T.C.
MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ
ANESTEZİYOLOJİ VE REANİMASYON ANABİLİM DALI

THE PROGNOSTIC VALUE OF CARDIAC POWER OUTPUT IN SEPTIC PATIENTS

Dr. MÜŞERREF TÜRKER
MASTER THESIS

Consultant: Prof. Dr. Zuhal Aykaç

İSTANBUL, 2017

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ÖNSÖZ

İhtisas eğitimini tamamlamış olmanın verdiği mutluluğu ve güzel insanlardan ayrılacak olmanın hüznünü bir arada yaşadığım bu günlerde, Prof. Dr. Zuhal Aykaç başta olmak üzere,

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Kişiliğimin ilk tohumlarını şefkat ve disiplinle yoğuran sevgili anne ve babama

Sonsuz teşekkürlerimi sunuyorum...

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SYMBOLS AND ABBREVIATIONS

ACCP: American Colege of Chest Physicians
ACHF: Advanced heart failure
APACHE II: Acute Physiology and Chronic Health Evaluation
ARDS: Acute respiratory distress syndrome
BNP: B-Type natriuretic peptide
BSA: Body surface area
CI: Cardiac index
CO: Cardiac output
CPI: Cardiac power index
CPO: Cardiac power output
CRP: C-reactive protein
CVP: Central venous pressure
DBP: Diastolic blood pressure
DO2: Oxygen delivery
ELAM: Endothelial-leukocyte adhesion molecule
ESICM: European Society of Intensive Care Medicine
HR: Heart rate
ICAM: Intercellular adhesion molecule
ICU: Intensive care unit
IL: Interleukin
INOS: Inducible nitric oxide synthase
LPS: Lipopolysaccharide
LV: Left ventricular
LVEF: Left ventricular ejection fraction
MAP: Mean arterial pressure
MODS: Multiple organ dysfunction syndrome
PAC: Pulmonary artery catheter
PCT: Procalcitonin
PCWP: Pulmonar capillary wedge pressure
PGRP: Peptidoglycanrecognition proteins
PLR: Passive leg- raising
PVR: Pulmonar vascular resistance
ROS: Reactive oxygen species
RV: Right venticular
RV: Right ventricular
SAB: Systolic arterial pressure
SBP: Systolic blood pressure
SCCM: Society of Critical Care Medicine
ScVO2: Central venous oxygen saturation
SIMD: Sepsis-induced myocardial dysfunction
SIRS: Systemic inflammatory response syndrome

SOFA: Sepsis related Organ Failure Assessment
SSC: Surviving Sepsis Campaign
SVR: Systemic vascular resistance
TLR: Toll-like receptor
TNF: Tumor necrotisan factor
TTE: Transthoracic echocardiography
VO2: Oxygen consumption
VTI: Velocity index
WBC: White blood cells
WHO: World health organisation

SUMMARY

The prognostic value of Cardiac Power Output in septic patients

Purpose: Sepsis is one of the leading reasons for the hospitalization with high mortality and morbidity; there is still a search for predictive values for mortality. Recently, a new hemodynamic parameter "Cardiac Power Index (CPO)" has been proposed to determine prognosis in heart failure. In this study, we aimed to evaluate the prognostic power of CPO in sepsis and ICU survivals of patients with septic shock.

Material and Methods: The study was carried out at Marmara University Pendik Training and Research Hospital Anaesthesiology Intensive Care Unit. Adult, sepsis and septic shock patients admitted in intensive care unit were included. Sepsis was defined as Sepsis 3 and patients were treated according to the recommendations in the Surviving Sepsis Guideline. Patients' age, gender, comorbidities, source of sepsis, pre-intensive care hospital admission, SOFA and APACHE II scores were recorded. Biochemical variables such as arterial blood gases, central venous oxygen saturation (ScVO2), leukocyte, procalcitonin (PCT), lactate, platelet, creatinine, brain natriuretic peptide (BNP) were followed daily. After excluding intravascular volume depletion by a passive leg-raising test, cardiac output volume, cardiac index**,** systemic vascular resistance, and stroke volume measurements were made and the measurements were repeated three times for every 12-hour. The cardiac power output (CPO) and cardiac power index (CPI) were calculated. Patients were grouped as survivors and non-survivors due to sepsis and ICU survivals.

Results: Survivor and non-survivor patients were comparable in demographic data, APACHE II, and SOFA scores, and the changes in biochemical variable according to sepsis and ICU survivals. The CPO values survivors according to sepsis survival were as followed: M1= 0.89, M2= 0.99, M3= 0.9, and M4= 1.05 (p1= 0.16, p2= 0.31, p3= 0.08, and p4= 0.07, respectively). The CPI values for survivors according to sepsis survival were as followed: M1= 0.48, M2= 0.49, M3= 0.45, and M4= 0.56 (p1= 0.124, p=0.521, P00.08, and p4= 0.09, respectively).

Conclusion: CPO and CPI values did not predict sepsis and ICU mortality in sepsis patients.

Keywords: sepsis, mortality, cardiac power output, cardiac power index

1 INTRODUCTION AND OBJECTIVES

Sepsis is one of the leading reasons for admission to intensive care units (ICU). In the last 20 years the incidence of sepsis has been raised by three times and is in the tenth place among causes of death with approximately 270 per 100,000 adults each year experiencing severe sepsis and septic shock leading to incremental health care investments[1].

In patients with sepsis and septic shock, fluid resuscitation and noradrenalin infusion is applied in order to provide tissue oxygenation, to optimize organ functions, to provide hemodynamic stability, and to increase the chances of survival, according to the "Sepsis Surviving Campaign Guideline"[2].

Cardiac output is necessary for the perfusion of organs and tissues, but is not sufficient alone; adequate mean arterial pressure (MAP) for a sufficient CO is also a must. Recently, a new hemodynamic parameter "Cardiac Power Output (CPO)" has been proposed to determine prognosis in heart failure. This parameter is obtained by multiplying MAP with CO and dividing by 451 and is expressed in watts. Thus, it is accepted that both the systemic flow and the blood pressure are shown to be physiologically appropriate[3].

Many new studies support the prognostic power of this new hemodynamic parameter. In a variety of studies it has been shown that CPO can predict the mortality in various conditions such as cardiogenic shock due to myocardial infarction, ischemic and non-ischemic cardiomyopathy, and fulminant myocarditis[2 4 5]. Neither CO nor other classical haemodynamic parameters were associated with mortality in studies conducted in this respect, CPO has emerged as a strong predictive parameter on the course of the patient. In patients with heart failure a CPO value <0.6 watts is showing that the cardiac insufficiency is getting worse and a CPO value <0.53 watts is a predictor for mortality in patients with cardiogenic shock[6].

In this study, we aimed to evaluate the prognostic power of CPO in sepsis and ICU survivals of patients with septic shock.

2 GENERAL PRINCIPLES

2.1 Sepsis

Hippocrates (ca. 460-370 BC) first introduced the Word “sepsis, which derives from the Greek word sipsi (“make rotten”). Ibn Sina (979-1037 BC) observed the coincidence of blood putrefaction (septicaemia) and fever. This concept of sepsis was used until the 19th century.

2.1.1 Epidemiology

Sepsis is one of the leading reasons for admission to intensive care units. In the last 20 years the incidence of sepsis has been raised by three times and is in the tenth place among causes of death with approximately 270 per 100,000 adults each year experiencing severe sepsis and septic shock leading to incremental health care investments[1].

Pneumonia is the most common infection leading to sepsis, followed by abdominal infections, primary bacteraemia and urinary tract infections[7].

2.1.2 Definition

Over the last two decades various definitions of sepsis have been developed. In 1991 the consensus conference defined the criteria for systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS)[8]. İf two or more of these criteria are met with an existing or suspected infection, one speaks of sepsis and if it was complicated by organ dysfunction, it was termed severe sepsis, which can

sometimes lead to a septic shock, defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation with systolic blood decrease > 40mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension. Beneath these SİRS criteria can also be seen in non-infectious causes like pancreatitis, ischemia, multiple trauma and tissue injury, haemorrhagic shock, and immune-mediated organ injury. MODS was defined as presence of altered organ

Fever ≥ 38°C or ≤36 °C
Heart rate >90 beats/min
Respiratory rate >20/dk
Leukocyte count ≥12.000/mL or ≤4.000/mL or although the number of leukocytes is normal immature (band) neutrophils> 10%

function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

This definition of sepsis had been used for over ten years but many clinicians believed that it does not provide a clear one. 2001 the SCCM, ESICM, ACCP, American Thoracic Society, and the Surgical Infection Society re-evaluated this definition and emphasized that these definitions may be insufficient in determining the stage and prognosis of the systemic response to infection but still preserved it as useful but too unspecific and added clinical symptoms listed in tabel1 below to recognize sepsis. Especially symptoms and biochemical markers related to hypoperfusion were emphasized in their roles as early diagnostical markers.

