical phenotype reminiscent of cardiogenic shock, with profound myocardial depression, normal to elevated filling pressures, elevated peripheral resistance and peripheral hypoperfusion.

3. LEFT VENTRICULAR DYSFUNCTION

Numerous studies consistently report a high incidence of impaired contractility is patients with sepsis and septic shock. In less severe septic patients early in their clinical course, Calvin *et al.* used gated nuclear scintigraphy to interrogate LV function and concluded that impaired contractility was frequently present, yet not a major feature of early human sepsis [10]. In their study of 20 patients with septic shock, a more severe phenotype, Parker *et al.* reported a 65% incidence of LVEF <40% in patients not previously known to have chronically altered LVEF. The mean initial LVEF in survivors was remarkably low at 32%, significantly lower than in non-survivors. Impaired contractility peaked at 3 days and had mostly resolved by 7 days in survivors. These findings were duplicated using echocardiography [12, 13]. There is less consistency as to the incidence of left ventricular dilatation and increased LVEDVI in the presence of adequate fluid resuscitation [14], some studies reporting no or minimal increase in LVEDVI [15]. Yet, the presence of increased LVEDVI seem to be an appropriate adaptive response to impaired contractility as this shift to a more favorable portion of the Frank-Starling curve appears to confer a survival advantage [11]. Septic cardiomyopathy is also characterized by left ventricular diastolic dysfunction [15, 16]. This decreased ability of the left ventricle to relax may be a particularly ominous sign, as it may partly explain an impaired ability to develop the aforementioned adaptive ventricular response [17]. Impaired relaxation also may tie in to impaired calcium fluxes in cardiac myocytes subject to an inflamed milieu, the impaired ability to pump calcium out following contraction, an ATP dependent process, and the finding that troponins are particularly elevated in patients with ventricular dysfunction, and are associated to worse outcomes [18].

4. RIGHT VENTRICULAR DYSFUNCTION

Right ventricular dysfunction in the form of impaired contractility was also documented to be present in septic patients [19, 20]. These early reports were confirmed in later, more detailed studies of patients [21, 22], where right ventricular dysfunction and dilatation were found to be present in at least 30% of adequately resuscitated septic patients and display much of the same characteristics as left ventricular dysfunction [22]. Sepsis can also be

CHAPTER 7

The Clinical Aspects of Septic Myocardiopathy

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Abstract: Sepsis-induced myocardial dysfunction (SIMD) is a common and reversible complication in severe sepsis and septic shock patients. Its pathogenesis is complex and probably mediated by cytokines. Echocardiography is the gold standard to make the diagnosis of SIMD. Cardiac biomarkers have a high negative predictive value for SIMD. Norepinephrine is the first line vasopressor. Inotropic drugs should be used in the case of left ventricular systolic dysfunction associated with persisting tissular hypoperfusion.

Keywords: Diastolic dysfunction, Echocardiography, Heart failure, Hemodynamic, Monitoring, Mortality, Natriuretic peptides, Sepsis, Septic cardiomyopathy, Septic shock, Severe sepsis, Troponins.

1. INTRODUCTION

Myocardial dysfunction is a common component of the hemodynamic alteration in patients with severe sepsis and septic shock. The evidence for sepsis-induced myocardial dysfunction (SIMD) has been highlighted in many studies over the last three decades. Despite many years of research on SIMD, there is a lack of consensus about its definition, clinical spectrum, pathophysiology, and treatment strategies. The aim of this paper is to review about the available data on new pathophysiological concepts, diagnosis tools (echocardiography, cardiac biomarkers) and potential therapies (inotropes, vaso-pressors...).

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2. CHARACTERISTICS

Current evidence suggests that SIMD is characterized by a reversible left ventricular (LV) systolic dysfunction without elevated LV filling pressure [1 - 3]. The reversibility in few days of LV systolic dysfunction, evaluated by LV ejection fraction, was highlighted by Jardin *et al.* and Bouhemad *et al.* [2, 3]. In the case of LV systolic dysfunction, the mean pulmonary capillary wegde pressure reported in the most studies was lower than 15 mmHg unlike the hemodynamic profile of cardiogenic shock where LV pressures are elevated [1 - 3]. Low LV pressures in this case can be explained by an acute LV dilation and a right ventricular (RV) dysfunction [4].

LV diastolic dysfunction in septic shock patients was reported as isolated or associated to LV systolic dysfunction [5]. Only few works with small sample size have investigated the sepsis-induced diastolic dysfunction using echocardiography [5 - 7]. However, one cannot exclude that diastolic dysfunction was already present in patients with sepsis and septic shock, and that it can be aggravated by the disease *per se* and the treatment (fluid overload and vasopressor therapy).