Table 1. Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:
General variables: - Fever (core temperature >38.3°C) or Hypothermia (core temperature <36°C) - Heart rate >90 /min or 2 SD above the normal value for age Tachypnea

-Altered mental status - Significant oedema or positive fluid balance (>20 mL/kg over 24 hours) - Hyperglycaemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables : - Leucocytosis (WBC count >12,000 /L) or Leukopenia (WBC count < 4000 /L) - Normal WBC count with > 10% immature forms - Plasma C-reactive protein >2 SD above the normal value - Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables: - Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease <40 mm Hg in adults or 2 SD below normal for age) -SvO_2 <70% or Cardiac index <3.5 L/min/m^3
Organ dysfunction variables: - Arterial hypoxemia (PaO_2/FIO_2 <300) - Acute oliguria (urine output <0.5 mL/kg/hr or 45 mmol/L for at least 2 hrs) - Creatinine increase >0.5 mg/dL - Coagulation abnormalities (INR >1.5 or aPTT >60 secs) - Ileus (absent bowel sounds) - Thrombocytopenia (platelet count <100,000 /L) - Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L)
Tissue perfusion variables: - Hyperlactatemia (>1 mmol/L) - Decreased capillary refill or mottling

In the following time it has been recognized that the SİRS criteria are less sensitive and specific and in February 2016 SCCM and ESİCM reformed sepsis definition and criteria as "Sepsis-3" as a life-threatening organ dysfunction due to dysregulated host response developed against infection[9 10]. Furthermore the SİRS criteria should not be used anymore in diagnosis of sepsis. It has been proposed to use the Sequential Organ Failure Assesment (SOFA) score to evaluate organ dysfunction[11]. The SOFA is scored according to Pa/FiO2 ratio, Glasgow Coma Scale (GCS), creatinine, bilirubin, platetes count, and MAP. Baseline SOFA score is considered as 0 in patients without previously known acute or chronic organ dysfunction. An increase by two or more SOFA points from baseline is considered as a positive SOFA.

Table 2. SOFA

Organ system	1	2	3	4
Respiratory PaO2/FiO2(mmHg)	<400	<300	<200	<100
Hematologic Platelets/nl	<150	<100	<50	<20
Hepatic Bilirubin, mg/dl	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular Hypotension	MAP <70 mmHg	Dopamine<5 or dobutamine (any dose)	Dopamine>5 or epinephrine<0.1 or norepinephrine<0.1	Dopamine >15 or epinephrine >0.1 or norepineprine >0.1
Neurologic Glasgow Coma Score	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl Urine output	1.2-1.9	2.0-3.4	3.5-4.9 <500ml/day	>5.0 <200ml/day

In addition septic shock has been no more defined as a merely acute circulatory failure but rather as a condition, which increases the mortality due to severe circulatory, cellular, and metabolic abnormalities.

2.1.3 Pathophysiology

The sepsis pathogenesis is a very complex interaction mechanism between the bacterium and the host. After exposure with bacteria the macrophages regulate the expression of more than 1000 gens up and the expression of more than 300 gens down[12]. The immune response to a bacterium occurs primarily through the cellular immune system, which recognizes immediately biochemical changes produced by the bacterium. The cellular immune system, which consists of macrophage and natural killer cells, affects directly the pathogens or release cytokines, which activate T and B cells and thus the humoral immune system is activated. The cellular immune system is activated by microbial cell wall components and released proteins. Lipopolysaccharide (LPS) and bacterial endotoksins are the most released products, which were seen the most during sepsis[13 14 15]. Lipopolysaccharide -binding protein binds LPS and transfers it to macrophages', monocytes' and neutrophils' cell membrane receptor (CD14)[14 16 17], which in turn induces a signal cascade that activates the toll-like receptors (TLR)[16 17 18 19 20]. There have been identified more than 10 TLRs with a wide spread ligand individuality[21]. The TLR activates the humoral immune system.

The congenital immune system is activated by microbial products like cell wall components or released proteins.

Toll-like receptors are transmembrane proteins and there have been detected 10 TLRs, which have a wide spreading ligand individuality for LPS, peptidoglycans, lipoteicoic acid and other pathogens[20]. These TLR are important for starting the humeral immune system.

Toll-like receptor 4 is a LPS receptor, TLR2 recognizes especially gram-positive cell wall components, TLR5 a flagellar receptor, and TLR9 detects the CpG elements of the bacterial DNA.

The toll proteins' domain sequence were alike the interleukin (IL)1 receptors' domain sequence, which are able to induce signal transduction pathways activating nuclear factor (NF-kB)[22]. In order to activate TLR4, a cell surface molecule, defined as MD2, is necessary, which makes TLR4-MD-2complex after LPS bind to CD14. Afterwards TLR4 activates some kinases, which activate I6B-kinaz-1 and I6B-kinas-2 by phosphorylating I6B by releasing NF-6B, which in turn reaches the nucleus and induces activating various inflammatory and immune response transcriptional genes[17]. In mice with spontaneous TLR4 gene mutation the endotoxic shock pathogenesis' role can be seen explicitly[23 24]. These mice haven't any answer to LPS or are resistant to an endotoxic shock. On the contrary mice with deleted TLR-2 genes have a normal response to LPS[25]. It has been shown that sepsis itself regulates the TLR-4 and TLR-2 expression[26]. In experimental models reducing the TLR expression or activation by immunmodulatoring decreases the mortality rates[26] (33). It was put forward that the increasing inflammatory response was depending on the increased expression of TLR and as a result of NF-kB and other nuclear transcription factors[26 27] (33,34).

There have been identified other ways detecting microbial cellular components. Peptidoglycanrecongnition proteins PGRP and their gens have been found, which are able to differentiate between gram-positive and gram-negative bacteria. After the first host-microorganism interaction, a spread of the congenital immune system takes place to regulate the humeral and cellular response. The most important role plays the mononuclear cells, which release usual proinflammatory cytokines like IL-1, İL-6, and tumor nectrotisan factor- α (TNF- α) and others cytokines like İL-8, İL-12, İL-15, İL-18 and a lot of other small molecules. İn order to clean the host of foreign antigens, anti-inflammatory mediators like İL-4, İL-10, are also formed. The pro- and anti-inflammatory pathways are very strictly controlled and regulated. These pathways are in close contact with coagulation/fibrinolysis, lipid mediator, acute phase and heat-shock proteins, neutrophil-endothelial cell activation, hypothalamic- pituar-adrenal axle, immune and immune and non-immune cell apoptosis, increased nitric oxide production, and oxidant/antioxidant and other homeostatic pathways. All pathways

have a negative and positive feedback pathway. Sepsis and septic shock are thought to be a deterioration of these mechanisms. TNF- α is the first released proinflammatuar cytokine in septic patients and after that IL-1, IL-6 and IL-8[28 29]. TNF- α and IL-1 are the most important proinflammatory cytokines, whichact synergistically, and are largely responsible for the clinical manifestations of sepsis[28 30 31]. After binding its receptor TNF- α and IL-1 active G-proteins, adenylatcylase, phospholipase A2, C and free oxygen radicals. Beneath that genes like the intercellular adhesion molecule 1 (ICAM-1) and endothelial-leukocyte adhesion molecule (ELAM) I, coagulation and fibrinolytic proteins, pro- and anti-inflammatory cytokines, induced nitric oxide senthetase and cyclooxygenase are transcripted. After TNF- α and IL-1 are released anti-inflammatory cytokines like Il-4, IL-10, IL-13, and tissue growth factor (TGF-b) are released, which suppress TNF- α and IL-1 genes' expression. Beside this these cytokines restrain antigen presentation to monocytes and the T- and B-Lymphocytes' function. Aneksin-1 (ANXA-1, a protein synthetized by mononuclear cells during the resolution phase, has potent anti-inflammatory properties and is able to protect from LPS lethal properties[32 33]. ANXA-1 increases the releasing of IL-10 by macrophages and inhibits the PLA_2, inducible nitric oxide senthetase and cyclooxygenase-2 (COX-2)[34]. ANXA-1 inhıbits neutrophil adhesion and migration to activated endothelial. The anti-inflammatory cytokines role is to keep the inflammatory answer under control. The majority of infected patients can maintain the balance between pro-and anti-inflammatory mediators, but in some patients this balance is disturbed and if the pro-inflammatory response is too much, it ends with a multisystem organ dysfunction[35 36].