The concept of preload adaptation by acute LV dilation in septic shock was investigated in studies using echocardiography [3, 8, 9]. The authors reported a slight increase in LV end-diastolic size in patients with LV systolic dysfunction compared to patients with preserved systolic function. These results suggest that there is an increase in LV compliance in these patients.

RV dysfunction is related to an alteration in RV contractility and an increase in pulmonary vascular resistance associated with adult respiratory distress syndrome. [10]. Vincent and coworkers reported a decreased RV ejection fraction evaluated by thermodilution technique in patients with septic shock compared to patients without sepsis [11]. Kimchi *et al.* and Parker *et al.* showed that RV dysfunction can occur even in the absence of acute pulmonary hypertension, suggesting that increased RV afterload could not be the principal cause of RV dysfunction in septic shock [10, 12]. RV dilation was also described in echocardiography studies in almost 30% patients in septic shock [8, 13].

3. INCIDENCE

The incidence of LV systolic dysfunction in septic patients varies among studies between 20% and 60% [1, 3, 8, 9, 14]. These discrepancies can be explained by the different time of evaluation and the different LV load conditions in septic shock. Indeed, the studies time of evaluation varies from the 6 first hours to the day 3 with a higher incidence of LV systolic dysfunction in the latter [8, 14]. Actually, LV ejection fraction (LVEF) is load dependent and does not reflect exactly the intrinsic contractility of the LV. A normal LVEF in septic shock may correspond to a systolic dysfunction in case of low LV afterload, and a norepinephrine infusion may unmask LV contractility impairment.

SIMD is a continuum from isolated LV diastolic dysfunction to both systolic and diastolic LV impairment. Poelaert *et al.* reported in a 25 septic shock patients study, 44% with an isolated diastolic dysfunction and 24% with both systolic and diastolic impairment [5]. In another study including 54 septic shock patients, Bouhemad *et al.* reported 20% with an isolated diastolic dysfunction and 20% with both systolic and diastolic impairment [15]. As mentioned previously, a diastolic dysfunction already present before sepsis cannot be excluded and may overestimate the incidence of diastolic dysfunction in septic shock patients.

Kimchi and coworkers studied 25 patients in septic shock and reported a depressed RV ejection fraction in almost 50% of their patients [12]. In a transesophageal echocardiography study, RV dilation was described in 24% patients in septic shock and there were no significant differences in RV fractional area contraction of patients without RV enlargement [14].

4. PATHOPHYSIOLOGY

A multitude of potential pathogenic mechanisms have been proposed. At the organ level, coronary hypoperfusion have been highlighted [16]. Circulating myocardial depressant substances (tumor necrosis factor α and interleukin 1-β) were also advocated [17, 18].

These effects are mediated through mechanisms that include cGMP and nitric oxide generation [19]. Furthermore, cellular respiration alteration with

CHAPTER 8

Septic Cardiomyopathy: an Echocardiographic Approach

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Abstract: Septic shock is one of the most complex hemodynamic failure syndromes, and its mode of expression is highly variable and may include each one to a variable degree: absolute or relative reduction of volemia, severe peripheral vasodilatation, right and left ventricular (RV and LV) myocardial failure and global myocardial dysfunction. Because of this variability and to optimize the treatment, it seems necessary to perform echocardiography at admission in intensive care unit (ICU) for septic shock and repeat it at least once a day or more in case of hemodynamic instability.

Echocardiographic findings should be integrated with clinical data and other monitoring information, especially with those related to peripheral tissue perfusion. Transesophageal echography (TEE) enables for a complete assessment, also detailing heart-lung interactions and fine volume responsiveness evaluation but TEE is not necessarily required if the transthoracic echography (TTE) provided answers to questions.

Echocardiography allows help intensivists to establish therapeutic such as inotropes, vasopressors or to optimize volemia after volume expansion. Thus, echocardiography is now an unavoidable tool in assessing hemodynamic instability in septic shock patients. A1ccordingly, echocardiography training is crucial to help its widespread use in all ICUs.

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Keywords: Echocardiography, Inotropes, Myocardial dysfunction, Right and left ventricular dysfunction, Septic shock, Tissue Doppler, Volemia.