2.1.4 Diagnosis and Biomarkers

The goal of treatment is early diagnosis and early treatment, in which there is no specific marker to diagnose sepsis. It is more an assessing of various nonspecific signs, symptoms, examination findings, and laboratory values. Several laboratory values like IL-1, IL-6 and TNF-α are pioneering, but are unable to differentiate between infectious and noninfectious causes of SIRS. Beneath this a PCT value > 0,5 ng/mL is suggestive

for a bacterial infection, whereas an accuracy is better than a single value.

2.1.5 Therapy

Early recognition, early control, and timely antibiotic administration are the key points of therapy.

It is essential to administer antimicrobial therapy as soon as possible after appropriate cultures have been obtained for effective treatment[37]. The antimicrobial therapy should be given within 3 hours of emergency department triage and within one hour of severe/septic shock recognition. The chosen antibiotic should include the probably organism which caused the sepsis. There must be paid attention to the patient history, comorbidities, clinical context, and the risk factors of a drug-resistant pathogen[38 39]. After isolation of a pathogen the antimicrobial therapy should be de-escalated[40]

Fluid resuscitation should be done properly in order to prevent iatrogenic injury[41]. The aim of fluid administration is to increase stroke volume (SV). By definition, a patient is considered to be fluid responsive if his or her SV increases by ≥10% following a fluid challenge, which can be determined the best with real-time SV monitoring like with transcutaneous Doppler ultrasound.

In order to target MAP above 65 mmHg vasopressors and inotropic agents should be considered to prevent organ dysfunction. First choice of vasopressors in patients with septic shock is norepinephrine[37 42] due to its characteristics restoring stressed blood volume, venous return, and cardiac output. Furthermore, it allows the reduction of administered fluid by achieving the target blood pressure. The application of vasopressin in persisting hypotension can be considered in cause of "relative vasopressin deficiency" seen among patients with septic shock and increases adrenergic sensitivity[43]. Similarly, the use of dobutamine should be considered in patients with concomitant left ventricular dysfunction.

These treatments were bundled in The Surviving Sepsis Campaign:

TO BE COMPLETED WITHIN 3 HOURS: 1) Measure lactate level 2) Obtain blood cultures prior to administration of antibiotics 3) Administer broad-spectrum antibiotics 4) Administer 30 mUkg crystalloid for hypotension or lactate 4 mmol/L
TO BE COMPLETED WITHIN 6 HOURS: 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP 65 mm Hg 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dU)

• Measure CVP • Measure central venous oxygen saturation ($Scv0_2$) Remeasure lactate if initial lactate was elevated

Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, $ScVO_2$ of 70%, and normalization of lactate.

2.2 Sepsis Induced Myocardial Dysfunction (SIMD)

Sepsis induced myocardial dysfunction has been defined as a reversible decrease in ejection fraction (EF) of both ventricles, with ventricular dilatation and less response to fluid resuscitation and catecholamines[44]. These are caused by increased venous capacitance, which leads to a reduced mean systemic filling pressure and thereby a decrease in cardiac output. Despite increased circulating catecholamine levels, the contractile response of cardiomyocytes to catecholamine stimulation is blunted because of down regulation of β–adrenergic receptors and consequently the β - adrenergic stimulant signal transduction is impaired. Therefore, treating with β - adrenergic blockers may be beneficial.

A large number of studies showed that myocardial dysfunction is a common finding with up to 60% of incidence in patients with sepsis developing during the early stages, which is also associated with increased mortality[45] . Septic patients at whom septic cardiomyopathy develop, the mortality is increased by more than twice compared to those patients who had organ failure without SIMD[7 46].

In sepsis-induced cardiac dysfunction, the stroke volume is low and the ejection fraction is reduced[47]. Septic cardiomyopathy develops in the context of the infectious process (inflammation, toxins, mitochondrial dysfunction), decreased myocardial perfusion (microtrombosis, flow maldistribution) and pulmonary damage (hypoxia, hypercarbia, ataxia). Pro-inflammatory cytokines like TNF A and IL-1β, nitric oxide, and reactive species have been shown to cause cardiac dysfunction, decreased peripheral vascular resistance[48], which lead to hemodynamic instability and multiple organ failure. Previous studies have shown that mortality rates in patients with cardiac dysfunction in the early period of sepsis are higher[49]. Septic cardiomyopathy treatment requires cardiovascular monitoring, mean arterial pressure, central venous pressure, and cardiac output.

Sepsis-induced cardiac myopathy was associated with decreased left ventricular ejection fraction, as well as a decrease in mean arterial pressure and end diastolic volume, and a normal yaw elevated cardiac index[50]. Clowens and McLean et al. observed that two distinct clinical manifestations of septic shock-related cardiovascular disorders. The first is an early hyper dynamic phase (hot shock) with increased cardiac output and a reduced systemic vascular resistance. The other is a late hypo dynamic phase (cold shock) with increased systemic vascular resistance and reduced cardiac output, resulting in tissue hypo perfusion, cold skin, and organ failure and resulting in death[51]. In these studies, it has been shown by using sentral venous catheter (SVC) and pulmonary artery catheter (PAC), that only the hyper dynamic phase persists in the use of SVC and the use of PAC if adequate resuscitation of fluid is done in septic patients. And the hypo dynamic phase was actually determined to be due to inadequate fluid resuscitation[52]. The accepted view nowadays is that reduced sepsis preload and afterload, myocardial dysfunction, blood flow redistribution between the organs and microcirculatory disorders cause hemodynamic changes[53]. Important mediators of this myocardial dysfunction include TNF- α and IL-1β.

Because of their very short half-life other mediators were thought to affect in the early period of sepsis. These were identified as nitric oxide (NO) and reactive oxygen species (ROS)[54 55].

2.2.1 Sepsis Induced Myocardial Dysfunction Pathogenesis

There are many mechanisms leading to SIMD like genetic factors, molecular and metabolic alterations, structural modification and hemodynamic alterations.

To go into detail the genetic factors contain the hypothesis that inducible NO synthase (iNOS) deficiency could confer decreased expression of contractile proteins and growth-related and energy-yielding genes.[56]

Molecular alterations include the calcium channels, nitric oxide, endothelin-1, cytokines, and toll-like receptors. Steng et al. has shown that the L-type calcium channel current is reduced which leads to a shortening of cardiac repolarization during hyper dynamic septic shock in pigs.[57]

Nitrit oxide, which can be synthesized by the cytokine-inducible synthase (iNOS), calcium-calmodulin-dependent synthase (cNOS) and cytokine-inducible synthase (iNOS), is thought to modulate systolic and diastolic cardiac function. İnos activity does not depend upon calcium or calmodulin, unlike eNOS and nNOS. Exposure to lipopolysaccharides and cytokines leads to an increased expression of iNOS, which results in releasing amounts of nitric oxide. Nitric oxide is able to bind to enzymes, to cause cellular dysfunction, to stimulate macrophages and the respiratory burst of neutrophils and to inhibit mitochondrial function, either directly or through interaction with free radicals resulting in the formation of peroxynitrite ($ONOO^-$). Beneath them nitric oxide alters protein kinase activity and thence the t-type calcium channel, decreases the myofibril's response to calcium and decreases cAmp via phosphodiesterase. This contributes to myocardial dysfunction by reducing sensitivity of myofibril response to calcium, inhibiting of β-adrenergic signalling, down regulating of beta-adrenergic receptor, and mitochondrial dysfunction.

Increasing Endothelin-1 blood and myocardial tissue levels during sepsis were associated with myocardial dysfunction by affecting myocardial contractility and increasing myocardial hypertrophy.[58]

The metabolic alterations include ischemia, mitochondrial dysfunction, oxidative stress, and autonomic dysregulation.

In previous years, it was postulated that coronary blood flow was inadequately caused by intravascular volume depletion, myocardial and endothelial cell oedema. Nowadays it is demonstrated that coronary flood in patients with sepsis with cardiac dysfunction is preserved or even increased. [59]

Mitochondrial dysfunction plays a key role in the mechanism of organ dysfunction in sepsis, including the heart. Takasu and colleagues reported oedema of the mitochondrial matrix, associated with cystic alterations of the cristae and collapse into small myelin-like clusters in the hearts of septic patients. This dysfunction was characterized by decreased rates of State 3 respiration and ATP synthesis, decreased respiratory control ratios and membrane potential, decreased activities of mitochondrial OXPHOS Complexes, increased rates of State 4 respiration, and increased mitochondrial size and fragility. Being highly dependent on continuous delivery of ATP to maintain contractile function, impairments in mitochondrial dysfunction are energetically detrimental for the heart. İn addition a decrease of the mitochondrial transmembrane potential or increased mitochondrial permeability transition was observed. This all leads to a functional impairment of cardiac mitochondria associated with cardiac dysfunction.