1. INTRODUCTION

Sepsis provokes alterations of the macrovascular and microvascular functions, which lead to organ dysfunction; septic cardiomyopathy being one of them. Septic cardiomyopathy refers to any cardiac dysfunction during sepsis: from diastolic dysfunction to bi-ventricular systolic failure, including arrhythmia. Septic cardiomyopathy is a frequent complication of sepsis which incidence varies from 30% to 64% according to the studies [1 - 3]. Sepsis-induced cardiomyopathies is one of the major predictors of morbidity and mortality in sepsis and its occurrence is associated with an increase in mortality by up to 70% [4]. Importantly and contrary to non-septic cardiomyopathies, myocardial depression is reversible in patients with septic shock , and its reversion is associated with a better prognosis [5].

One of the hallmarks of sepsis-induced cardiomyopathies is hemodynamic instability. It is therefore essential to assess the hemodynamic status of the patient in septic shock, in order to diagnose, hence to guide the treatment of these patients according to their hemodynamic characteristics. Echocardiographic evaluation has proven to be invaluable in the evaluation of myocardial dysfunction. In intensive care unit (ICU), simple echocardiographic assessment can be performed at bedside by intensivists, to quickly detect a possible hemodynamic instability in critical care population [6]. Accordingly, echocardiography in the hemodynamically unstable patient is a class I indication [7], and guidelines strongly recommend echocardiography as part of the basic training of all intensivists (Fig. **1**).

Echocardiography allows determining volemia and, left and right cardiac function, which can be assessed according to a step-by-step procedure [8]. Furthermore, qualitative echocardiography remains useful, even when performed by a minimally trained physician when interpreted with the clinical data before considering therapeutic options [9]. However, in recent years, new echographic techniques for hemodynamic monitoring in intensive care with ultrasound have

been developed to better quantify volemia and cardiac function. Among these new methods is the functional hemodynamic monitoring that is defined by the assessment of the dynamic interactions of hemodynamic variables in response to a defined perturbation [10].

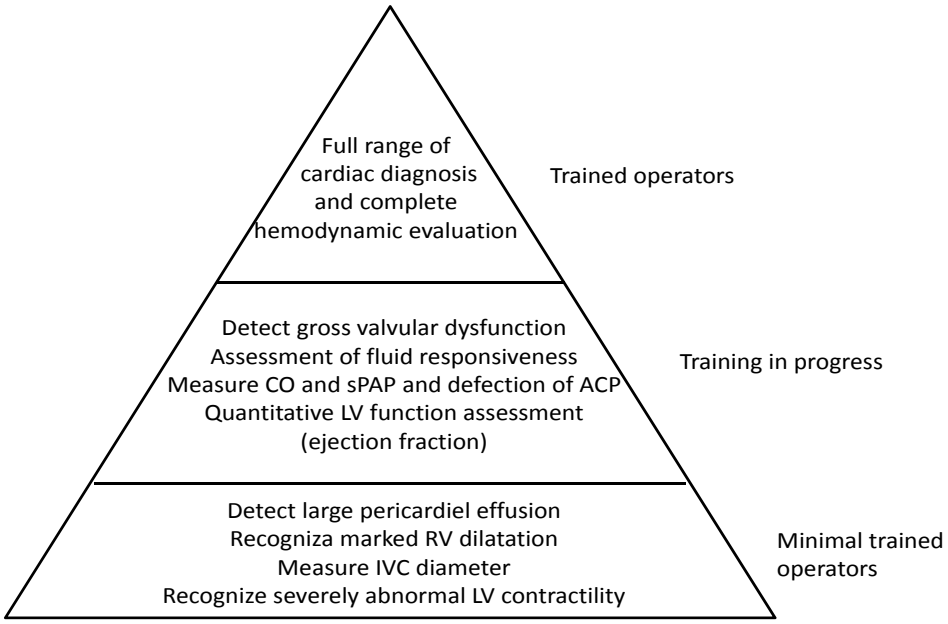

Fig. (1). The pyramid of echocardiography skills in ICU (adapted from [46], with permission).

In this comprehensive review, we present rational emerging from the medical literature concerning the use of echocardiography in septic shock patients. We explain, first, echocardiography for volemia, left and right function assessment, and secondly, we expose the impact of echocardiography to therapeutic options.