Beneath this, formation of important reactive oxygen species (ROS) plays another key role in effecting the cellular homeostasis. ROS include superoxide (O^{-}_{2}), hydrogen peroxide (H_2O_2), and hydroxyl radicals (HO). Reactive nitrogen species (RNS) include the free radical nitric oxide (NO) and the nonradical peroxynitrite ($ONOO^{-}$). Oxidative stress is the imbalance between the formation of oxidant substances and their removal by antioxidant scavenging compounds.[60]

The key mechanism of autonomic dysregulation contains down regulation of β_1-adrenergic receptor and disturbance of β-adrenergic signalling by reduced levels of stimulatory G-proteins and increased expression of inhibitory G-proteins. This results in a blunted contractility of cardiomyocytes although there is an increase of circulating

catecholamine levels in patients with sepsis.[48]

During sepsis, there are various structural modifications caused by myocardial infiltration by immune cells, especially polymorphonuclear cells (PMN), which form the basis of inflammatory myocardial oedema during experimental sepsis and monocytes/macrophages, swelling of cardiac endothelial cells, and formation of fibrin thrombi in blood vessels. [61]

Hemodynamic alterations are due to decreased intravascular volume, decreased vascular tone, and blood flow redistribution between organs; microcirculatory alterations, VO_2/DO_2 dependency, and high lactate levels represent other important alterations.

As a result of high vascular permeability, the intravascular volume is decreased and therefore the cardiac preload is insufficient. Peripheral vasodilatation and reduced systemic vascular resistance are the characteristical hemodynamic features seen in septic patients. This reduced afterload allows the left ventricular (LV) systolic function to be preserved despite myocardial depression.[62] These alterations occur due to an imbalance between vasoconstrictor and vasodilator factors. In sepsis the vasoconstrictor response to angiotensin II, catecholamines, and serotonin is diminished[63] and several vasodilatating factors such as TNF α, histamine, kinine, prostaglandins, and NO are released.

Reduced vessel density and altered blood flow lead to microcirculatory alterations[64] characterized by heterogeneous abnormalities in blood flow and a decrease in vascular density together with an increased number of capillaries with stopped or intermittent flow[65], which is associated with varying oxygen extraction capabilities and therefore heterogeneity in oxygenation. Thus, oxygen extraction is frequently impaired, inducing dependence of VO_2 on DO_2—so-called VO_2/DO_2 dependency. Also, endothelial dysfunction, leukocyte-endothelium interactions, coagulation, inflammatory disorders, hemorheologic abnormalities, functional shunting as well as autoregulation mechanisms failure trigger microcirculatory dysfunction[66].

2.2.2 Sepsis Induced Myocardial Dysfunction Diagnosis

In patients with circulatory shock, identifying the shock's type is crucial to adequately guide causal and supportive therapeutic approaches[67]. If physical examination does not lead to a clear diagnosis of the underlying type of shock, further hemodynamic assessment by echocardiography or—in complex patients—advanced hemodynamic monitoring (pulmonary artery catheter or transpulmonary thermodilution) is recommended[12]. Invasive measured arterial and venous pressures are the best methods to diagnose and therapy critically ill patients, although they are related with an increased risk of complications. Though it is known for a long time that in sepsis the central venous pressure does not correlate with the left ventricular end-diastolic pressure, thus the optimal left ventricular filling pressure[68]. In contrast the PAC enables precised differentiated hemodynamic measuring such as CO and as well as pulmonary arterial and systemic vascular resistance (SVR). Furthermore, the mixed-venous saturation in the pulmonary vessels determined by the PAC represents an indirect correlate for the oxygen delivery (DO_2) and its consumption (VO_2). Continuous pulmonary artery pressure monitoring can be useful to determine the right ventricular (RV) function und the therapy strategy. Its use is warranted only in patients with right heart failure, pulmonary artery hypertension, and in the context of complex operative due to significant risk profiles[69]. There is no clear recommendation for its use even though some authors advocate its use in cooperation with the echocardiography in the context of multimodal diagnosis for the septic cardiomyopathy[70]. The less invasive pulse contur analysis has a strong dependency on systemic vascular resistance, which can vary too much in sepsis and therefore its use is limited[71]. Beneath the evaluation of classic inflammation parameters like procalcitonin (PCT), C- reactive protein (CRP) and leukocytes, markers of a heart failure like the N-terminal pro B-Type natriuretic peptide (NT-pro-BNP) help to diagnose[72]. The main problem in determining heart function in sepsis is the usually isolated view of the heart, ignoring the extracardiac circulation situation. No currently available measurement procedure unites the evaluation of heart and circulatory adequately[73]. Although an echocardiographic examination is indispensable in the

septic, hemodynamically unstable patient, the echocardiography for the detection of the extent of septic cardiomyopathy has been in the scientific discussion for years. The evaluation of the cardiac function using conventional echocardiographic parameters (LVEF) is, as already noted, mostly influenced by changes in the complex system of pre- and afterload.[74]

2.2.3 Sepsis Induced Myocardial Dysfunction Therapy

There is no specific therapy of the SIMD. The current guidelines for therapy of septic shock represent the keystone in the therapy of septic cardiomyopathy. The recommendations contained in the Surviving Sepsis Campaign (SSC) represent good clues for the treatment of sepsis and its complications. The first aim to be achieved is a MAP >65 mmHg. Early and aggressive fluid resuscitation is required to restore CO to normal or high levels. The actual valid guidelines advise primarily the use of norepinephrine in patients with hypotension despite adequate volume substitution[75]. İn common α- receptor stimulating substances should be preferred, which have β -stimulating effects beneath their α-stimulating effects, because of their positive impact on tissue perfusion and the right heart[76]. Beside these, vasopressin is another potent vasopressor, which can increase the effects of the other vasopressors[53]. The use of inotropic agents is recommended in patients with sepsis, in whom a low CO prevails despite sufficient fluid substitution.[2]

2.3 Heart Failure

The primary function of the cardiac pump is to achieve maintaining a physiologically viable circulation by converting chemical energy into hydraulic energy. According to World Health Organisation (WHO), heart failure is defined as a decreased exercise capacity due to ventricular dysfunction. During heart failure the heart is unable to

provide the cardiac output needed by the organism at normal end-diastolic ventricular pressure.

Each year 1-4/1000 suffer from chronic heart failure, in which the incidence doubles every decade after the 45th year. The 5-year- survival-probability is all in all 40-50%. About half of patients with severe heart failure (NYHA stage III-IV) are dying within a year. Heart failure is defined as the inability of the heart to forward sufficient heart time volume despite sufficient filling pressure to achieve the needs of the organism, and/or to incorporate adequately the venous backflow. Heart failure is a clinical sign, which is caused or favoured by a variety of cardiac and extra cardiac disturbances and hence it cannot be seen irrespective of the underlying disease.[77]

2.4 Cardiac Power Output

Cardiac output is necessary for the perfusion of organs and tissues, but it is not sufficient as the only parameter for evaluating, because it is influenced by many factors like preload, afterload, and systemic vascular resistance. In order to be able to evaluate accurately these confounding parameters are included in the calculation, a formula has been developed: Cardiac power index (CPI) and Cardiac power output (CPO).

Based on the classical rules of fluids, cardiac power can be calculated with the formula power = flow x pressure. Applied to the heart cardiac power index (CPI) is the product of simultaneously measured mean arterial pressure (MAP) and cardiovascular flow (CI). CPI= MAP X CI X 0.0022. While 0.00222 represents a correction constancy.

Cardiac power output takes into account the stroke volume, so that the equation is similar to that used in electrical theory: W= V x I. That is: Power output (Watts)=Pressure (Volts) x Current (Amperes) or: CPO= mean arterial pressure x cardiac output (Qt). Both represent the cardiac contractility.

In recent studies with patients with advanced heart failure and it has been shown, that CPI values (<0.44 W/m^2) were associated with increased adverse outcomes and also CPO values of 0.53 W were found to be as the most accurately

predictor of in-hospital mortality, in which CPO values < 0.53 W were associated with increased probability of in-hospital mortality and CPO values >0.53 W were associated with increased probability of survival.[78 79]

2.5 Transcutaneous Doppler Ultrasound

Transcutaneous Doppler ultrasound devices like the ultrasonic cardiac output monitoring (USCOM) provides a rapid non-invasive measure of hemodynamic parameters using continuous Doppler wave Doppler ultrasound[80]. The probe can be applied to the supra-sternal notch for the aortic valve or to the left sternal edge for the pulmonary valve. The device is able to measure heart rate (HR) and the velocity time integral (VTI) of the ejection flow via an algorithm, which is incorporated into the software. With these parameters stroke volume is calculated as SV= CSA x VTI, whereby a proprietary algorithm based on height or weight is used to derive the cross-sectional area (CSA) of the two valves. The interval between systolic ejections is used for calculating the HR. By manually entered systolic and diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP) can be calculated. MAP is calculated as MAP= DBP+((SBP-DBP)/3). From these data USCOM provides values for cardiac output (CO) CO=SV x HR, systemic vascular resistance (SVR) SVR= MAP/CO[81]. The USCOM can be used from neonates of 23 weeks gestational ages to 86 years old adults and have been specifically validated for COs ranging from 0.12 to 18.7 l/min[82]. USCOM's advantage is the rapid non-invasive measuring of hemodynamic parameters compared to the pulmonary artery catheter, which still remains the gold standard for measuring CO in critical ill patients by thermodilution technique, which holds its own risks like infection, arrhythmias on insertion, cardiac valve damage during prolonged use, catheter knotting, pulmonary artery rupture and pulmonary embolism[83]. Therefore, the USCOM is ideal for management in shocks where the treatment should be based on individualized optimization of oxygen delivery based on CO, HR, and SV and hence the USCOM has been used in a wide range of clinical settings, including

critical care, anaesthesiology, emergency medicine, obstetrics, and neonatology since its introduction in 2001.[84]

2.6 Dynamic Tests for Intravascular Volume Assessment

In the initial phase of the circulatory shock, it is easy to assess the volume status and to make the decision on fluid substitution.
In order to be able to judge that the fluid substitution has been carried out successfully, there are various dynamic and static tests.

According to the Frank-Starling relationship after a certain size it is not possible to increase the preload and thus the cardiac output, if the heart is functioning on the flat part of the Frank-Starling relationship curve. In addition to adequate substitution, the overload is also significant, as the excessive fluid administration leads to increased mortality during septic shock[85] and of prolonged mechanical ventilation during acute respiratory distress syndrome (ARDS)[86]. The central venous pressure, pulmonary artery occlusion pressure, left-ventricular and-diastolic dimensions, early/late diastolic wave ratio, and B-type natriuretic peptide concentration belong to the dynamic tests. None of these tests are able to determine the cardiac preload accurately, but rather to confirm that the fluid filled the cardiac chambers. On the other hand there are dynamic tests, which can be measured by respiratory variability of haemodynamic signals, like pulse pressure variation, stroke volume variation, the pulse oximetry amplitude variability, plethysmography, plethysmographic variability index (PVİ), and respiratory variation of inferior vena cava diameter. Alternatives to the respiratory variability of hemodynamic signals are the end-expiratory occlusion (EEO) test, the 'mini' fluid challenge, and the passive leg-raising (PLR) test.

The advantages of the PRL test are the independence of heart-lung interactions, so that it can also be applied to intubated patients[87]. The simple implementation, in which the legs are lifted out of its horizontal position, leads through the gravitate transfer blood from the lower limbs in the thoracic region, resulting in a significant increase in the right and left cardiac preload[88]. An increase in cardiac output of 10-

12% can be seen as a sign of the necessity of fluid substitution[89]. It should be borne in mind, that an increase in arterial blood pressure cannot be used as a hemodynamic response to the PLR, because it can lead to false negative cases[89], so the cardiac output must be measured shortly with a real-time monitoring device, because the effects of PRL are transient and reach their maximum after only 30-90 seconds, and thereafter compensatory mechanisms develop[87]. Thus, real-time cardiac output monitoring technologies like transcutaneous Doppler ultrasound is an easy bedside option, which can be used in ICU.

3 MATERİAL AND METHODS

The study was carried out at Marmara University Pendik Training and Research Hospital Anaesthesiology Intensive Care Unit. Adult, sepsis and septic shock patients admitted in intensive care unit were included. Sepsis was defined as Sepsis 3[10]. Septic shock was defined as a systolic arterial pressure (SAB) <90 mmHg and mean arterial pressure (OAB) <60 mmHg as the need for a vasopressor (noradrenalin> 0.05 mcg / kg / min) for more than one hour despite adequate intravascular fluid replacement. Septic shock treatment was performed in accordance with the current recommendation of the Sepsis Surviving Campaign Guideline[1].

Patient characteristics: Age, gender, comorbidities, sepsis source, pre-intensive care hospital stay, intensive care hospital stay, SOFA score, APACHE II score, exit status were recorded.

Biochemical tests: Arterial blood gases, central venous oxygen saturation (ScVO2), leukocyte, procalcitonin (PCT), lactate, platelet, creatinine, brain natriuretic peptide (BNP). These biochemical tests were performed daily from patients treated with sepsis and septic shock in intensive care unit. There were not any biochemical tests and blood sample except for the patient's routine.

Patients included in the study did not receive any additional treatment other than routine treatment. Before the patients were included in the study, the intravascular volume status was assessed, if necessary fluid replacement was performed, and euvolemia was provided.

Noradrenalin infusion titration was performed until MAP is 65-75 mmHg. Cardiac dynamical functions were measured when targeted MAP was reached. If targeted MAP was unattainable, adrenaline infusion was initiated and measurements were repeated.

If ScvO2 <70% and / or cardiac index <2.5 L / min / m2, dobutamine infusion was initiated and cardiac functions were measured.

Once the target values have been reached, a cardiac dynamic function measurement was made (M1) and the measurements were repeated every 12 hours (M2, M3, M4). Cardiac dynamic functions were performed via transcutaneous Doppler ultrasound

ultrasonographically from the jugular notch. The cardiac dynamic functions to be measured were: cardiac output volume, cardiac index**,** systemic vascular resistance, and stroke volume.

The cardiac power output (CPO) was calculated using the cardiac output X (MAP/ 451) formula. The cardiac power index was calculated using MAP X Cİ X 0,0022.
In assessing the patient's intravascular volume status passive leg raising test was used.

Passive leg raising test: Patients were placed in the supine position and the cardiac index was measured with a non-invasive hemodynamic monitor. After the measurement, the patient's head was raised 45 degrees and after 60 seconds the patient's back was flattened and the legs were raised 45 degrees and the cardiac index and cardiac output were measured again. A cardiac index and cardiac output change <10%, shows that there was no fluid deficiency measured by transcutaneous Doppler ultrasound

After evaluating patients were divided into two groups as survivors and non-survivors due to sepsis and ICU survivals.

4 STATISTICAL EXAMINATION

For statistical analysis, R vers. 2.15.3 program (R Core Team, 2013) was used. When the study data were evaluated, descriptive statistical methods (median, first quarter, third quadrant, frequency and percentage) as well as normal distribution fitness of quantitative data were assessed by Shapiro-Wilk test and graphical examination. Mann-Whitney U test was used for two groups of non-normal distribution variables. The Friedman test was used twice in the intra-group evaluations of normal non-dispersive quantitative data, and intra-group binary evaluations were performed by Wilcoxon-signed-ranks test. The relationship between qualitative data was assessed by Fisher exact test. Statistical significance was accepted as $p < 0.05$.

5 RESULTS

5.1 Sepsis Survival and Patient Outcomes

In the period from February 2016 to February 2017, a total of 29 patients were enrolled, of whom 8 were women and 21 were men.

When patients were grouped according to the sepsis survival, 25 patients were survivors and 4 patients were non-survivors. The median age of the survivors was 55 years and 41.5 years for non-survivors. While fourteen (48.3%) of the patients had comorbid diseases, fifteen patients (51.7%) had no comorbid diseases. While seven (24.1%)of the patients were hospitalized before being enrolled to the intensive care unit, 22 patients (75.9%) were directly taken from the emergency room or the operating room. In 21 Patients (72.4%) pneumonia was the sepsis source and in the eight left over patients the sepsis sources were seldom sources like intrabdominal sepsis with four patients (13.8%), meningitis with 3 patients (10.3%), and one patient (3.4%) with catheter-related sepsis.

Median SOFA and APACHE II scores in surviving patients were 10 and 23 respectively, in non-survivors patients the scores were 9.5 and 19 (p=0.6, p=0.4, respectively) (Table 3).