2. VOLEMIA

Volume expansion is the first line of treatment in patients with hemodynamic instability [11]. However, volume expansion is not always necessary, and can be deleterious. The predictability of response to filling is named fluid responsiveness and consists to assess the preload-dependence of cardiac output. Hence, evaluation of volemia is frequently the primary aim of echocardiography in hemodynamically unstable patients (Fig. **2**). The volume status assessment allows

CHAPTER 9

Which Biomarkers Can I Use to Manage Septic Cardiomyopathy

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Abstract: Alteration of myocardial performance, characterized by left ventricular systolic and diastolic dysfunction, is a common and early complication of septic shock and has a significant impact on patient's prognosis. Cardio-vascular biomarkers are commonly used for diagnosis and risk stratification in cardiac patients. In particular, troponins are included in the definition of acute coronary syndrome and natriuretic peptides are the gold standard biomarkers for the diagnosis and the risk stratification of acute heart failure. Interest has recently focused on the use of these biomarkers as tools to identified cardiac sepsis-induced dysfunction and prognosis. Although echocardiography would be needed to confirm the diagnosis of cardiac dysfunction, biomarkers can alert physician and lead to perform a cardiac ultrasound. Whereas many evidences suggest that cardiac troponins are useful in severe sepsis or septic shock to identify those patients requiring early and aggressive therapy more studies are needed before considering natriuretic peptides in this indication. Among the most recently described biomarker, few data suggest that mid-regional pro-adrenomedullin (MR-proADM) could be useful for risk stratification of septic patients.

Keywords: Biomarkers, BNP, Lactate, Myocardial Depression, Septic Shock, Troponin.

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1. INTRODUCTION

Biomarkers can have two functions: (1) to help to confirm a diagnosis and improve risk prediction and (2) to guide therapy. Biomarkers need sufficient specificity and sensitivity to be routinely employed in clinical practice. Physiopathology of the sepsis response is complex; for this raison not only one but may be an association of biomarkers will be useful. Cardiac sepsis-induced dysfunction is associated with increased morbidity and mortality [1]. Mechanisms involved were not elucidated. Nevertheless, hemodynamic factors and genetic, molecular, metabolic and structural alterations seem involved [2]. Cardiac sepsis-induced dysfunction includes depression of left and/or right ventricular systolic function and/or diastolic dysfunction and may be associated with ventricular dilatation. In early stages of septic shock, cardiac sepsis-induced dysfunction impacts the outcome. Early detection of myocardial dysfunction is crucial for the management of the patient in the first hours of sepsis to adapt therapy. Useful biomarkers can alert physicians in charge on the severity of cardiac alteration and lead to perform cardiac ultrasound to confirm and to guide therapies.

Cardiac troponins and natriuretic peptides are routinely used biomarkers for diagnosis and risk stratification in patients with heart dysfunction. Troponins are used as specific markers for the diagnosis of acute coronary syndrome [3]. N-terminal pro-BNP (NT pro-BNP) and B-type natriuretic peptide (BNP) are tools used for the diagnosis of acute congestive heart failure [4]. Interest has recently focused on the use of these biomarkers as indices of cardiac sepsis-induced dysfunction diagnosis and prognosis. In addition, sepsis-induced cardiac dysfunction may limit fluid responsiveness. Some authors proposed to use lactate clearance in the early shock management.

2. USEFULNESS OF TROPONINS AND NATRIURETIC PEPTIDES FOR SEPTIC CARDIOMYOPATHY

2.1. Troponins

The mechanisms involved in the increase of the troponin in patients with sepsis are still unclear. Decrease of coronary artery flow secondary to thrombotic occlusion could be involved but also a modification of membrane permeability or

microvascular events. Nevertheless, many studies suggested that cardiac troponin I (cTnI) or T (cTnT) (Table **1**) may be help in the recognition of cardiac sepsis-induced dysfunction in a noninvasive and readily available way. Fernandes *et al.* [1], analyzed the data of 10 septic patients without history of cardiac dysfunction and made a comparison of echocardiographic left ventricular ejection fraction (LVEF) with serum levels of troponin. LVEF <50% was associated with elevated cTnI measurement ($p = 0.035$). In addition, in a cohort of 106 patients within the first days of severe sepsis or septic shock, Landesberg *et al.* [5] showed that echocardiographic parameters as left ventricular diastolic dysfunction and right ventricular dilatation had the best correlation with concomitant high-sensitivity cTnT levels. These results could provide an explanation to the association of troponin and mortality in severe sepsis and septic shock.

Table 1. Studies who investigated troponins in septic cardiomyopathy.

Authors	Journal and Years	Number of Patients	Objectives of the Study	Results of the Study
Fernandes Jr. CJ *et al.*	Int. Care Med,1999	10 septic patients	Determined if cTnI, may detect LV involvement by the septic process	Patients whose LVEF was <50% had elevated cTnI levels ($p = 0.035$).
Landesberg G. *et al.*	Crit Care Med, 2014	106 patients with severe sepsis or septic shock	Investigated the association between echographic myocardial dysfunction,troponin level and outcome	LV diastolic dysfunction and RV dilatation were correlated with elevated hsTnT ($p = 0.001$ and 0.0002). hsTnT predicted mortality in univariate analysis ($p = 0.004$
Ver Elst KM *et al.*	Clin Chem., 2000	46 with septic shock	Analyzed relationship between cardiac troponin I (cTnI) and T (cTnT) and cardiac sepsis-induced dysfunction.	cTnI and cTnT were associated with LV dysfunction ($P <0.0001$).
Ammann P. *et al.*	Int. Care Med, 2001	20 patients with sepsis, septic shock or SIRS	Detected cardiac sepsis induced dysfunction by cTnI levels in patients without acute coronary syndromes	cTnI was elevated in 85% of patients associated with higher incidence of cardiac echographic dysfunction of wall motion ($p = 0.002$) and lower LVEF ($p = 0.04$).