Table 3: Demographic data of the patients

		Sepsis survival		**p**
		Survivors (n: 25)	**Non-survivors (n: 4)**	
		Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
Age		55 (46, 66)	41.5 (28.5, 51.5)	[a]0.160
Gender, n (%)	Female	6 (75)	2 (25)	[b]0.300
	Male	19 (90.5)	2 (9.5)	
Comorbidity n (%)	No	12 (80)	3 (20)	[b]0.598
	Yes	13 (92.9)	1 (7.1)	
Prehospitalization before ICU admission n(%)	No	20 (90.9)	2 (9.1)	[b]0.238
	Yes	5 (71.4)	2 (28.6)	
Sepsis source, n (%)	Pneumonia	20 (95.2)	1 (4.8)	[b]0.052
	Others	5 (62.5)	3 (37.5)	
SOFA		10 (9, 12)	9.5 (8.5, 11)	[a]0.604
Apache II		23 (16, 29)	19 (15.5, 22.5)	[a]0.408

[a]Mann-Whitney U test [b]Fisher's exact test *p<0.05
Q_1: first quarter, Q_3: third quarter

The two groups were comparable in respect to pH (p=0.88), pCO_2 (p=0.78), pO_2 (p=0.6), SpO_2 (p=0.98), hb (p=0.98), hct (p=0.99), Na (p=0.65), K (p=0.74), Cl (p=0.74), Ca (p=0.34), HCO_3 (p=0.6), BE (p=0.74), lactate (p=0.31), glucose (p=0.41), ProBNP (p=0.67), $ScvO_2$ (p=0.8), WBC (p=0.69), Plt (p=0.88), procalcitonin (p=0.25), and creatinin (p=0.2) value changes between the first and second study days (Table 4).

Table 4: Comparison of first and second day biochemical variables

	Sepsis survival		**p**
	Survivors (n:25)	**Non-survivors (n:4)**	
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
Ph change	0 (-0.05, 0.08)	0.01 (-0.04, 0.05)	[a]0.879
pCO2 change	0 (-5, 9)	2 (-5.5, 5.5)	[a]0.784
pO2 change	2 (-19, 37)	-3.5 (-46, 26)	[a]0.604
SpO2 change	0 (-1, 1)	0 (-1, 1)	[a]0.976
Hb change	-0.5 (-1, 0.2)	-0.65 (-1.7, 0.7)	[a]0.976
Hct change	-0.9 (-3.5, 1.2)	-1.75 (-4.65, 2.2)	[a]0.999
Na change	1 (0, 4)	6 (-1.5, 17.5)	[a]0.647
K change	-0.1 (-0.4, 0.3)	0.05 (-0.45, 0.5)	[a]0.737
Cl change	3 (0, 5)	4.5 (-1, 13.5)	[a]0.737
Ca change	-0.1 (-0.6, 0.3)	0.25 (-0.3, 0.85)	[a]0.341
HCO3 change	1.3 (-1.6, 4.3)	-0.65 (-1.6, 1.85)	[a]0.604
BE change	1.5 (-1.1, 3.5)	0.25 (-1.4, 2.05)	[a]0.737
Lactate change	0.2 (-0.3, 0.4)	0.35 (0.05, 1.05)	[a]0.310
Glucose change	8 (-15, 66)	32 (-1.5, 88.5)	[a]0.408
ProBNP change	-8 (-81, 825)	-1137.7 (-2286, 10.6)	[a]0.667
SvO2 change	0 (-8, 9)	2 (2, 2)	[a]0.800
WBC change	800 (-1200, 5100)	-750 (-4400, 8800)	[a]0.692
Plt change	1000 (-31000, 13000)	1500 (-92500, 48000)	[a]0.879
Procalcitonin change	-0.13 (-2.99, 0.07)	9.88 (-0.3, 23.03)	[a]0.252
Creatinin change	-0.01 (-0.29, 0.09)	0.35 (-0.08, 1.03)	[a]0.203

[a]Mann-Whitney U test [b]Fisher's exact test *p<0.05
Q_1: first quarter Q_3: third quarter

The first measurement done at the time of sepsis diagnosis; CPO was 0.89 in survivors and 0.64 in non-survivors (p = 0.16). In the second measurement CPO was 0.99 in survivors and 0.93 in non-survivors (p=0.31). In the third measurement CPO was 0.9 in survivors and 0.68 in non-survivors (p=0.08). In the fourth measurement CPO was 1.05 in survivors and 0.76 in non-survivors (p=0.07).

The changes in CPO values over time were assessed in both groups of patients by evaluating dual measures. When survivors and non-survivors were compared; 1th measurement to 2nd measurement (p= 0.31); 1th measurement with 3rd measurement (p=0.48); 1st measurement with 4th measurement (p=0.78); 2nd measurement with 3rd Measurement (p=0.09), 2nd measurement with 4th measurement (p=0.10) and 3rd measurement with 4th measurement (p= 0.87), there were no significant differences (Table 5).

Table 5: Assessment of the relationship between sepsis survival and CPO measurements

CPO	**Sepsis survival**		
	Survivors (n: 25)	**Non-survivors (n: 4)**	**[a]p**
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
1st Measurement	0.89 (0.71, 1.22)	0.64 (0.59, 0.81)	0.160
2nd Measurement	0.99 (0.74, 1.19)	0.93 (0.68, 1)	0.310
3rd Measurement	0.9 (0.75, 1.25)	0.68 (0.5, 0.76)	0.082
4th Measurement	1.05 (0.85, 1.24)	0.76 (0.57, 0.88)	0.070
Change	[c]0.336	[c]0.145	
Binary reviews	**[d]p**	**[d]p**	**[a]p**
2nd M-1st M	0.999	0.999	0.310
3rd M-1st M	0.999	0.999	0.482
4th M-1st M	0.995	0.999	0.784
3rd M-2nd M	0.999	0.407	0.095
4th M-2nd M	0.855	0.407	0.109
4th M-3rd M	0.496	0.999	0.879

[a]Mann-Whitney U test [c]Friedman test [d]Wilcoxon signed-ranks test
Q_1: first quarter Q_3: third quarter

The first measurement done at the time of sepsis diagnosis; CPI was 0.48 in survivors and 0.36 in non-survivors (p = 0.12). İn the second measurement CPI was

0.49 in survivors and 0.49 in non-survivors (p=0.52). İn the third measurement CPI was 0.45 in survivors and 0.35 in non-survivors (p=0.08). In the fourth measurement CPI was 0.56 in survivors and 0.38 in non-survivors (p=0.09).

The changes in CPI values over time were assessed in both groups of patients by evaluating dual measures. When survivors and non-survivors were compared; 1th measurement to 2nd measurement (p= 0.28); 1th measurement with 3rd measurement (p=0.56); 1st measurement with 4th measurement (p=0.83); 2nd measurement with 3rd Measurement (p=0.08), 2nd measurement with 4th measurement (p=0.16) and 3rd measurement with 4th measurement (p= 0.88), there were no significant differences (Table 6).

Table 6: Assessment of the relationship between sepsis survival and CPI measurements

CPI	**Sepsis survival**		
	Survivors (n:25)	**Non-survivors (n:4)**	**[a]p**
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
1st Measurement	0.48 (0.37, 0.63)	0.36 (0.34, 0.41)	0.124
2nd Measurement	0.49 (0.39, 0.63)	0.49 (0.39, 0.51)	0.521
3rd Measurement	0.45 (0.35, 0.68)	0.35 (0.26, 0.39)	0.082
4th Measurement	0.56 (0.45, 0.65)	0.38 (0.29, 0.48)	0.095
Change	[c]0.615	[c]0.132	
Binary reviews	**[d]p**	**[d]p**	**[a]p**
2nd M-1st M	0.999	0.999	0.281
3rd M-1st M	0.999	0.999	0.562
4th M-1st M	0.999	0.999	0.831
3rd M-2nd M	0.999	0.407	0.082
4th M-2nd M	0.999	0.653	0.160
4th M-3rd M	0.403	0.999	0.879

[a]Mann-Whitney U test [c]Friedman test [d]Wilcoxon signed-ranks test
Q_1: first quarter Q_3: third quarter

5.2 Intensive Care Unit Survival and Patient Outcomes

When patients were grouped according to ICU survival, 10 patients were survivors and 19 patients were non-survivors. The median age of the survivors was 50 years and 56 years for non-survivors. While fifteen (51.7%) of the patients had comorbid diseases, fourteen patients (48.3%) had no comorbid diseases. While twenty-two (75.9%) of the patients were hospitalized before being enrolled to the intensive care unit, seven patients (24.1%) were directly taken from the emergency room or the operating room. In 21 Patients (72.4%) pneumonia was the sepsis source and in the eight left over patients the sepsis sources were seldom sources like intrabdominal sepsis with four patients (13.8%), meningitis with 3 patients (10.3%), and one patient (3.4%)with catheter-related sepsis.

Median SOFA and APACHE II scores in surviving patients were 9.5 and 23 respectively, in non-survivors patients the scores were 10 and 21 (p=0.195, p=0.636, respectively) (Table 7)

Table 7: ICU survival associated demographic data

		ICU survival		
		Survivor (n:10)	**Non-survivor (n:19)**	**p**
		Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
Age		50 (36, 65)	56 (42, 66)	[a]0.636
Gender, n(%)	Female	4 (50)	4 (50)	[b]0.390
	Male	6 (28.6)	15 (71.4)	
Comorbidity, n (%)	Yes	8 (53.3)	7 (46.7)	[b]0.049
	No	2 (14.3)	12 (85.7)	
Prehospitalization before ICU admission, n (%)	Yes	8 (36.4)	14 (63.6)	[b]0.999
	No	2 (28.6)	5 (71.4)	
Sepsis source, n (%)	Pneumonia	8 (38.1)	13 (61.9)	[b]0.675
	Others	2 (25)	6 (75)	
SOFA		9.5 (8, 11)	10 (9, 13)	[a]0.195
Apache II		23.5 (16, 29)	21 (15, 26)	[a]0.636

[a]Mann-Whitney U test [b]Fisher's exact test *p<0.05
Q_1:first quarter, Q_3:third quarter

The two groups were comperable in respect to pH (p=0.95), pCO_2 (p=0.74), pO_2 (p=0.05), SpO_2 (p=0.04), hb (p=0.1), hct (p=0.05), Na (p=0.98), K (p=0.8), Cl

(p=0.38), Ca (p=0.48), HCO_3 (p=0.51), BE (p=0.29), lactate (p=0.43), glucose (p=0.19), ProBNP (p=0.71), $ScvO_2$ (p=0.27), WBC (p=0.8), Plt (p=0.35), procalcitonin (p=0.99), and creatinin (p=0.15) value changes between the first and second study days (Table 8).

Table 8: ICU survival associated comparison of first and second day biochemical variables

	ICU survival		**p**
	Survivor (n:10)	**Non-survivor (n:19)**	
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
Ph change	-0.02 (-0.05, 0.09)	0.01 (-0.06, 0.08)	[a]0.946
pCO2 change	-2 (-6, 10)	3 (-4, 6)	[a]0.735
pO2 change	22 (0, 51)	-9 (-34, 15)	[a]0.049*
SpO2 change	1 (0, 2)	0 (-2, 0)	[a]0.040*
Hb change	-0.95 (-1.8, -0.1)	-0.1 (-1, 0.7)	[a]0.104
Hct change	-2.9 (-7.2, -1)	-0.1 (-3.5, 2.7)	[a]0.049*
Na change	1 (0, 5)	2 (-1, 5)	[a]0.982
K change	-0.2 (-0.4, 0.3)	-0.1 (-0.5, 0.3)	[a]0.804
Cl change	4.5 (-1, 11)	3 (0, 5)	[a]0.377
Ca change	-0.1 (-0.4, 0.6)	-0.1 (-0.8, 0.3)	[a]0.484
HCO3 change	2.6 (-2.4, 5.6)	0.3 (-1.6, 3)	[a]0.512
BE change	1.9 (-0.9, 9.7)	1 (-1.4, 2.1)	[a]0.286
Lactate change	0 (-0.5, 0.5)	0.2 (-0.1, 0.5)	[a]0.429
Glucose change	38.5 (8, 75)	-2 (-50, 66)	[a]0.195
ProBNP change	-8 (-2505, 241)	-1.2 (-81, 825)	[a]0.714
SvO2 change	-14 (-28, 9)	2 (-3, 10)	[a]0.267
WBC change	-50 (-6100, 6900)	800 (-1000, 5100)	[a]0.804
Plt change	-10500 (-31000, 3000)	6000 (-36000, 21000)	[a]0.353
Procalcitonin change	0 (-7.15, 0.07)	-0.17 (-1.06, 0.09)	[a]0.999
Creatinin change	-0.12 (-0.32, -0.01)	0.03 (-0.18, 0.12)	[a]0.151

[a]Mann-Whitney U test [b]Fisher's exact test *p<0.05
Q_1:first quarter, Q_3:third quarter

The first measurement done at the time of sepsis diagnosis; CPO was 1.14 in survivors and 0.79 in non-survivors (p = 0.46). In the second measurement CPO was 1.04 in survivors and 0.99 in non-survivors (p=0.74). In the third measurement CPO was 0.91 in survivors and 0.82 in non-survivors (p=0.95). In the fourth measurement CPO was 1.07 in survivors and 0.95 in non-survivors (p=0.54).

The changes in CPO values over time were assessed in both groups of patients by evaluating dual measures. When survivors and non-survivors were compared; 1th measurement to 2nd measurement (p= 0.35); 1th measurement with 3rd measurement (p=0.29); 1st measurement with 4th measurement (p=0.43); 2nd measurement with 3rd Measurement (p=0.33), 2nd measurement with 4th measurement (p=0.95) and 3rd measurement with 4th measurement (p= 0.43), there were no significant differences (Table 9).

Table 9: Assessment of the relationship between ICU survival and CPO measurements

CPO	**ICU survival**		
	Survivors (n:10)	**Non-survivors (n:19)**	**[a]p**
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
1st Measurement	1.14 (0.57, 1.36)	0.79 (0.63, 1)	0.456
2nd Measurement	1.04 (0.74, 1.19)	0.99 (0.62, 1.07)	0.735
3rd Measurement	0.91 (0.61, 1.11)	0.82 (0.66, 1.3)	0.946
4th Measurement	1.07 (0.84, 1.24)	0.95 (0.7, 1.16)	0.542
Change	[c]0.540	[c]0.345	
Binary reviews	**[d]p**	**[d]p**	**[a]p**
2nd M-1st M	0.999	0.999	0.353
3rd M-1st M	0.999	0.999	0.228
4th M-1st M	0.999	0.645	0.429
3rd M-2nd M	0.999	0.999	0.330
4th M-2nd M	0.999	0.999	0.946
4th M-3rd M	0.685	0.999	0.429

[a]Mann-Whitney U test [c]Friedman test [d]Wilcoxon signed-ranks test
Q_1: first quarter Q_3:third quarter

The first measurement done at the time of sepsis diagnosis; CPI was 0.56 in survivors and 0.45 in non-survivors (p = 0.60). İn the second measurement CPI was 0.53 in survivors and 0.49 in non-survivors (p=0.84). İn the third measurement CPI was 0.43 in survivors and 0.4 in non-survivors (p=0.84). In the fourth measurement CPI was 0.58 in survivors and 0.5 in non-survivors (p=0.6).

The changes in CPI values over time were assessed in both groups of patients by evaluating dual measures. When survivors and non-survivors were compared; 1th

measurement to 2nd measurement (p= 0.27); 1th measurement with 3rd measurement (p=0.35); 1st measurement with 4th measurement (p=0.78); 2nd measurement with 3rd Measurement (p=0.64), 2nd measurement with 4th measurement (p=0.86) and 3rd measurement with 4th measurement (p= 0.84), there were no significant differences (Table 10).

Table 10: Assessment of the relationship between ICU survival and CPI measurements

CPI	**ICU survival**		
	Survivors (n:10)	**Non-survivors (n:19)**	**[a]p**
	Median (Q_1, Q_3)	**Median (Q_1, Q_3)**	
1st Measurement	0.56 (0.29, 0.63)	0.45 (0.35, 0.59)	0.604
2nd Measurement	0.53 (0.36, 0.57)	0.49 (0.41, 0.64)	0.839
3rd Measurement	0.43 (0.33, 0.54)	0.4 (0.35, 0.7)	0.839
4th Measurement	0.58 (0.44, 0.65)	0.5 (0.42, 0.59)	0.604
Change	[c]0.840	[c]0.488	
Binary reviews	**[d]p**	**[d]p**	**[a]p**
2nd M-1st M	0.999	0.999	0.266
3rd M-1st M	0.999	0.999	0.353
4th M-1st M	0.999	0.999	0.456
3rd M-2nd M	0.999	0.999	0.636
4th M-2nd M	0.999	0.999	0.875
4th M-3rd M	0.999	0.671	0.839

[a]Mann-Whitney U test [c]Friedman test [d]Wilcoxon signed-ranks test
Q_1: first quarter Q_3: third quarter

Patients who had survived at ICU discharge, also survived at hospital discharge. The hospital survival rate 34.4% was exactly the same as the ICU survival rate.

6 DISCUSSION

This study is the first, which investigates the prognostic value of CPI and CPO in septic shock patients admitted to ICU. CPO and CPI values were determined at the time of sepsis diagnosis and up to 36 hours with 12 hours intervals. CPO and CPI values did not predict neither sepsis nor intensive care unit survivals and patient outcomes in any measurement times.