CHAPTER 10

Current and New Therapeutic Interventions in Septic Cardiomyopathy

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Abstract: Septic cardiomyopathy is frequently observed in patients with severe sepsis however it often does not require specific therapy. In patients presenting signs of tissue perfusion and inadequate cardiac output, manipulation of cardiac output should be considered. The first line therapies consist in optimization of preload by fluid administration and of afterload by decreasing the doses of vasopressor agents whenever possible. Inotropic agents should then be considered. Among these dobutamine remains the most commonly used, even though there is a huge individual variability in the response to it. The lowest dose associated with a satisfactory hemodynamic state should be used, as high doses for a prolonged period of time can be associated with impaired outcome. Phosphodiesterase inhibitors are often limited by their peripheral dilatory properties. Levosimendan is a promising inotropic agent, but its superiority to classical adrenergic inotropic agents remains to be determined.

Keywords: Adrenergic agents, Cardiac function, Cardiac output, Circulatory failure, ECMO, Inotropic agents, Levosimendan, Phosphodiesterase inhibitors, Tissue perfusion.

1. INTRODUCTION

Septic shock usually characterized by high cardiac output and decreased vascular tone [1]. However, myocardial depression frequently observed in septic shock [2, 3]. It can affect the left and right ventricles, as well systolic and diastolic functions [4 - 7]. Echocardiography is the most useful tool to identify septic cardiomyopathy, but also to identify which component is mostly affected and to

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evaluate their hemodynamic consequences [8]. This will be particularly important to decide whether or not it should be treated, and then which intervention to apply as therapies of right and left ventricular dysfunctions may differ. However, echocardiography has the disadvantage to be discontinuous and requires skills for the hemodynamic evaluation of septic cardiomyopathy that go beyond the basic level [9]. Accordingly other hemodynamic tools are often used in conjunction with echocardiography. The reliability of the various techniques is quite variable in severely ill patients and often inversely proportional to its invasiveness. More invasive techniques also provide additional information such as intravascular pressures and volumes. Accordingly, the choice of the hemodynamic tool should not be guided only on invasiveness but should also take into account the potential interest of additional measured variables and accuracy of the technique in the condition presented by the patient. The choice of the hemodynamic monitoring device should thus be individualized and there is clearly still a place for invasive techniques in the management of septic cardiomyopathy.

2. SEPTIC CARDIOMYOPATHY: SHOULD WE TREAT?

Identifying an impaired cardiac function in a patient with sepsis does not imply that hemodynamic targeted therapies should be implemented. Indeed, cardiac output can be preserved even when ejection fraction is impaired thanks to the decrease in afterload and to compensatory tachycardia. Evaluating simultaneously cardiac output and left ventricular ejection fraction in 183 septic shock patients, Vieillard-Baron *et al.* [4] observed that many patients had an impaired ejection fraction, but that cardiac index was impaired in only 50% of these. So, when therapy is indicated? When cardiac output is considered inadequate and tissue perfusion impaired, which occurs in one fourth of the patients.

Adequacy of cardiac output should be judged on several factors. Measurement of mixed- or central venous oxygen saturation (SvO_2 or $ScvO_2$) provides important information on the adequacy of oxygen transport, and hence cardiac output. A decrease in SvO_2 or $ScvO_2$ suggests an inadequate cardiac output if hemoglobin and PaO_2 are within the normal range. On the contrary a normal SvO_2 suggests that cardiac output is adapted to the metabolic needs. This approach is unfortunately potentially biased in sepsis when alterations in microvascular

perfusion alter oxygen extraction capabilities [10]. Veno-arterial PCO_2 gradient may help in these conditions as an increased veno-arterial PCO_2 gradient is associated with poor outcome [11, 12]. Other signs of tissue perfusion may indicate therapy, such as lactate plasma levels which reflects the balance between oxygen consumption and oxygen requirements. When VO_2 cannot meet oxygen requirements, anaerobic metabolism develops which is reflected by increased lactate levels.