There are several similar studies that have determined the CPO and CPI value as prognostic parameters in heart failure. In a study including 495 patients with advanced heart failure who underwent invasive hemodynamic assessment, the prognostic value of CPI was evaluated. The patients were ≥ 18 years old with advanced chronic heart failure (ACHF, >6 months) and had undergone PAC as part of an outpatient assessment. Patients with congenital heart disease, long-term inotropic drug infusion, or admitted into the hospital directly after PAC for management of decompensated heart failure were excluded. They calculated CPI and put it in relation to age, gender, pulmonary capillary wedge pressure, cardiac index, pulmonary vascular resistance, LVEF, and creatinine. B-type natriuretic peptide (BNP) and peak-exercise oxygen consumption (Peak VO2) were collected in the follow-ups. The patients were followed up over a median of 3.3 years. There were 117 deaths, 104 transplants, and 20 ventricular assist device placements. The median CPI was 0.44 W/m^2 (interquartile range 0.37, 0.52) and the prognostic value remained significant after adjustment. CPI (<0.44 W/m^2) was associated with increased adverse outcomes (Hazard ratio (95% confidence interval) 2.4 (1.8-3.1), p<0.0001). Lower CPI was associated with lower MAP and CI (p<0.001 for both), but higher RAP, pulmonary arterial pressures, PCWP, SVR, and PVR (p<0.001 for all). Lower CPI was also associated with higher baseline creatinine (p=0.0008) and BNP (p<0.0001). Lower baseline CPI was associated with a significantly lower transplant and ventricular assist device-free survival (Log-rank, chi-square 43.9, p<0.001). They concluded that cardiac power index provides independent and incremental prediction in adverse outcome in patients with advanced heart failure[90].

In another study with 541 patients who were enrolled in the “Should we

emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK)"[91], CPO was evaluated. The only requirement to be registered in the SHOCK trial was the suspicion of cardiogenic shock, which was suspected on clinical grounds. Patients were excluded if one of the following shock categories was thought to be present: isolated right ventricular shock, acute severe mitral regurgitation, ventricular septal rupture, cardiac tamponade or rupture, prior severe valvular heart disease, dilated cardio- myopathy, excess beta or calcium channel blockade, and cardiogenic shock associated with recent haemorrhage or cardiac catheterization laboratory complication. Hemodynamic measurements were made between 6 hours before and up to 12 h after shock diagnosis. The hemodynamic measurements contain expansion of the case report forms during the study period: CPO, CPI, mean right atrial pressure, pulmonary artery systolic pressure, and pulmonary artery diastolic pressure, right ventricular systolic pressure and right ventricular diastolic pressure, Cardiac index, PCWP, and SVR. They concluded that CPO was the strongest independent hemodynamic correlate of outcome. A CPO of 0.53 W was found as the most accurately predict in-hospital mortality with an approximately equal sensitivity and specificity of 0.66. A CPO value < 0.53 W was associated with 58% probability of in-hospital mortality (positive predictive value) and a CPO >0.53 W with 71% a probability of survival (negative predictive value).[79]

In these two studies, both CPO and CPI predicted survival in heart failure due to cardiogenic shock. The reason why these indices predicted survival in cardiogenic shock but not in septic shock might be the differences in the pathophysiology between the two forms of shock.

The main difference between cardiogenic and septic (distributive) shock is the normal or high CO whereas in cardiogenic shock it is reduced[92]. Another difference is that septic shock is leading to LV systolic dysfunction, LV diastolic dysfunction, and right ventricular (RV) dysfunction, where all types of myocardial dysfunction can be present isolated or in combination. All these types of dysfunction are reversible[93] with full recovery of cardiac function at seven to ten days after the onset of sepsis. On the contrary, left ventricular dysfunction is the most frequent cause of cardiogenic shock[94]. Although systolic dysfunction is a common finding in septic patients[50], diastolic dysfunction is the strongest independent predictor of early mortality[95]. Beneath the

fact, that systolic dysfunction is associated with better survival, the underlying mechanism has never been elucidated[96]. Beneath this, diastolic dysfunction is the strongest independent predictor of early mortality[95]. Whereas in cardiogenic shock mortality can be predicted by initial left ventricular systolic function.[97]

In a meta-analysis a new developed LV systolic dysfunction associated with sepsis was evaluated as a sensitive or specific predictor of mortality. The diagnosis of LV systolic dysfunction associated with sepsis and was assessed by TTE as a predictor of in-hospital mortality showed a pooled sensitivity of 48% (95% CI, 39%-59%) with I^2 of 83.9% and a pooled specificity of 65% (95% CI, 59%-71%) with I^2 of 58%. They concluded that sepsis induced systolic dysfunction with LVEF lower than 50% is neither sensitive nor specific as a predictor of 30-day mortality.[98]

During the hyperdynamic response CO is elevated or normal, whereas the SVR is reduced.[51] Anatomical shunts and use of oxygen is reduced, which lead to a lowered A-V oxygen difference. The hypodynamic response includes fever, diarrhea, sequestration, collection of blood in the venous bed, leading to hypovolemia and at least to a reduced CO. During hypodynamic response the SVR is elevated, which leads to peripheral vasoconstriction with reduced CO and hypotension[99]. Due to the hyperdynamic state, myocardial depression may not be apparent.[100] Although impaired cardiac contractility with biventricular dysfunction is characterized by cardiac dilatation and decreased stroke volume.[50]

The main cause of cardiogenic shock is the heart muscle's damage (myocardial infarction or cardiomyopathy), arrhythmia or cardiac valve disease with reduced CO and systolic pressures lower than 90 mmHg. Another hemodynamic criteria are a decreased cardiac index (<2.2 L/min/m^2) and elevated left ventricular filling pressures (pulmonary capillary wedge pressure or left ventricular end-diastolic pressure > 15 mmHg) with vasoconstriction and fluid retention in order to restore organ perfusion in vital organs (i.e., CNS and heart)[101]. This leads to mobilization of blood from the splanchnic area and shifting fluid from the interstitium to the blood, which overall leads to hypoperfusion of end organs and activation of inflammatory cascades.

The heart can be compared with a hydraulic pump. It has to generate flow (cardiac output) and pressure to achieve a sufficient blood flow. In this matter CO contains intrinsic cardiac contractility, vascular compliance and resistance to flow in addition

to intravascular volume and cardiac filling pressures. Therefore, it can be formulized as the product of flow (CI or CO) and mean arterial pressure[102]. It has to be mentioned that cardiac output and mean arterial pressure are both measures of cardiac function, which do not predict each other. The calculation of CPO and CPI is an integration of both measures and is more accurate in representation of cardiac pump efficiency. In sepsis the main reason for the hypotension is the low SVR due to vasodilatation and fluid loss into the interstitium.

Cardiac output is calculated from the stroke volume and the heart rate, and is influenced by contractility, preload and afterload. Further determining factors are anatomical conditions such as ventricle size, cardiac wall thickness and valve function. In order to standardize the CO and compare between patients, the CI value is used. This results from CO divided by the BSA. It is far too little attention that the CO and CI reflect above all the state of the SVR, less the actual heart function. In contrast Cardiac power output is a direct measure of overall cardiac function that integrates both flow- and pressure-generating capacities of the heart, where CO and mean arterial pressure is integrated and represents the mean hydraulic power and is therefore a descriptor of cardiac function derived from preload, blood pressure and cardiac output.

In septic patients even with reduced left ventricular function, high CO levels can be found by reducing SVR alone. The CPI, on the other hand, is an "after-load-sensitive" parameter, which is "afterload-corrected" because the MAP and a correction factor are included in the calculation.

Limitations of the study are the few number of the patients and that an existing septic cardiomyopathy was not verified by echocardiography.

Strengths of the study are that the same person in all patients made all measurements, so there is not any interobserval variability. The same protocol was applied to all patients in accordance with the Sepsis Surviving Guidelines, especially the vasopressor therapy. There is no difference in treatment practice. All patients were treated in the same intensive care unit.

7 CONCLUSION

Sepsis is one of the leading reasons for the hospitalization with high mortality and morbidity; there is still a search for predictive values for mortality. The prognostic power of CPO and CPI values for mortality is supported in various conditions such as cardiogenic shock due to myocardial infarction, ischemic and non-ischemic cardiomyopathy, and fulminant myocarditis[2]. A large number of studies showed that sepsis induced myocardial dysfunction is a common finding with up to 60% of incidence in patients with sepsis developing during the early stages, which is also associated with increased mortality[45]. We questioned if CPO and CPI could predict mortality in sepsis.

According to results, CPO and CPI values did not predict mortality in sepsis patients. The reason why these values failed to predict mortality in sepsis could be due to the differences in the pathophysiology of cardiogenic and septic shocks.

In the early phase of septic shock the CO is normal or high, whereas in cardiogenic shock it is reduced[92]. Another difference is that septic shock causes LV systolic dysfunction, LV diastolic dysfunction, and right ventricular (RV) dysfunction and only the diastolic dysfunction is the strongest independent predictor of early mortality in septic patients, where as left ventricular systolic dysfunction is the most frequent cause and mortality predictor of cardiogenic shock.

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