When cardiac output is inadequate, as assessed by any of these indices, it seems justified to manipulate it with vasoactive agents [13].

When we decide to treat, what should be the target for therapy? Hemodynamic optimization has been proposed initially [14] but later trials failed to confirm the promising initial results [15] and this approach is now discouraged [16]. Individualized therapy should be preferred. Unfortunately it is difficult to recommend a specific target for resuscitation. $ScvO_2$ [17] within 6 hours of admission to Emergency Department and lactate clearance [18] within the first 8 hours after ICU admission are the solely supported targets, even if challenged. After these initial stages of resuscitation, various clinical (mental state, urine output, mottling score [19]) and biological (lactate, veno-arterial PCO_2 gradients [11, 12, 20]) signs of tissue hypoperfusion can be used, but proof that targeting resuscitation on this endpoints improves outcome is still lacking. It sounds reasonable to target resolution of the signs of tissue hypoperfusion that indicated introduction of inotropic therapy.

3. CURRENT THERAPEUTIC INTERVENTIONS

3.1. Fluids

Fluids do not affect myocardial contractility, however it is important to optimize preload before introducing inotropic agents. However, after initial resuscitation, many patients may fail to respond to fluids. In addition, the impaired diastolic function [5, 6] and/or impaired right ventricular function [7] increases the risk that fluid administration would not be tolerated. In addition, a positive balance is associated with a poor outcome. Accordingly, identifying the patients who have the greatest chances to respond to fluids is thus highly desirable. Even though

CHAPTER 11

Tachycardia and Its Pathophysiological Implications in Septic Myocardial Dysfunction

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Abstract: Tachycardia is an independent risk factor for mortality and morbidity in different clinical conditions such as coronary artery disease, myocardial infarction, as well as congestive heart failure. Evidence suggests that an elevated heart rate is associated to increased mortality even in septic shock. It has been recently demonstrated that tachycardia persisting at 24 hours, after volume resuscitation and commencement of vasopressors, early identifies a particularly severe subset of septic shock patients. These high-risk patients would likely benefit most from HR control. A reduction in HR should be therefore considered as one of the therapeutic targets to improve patient outcome. Nevertheless, reducing HR in septic shock is difficult, because the right time for treatment and the optimal HR range are not currently defined. Based on the underlying mechanisms of elevated heart rate in septic shock, both beta blocker esmolol and hyperpolarization-activated cyclic nucleotide gated channel inhibitor ivabradine appear to be the most appropriate drugs for treating elevated HR. Nevertheless, the effectiveness and safety of these agents, the degree of HR reduction, as well as the appropriate target population, should be better defined before widely adopting this therapeutic strategy in the common clinical practice. The aim of this chapter is therefore to provide an overview of the underlying mechanisms of sepsis-induced tachycardia and their implications in the clinical management of affected patients.

Keywords: Adrenergic receptors, Beta-blockers, Ivabradine, Septic shock, Tachycardia.

1. INTRODUCTION

Tachycardia is an independent risk factor for mortality and morbidity in different

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clinical conditions such as coronary artery disease, myocardial infarction, as well as congestive heart failure [1 - 4]. Likewise, in critically ill patients HR has been proven to be the best predictor of major cardiac events and mortality in different categories of patients [5, 6]. This is true even in the general population, in which the increase in HR is associated with a worse outcome [7]. Beyond the prognostic implications, it is now well recognized that an elevated HR also contributes to cardiac dysfunction. Even though it has been demonstrated that an elevated HR negatively affects outcome in cardiology patients, the role of tachycardia has gained less attention in the septic patients. To date only few and small clinical studies have investigated the relationship between tachycardia and mortality in patients suffering from septic shock [8 - 10]. Nevertheless, these studies clearly demonstrate that a relatively low HR or a decrease at 24 hrs predicts survival, reflecting the successful of hemodynamic optimization. A lack of decrease or an increase in HR from 0 to 24 hrs is associated with increased mortality [8 - 12]. On this basis, a decrease in HR may potentially improve outcome of septic shock patients.

2. ELEVATED HEART RATE IN SEPTIC SHOCK: PROGNOSTIC IMPLICATIONS

Only few clinical studies specifically aimed to investigate the relationship between tachycardia and mortality in septic shock patients are available in the current literature. Azimi and Vincent reported that despite achieving hemodynamic stability, septic shock patients with a persistently high HR (102±6 bpm) and greater ongoing norepinephrine requirements after 24 hours subsequently died. Interestingly in non-survivors lactate levels were only slightly elevated. In survivors, HR decreased to 87±4 bpm after stabilization and lactate levels were similar. [8]. In another study of 48 patients with septic shock, HR <106 bpm on ICU admission or <95 bpm at 24 hours, or a reduction in HR >18 bpm within 24 hour were predictors of survival [9]. In a monocentric trial aimed to study the hemodynamic effects of reducing HR with the beta blocker esmolol in septic shock, patients with persistent tachycardia (>95 bpm) after hemodynamic stabilization showed a mortality rate of 80% [10]. These findings have been recently confirmed by retrospective analysis of records of 711 consecutive septic shock patients in eight European intensive care units, showing that mortality was

higher in patients with HR ≥95 bpm and increasing catecholamine dose requirements [13, 14]. Taken together, all these findings [8 - 14] suggest that by applying HR as prognostic factor, a very high risk subgroup of septic shock patients can be identify early in their course.

3. THE MEANING OF TACHICARDIA IN SEPTIC SHOCK

In the early phase of septic shock, the massive inflammation leads to vasodilation and capillary leakage, which decrease cardiac output due to both absolute and relative hypovolemia [15 - 17]. Such alterations lead to arterial hypotension, which trigger a massive adrenergic activation aiming at maintaining vital organ perfusion. Tachycardia and vasoconstriction are the hallmark of this activation and compensate for systemic vasodilatation [17, 18]. In the very initial phase of sepsis thachycardia therefore is the main compensatory mechanism to maintain cardiac output despite a reduction of preload. Accordingly, current sepsis guidelines recommend intravascular fluid administration as first step to counteract hypotension [19]. Thanks to this compensatory mechanism, which implies preserved baro- and chemo-receptor activities, the majority of septic patients rapidly respond to volume administration with a reduction of tachycardia. However, even after treating hypovolemia, septic patients often have an elevated HR. This tachycardia typically does not respond to aggressive fluid resuscitation indicating an altered chronotropic response, which is caused by an impairment of the sympathetic nervous system. In this regard it has been demonstrated that some septic shock patients may suffer from a protracted overstimulation by the sympathetic nervous system, which exceeds in time and scope the beneficial short-term compensatory effect, leading to several adverse effects including an elevated HR [5, 10 - 12, 19, 20]. This abnormal stimulation is further sustained by high levels of circulating catecholamines produced at the level of gut, lymphocyte, macrophages and neutrophils [19]. Since 75-80% of adrenergic receptors in the heart are β1 and adrenergic stress is manly mediated by β receptors, it is easy to understand why tachycardia is the main clinical sign of adrenergic overstimulation [19]. The autonomic dysfunction in these patients is extremely complex and also involves an imbalance of the two sympathetic and parasympathetic components with the latter strongly attenuated [21]. It is still unclear why the autonomic nervous system is impaired in some patients and not in

CHAPTER 12

Septic Cardiomyopathy: Quo Vadis? From Past-to -the Future

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Abstract: Sepsis remains the most common admission diagnosis to ICU and approximately half of these patients develop some form of cardiac dysfunction. Genetic factors, large vessel and microcirculatory changes, depressant factors, metabolic changes, autonomic dysregulation and a myriad of cellular regulators have all been implicated in the myocardial dysfunction. The cardiomyopathy is reversible may include elements of LV and RV systolic and diastolic dysfunction. Current approaches to treatment include guideline based septic shock therapy often along with inotropic support, however a new approach may include heart rate control.

Keywords: Left ventricular ejection fraction, Sepsis, Septic shock, Ventricular dysfunction.

1. INTRODUCTION

Cardiovascular dysfunction contributes substantially to mortality from sepsis. Sepsis is the most common admission diagnosis to Intensive Care Units (ICU) [1] with about half of the approximately million, and increasing [2], severe sepsis patients per year in the USA requiring ICU admission [3]. Approximately half of these patients present with cardiovascular dysfunction manifest as septic shock. Mortality from septic shock is improving but remains unacceptably high. In recent clinical trials with rigorous exclusion criteria septic shock mortality is as low as 20% [4] while in observational studies without exclusion criteria mortality is ~50% [1].

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Three decades ago Parker and colleagues noted that reversible septic cardiomyopathy contributes to the cardiovascular dysfunction of septic shock [5]. Even though patients had hyperdynamic septic shock with elevated cardiac index, left ventricular ejection fraction (LVEF) was found to be less than 40% in about half of these patients; a fractional incidence that has recently been confirmed [6]. Ejection fraction returned to normal in survivors over the course of approximately a week. Decreased left ventricular contractility is also accompanied by right ventricular dysfunction [7]. This septic cardiomyopathy appears to contribute to increased mortality in septic shock [8]. Initial observations suggested that a circulating myocardial depressant factor may be the cause [9].

Over the intervening three decades the features and clinical significance of myocardial depression of sepsis have been further characterized. The underlying mechanisms have been investigated extensively and been found to involve many parallel and intersecting signalling pathways. From this greater understanding hints at potentially beneficial therapeutic strategies have been suggested.

2. CHARACTERISTICS OF VENTRICULAR DYSFUNCTION IN SEPTIC SHOCK

2.1. Pathology

Schmittinger *et al.* performed a prospective, observational, combined clinical and post-mortem study on 20 patients dying of septic shock [10]. 'Stress-induced pathologies were found in 90% to 100% of patients in all heart sections (myocytolysis, 100%; interstitial fibrosis, 100%; contraction band necrosis, 95%; mononuclear infiltrates, 90%; interstitial edema, 90%; tissue hemorrhage, 30%)'. 'The incidence and extent of contraction band necrosis, mononuclear infiltrates, and myocytolysis did not differ between sexes; patients with or without chronic β-blocker, calcium antagonist, and/or statin premedication; or between the binary use of different catecholamine agents (all comparisons $P > 0.05$)' [10]. Interesting also, 'the maximum epinephrine dose correlated with the overall extent of mononuclear infiltrates' and myocytolysis and the total duration of catecholamine therapy was correlated with the extent of mononuclear infiltrates in the apex and right atrium. Takasu and colleagues made similar observations [11]. Additional

pathologic features of septic cardiomyopathy observed in this study included redistribution of connexin-43 to lateral membranes from intercalated disks and hydropic mitochondria.

3. DECREASED LV CONTRACTILITY

In a recent study of patients who fulfilled the criteria defining septic shock transesophageal echocardiography performed at admission and again after 24-48 hours demonstrated myocardial depression (LVEF <45%) at one or more time points in 60% of these patients [6]. Thus, septic cardiomyopathy is very common. The observation of decreased ventricular contractility during hyperdynamic septic shock was surprising because the volume-resuscitated septic shock circulation is most commonly hyper-dynamic with increased cardiac output and stroke volume. Interestingly, a dilated diastolic ventricle is observed more frequently in survivors and may allow for normal or increased cardiac output in the face of decreased systolic contractility (Fig. **1a**, **1b**) [12]. In contrast, impaired diastolic filling is a prominent feature in non-survivors of septic shock [12, 13] where the progression of shock is characterized by decreasing cardiac output and stroke volume. Concordant results were observed in a murine model where dilators survived significantly more [1, 14].

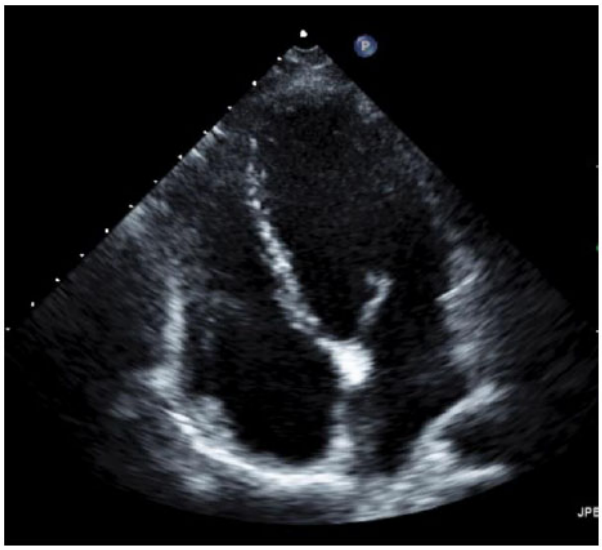

Fig. (1a). Transthoracic echocardiogram images of a normal diastolic left ventricular function.

SUBJECT INDEX

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The scientific interests of Dr. Papaioannou include analysis of complex biological signals derived from critically ill patients in the Intensive Care Unit. He is an Anesthesiologist and Intensive Care Physician and his postgraduate studies from Aristotle University of Thessaloniki, Greece in biomedical engineering have led him to analyse complexity loss of different biosignals from patients during severe illness. He has been awarded with many European and American awards and has published more than 60 original, review articles and conference papers about hemodynamics, respiratory failure and neuro-immunological cross-talk alterations during severe sepsis and septic shock. His post-doc research in cardiac cellular electrophysiology in Amsterdam and his clinical work in Paris have also allowed him to study in more detail cardiac dysfunction during sepsis, in both medical and surgical patients. He is currently working as a physician and university tutor, trying to implement a complex systems approach, for better understanding the pathophysiology of critical illness.