Review Article
Cardiorenal Syndromes and Sepsis

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The cardiorenal syndrome is a clinical and pathophysiological entity defined as the concomitant presence of renal and cardiovascular dysfunction. In patients with severe sepsis and septic shock, acute cardiovascular, and renal derangements are common, that is, the septic cardiorenal syndrome. The aim of this paper is to describe the pathophysiology and clinical features of septic cardiorenal syndrome in light of the actual clinical and experimental evidence. In particular, the importance of systemic and intrarenal endothelial dysfunction, alterations of kidney perfusion, and myocardial function, organ “crosstalk” and ubiquitous inflammatory injury have been extensively reviewed in light of their role in cardiorenal syndrome etiology. Treatment includes early and targeted optimization of hemodynamics to reverse systemic hypotension and restore urinary output. In case of persistent renal impairment, renal replacement therapy may be used to remove cytokines and restore renal function.

1. Introduction and Definitions

The cardiorenal syndromes (CRSs) are relatively new clinical and pathophysiological entities which have been defined as the concomitant presence of renal and cardiovascular dysfunction [1]. According to Ronco and colleagues, five subtypes of the syndrome exist [2]. Type 1 CRS is defined as acute renal failure secondary to an abrupt worsening of cardiac function, for example, cardiogenic shock or acute congestive heart failure. Type 2 CRS describes a progressive and permanent chronic kidney dysfunction which is caused by chronic worsening in cardiac function, for example, chronic congestive heart failure. Type 3 CRS consists of an acute cardiac dysfunction (e.g., heart failure, arrhythmia, and ischemia) secondary to an abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis). Type 4 CRS describes a state of chronic kidney disease (e.g., chronic glomerular disease) causing a decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects concomitant cardiac and renal dysfunctions in the setting of a systemic condition which primarily affect both organs (e.g., diabetes mellitus and sepsis) [2].

The simultaneous presence of acute cardiovascular and renal alterations in septic patients is defined as septic cardiorenal syndrome. Cardiac and renal dysfunctions are often part of the clinical picture of severe sepsis and septic shock [3]. Following classification of Ronco, sepsis may represent an acute cause of Type 5 cardiorenal syndrome [2].

Renal dysfunction can be observed during severe sepsis and is part of the clinical picture of septic shock and multiple organ failure [1]. Acute renal failure is defined as an acute worsening of renal function based on increasing levels of serum creatinine or reduced urinary output [4]. Following RIFLE criteria, acute kidney injury (AKI) ranges from minor alterations in renal function to indication for renal replacement therapy [5]. AKI is common among critically ill patients, and sepsis and septic shock account for more than 50% of cases [6–8]. As suggested by Bellomo et al., sepsis-induced inflammatory injury of microvessels, hypotension and hypoperfusion during septic shock may play a causative role on development of AKI [2].

Moreover, a high proportion of septic patients develop left ventricular systolic impairment, either with or without involvement of other organs [9]. Cardiac dysfunction in sepsis is characterized by decreased contractility, impaired ventricular response to fluid therapy, and, in some patients, progressive ventricular dilatation. Current data support a complex underlying pathophysiology with a host of potential pathways leading to myocardial depression [10]. This is
Under resuscitated patients in sepsis/septic shock
↓
Systemic vascular resistance and fluid shift
↓
Cytokines, endothelin and nitric oxide
↓
Myocardial dysfunction
↓
CO
↓
RBF
↓
Mechanical ventilation, abdominal hypertension
↓
Hypoperfusion and ischemic kidney injury
↓
AKI

Figure 1: Hemodynamic alteration in underresuscitated sepsis patients (see text for details).

a well-described but poorly understood phenomenon in which microvascular alterations, autonomic dysregulation, metabolic changes and inflammatory signalling have all previously been hypothesized as potential mechanism for cardiac dysfunction [11].

Despite several studies investigate the incidence of AKI in sepsis or pathophysiology of septic cardiomyopathy, data are lacking about concomitant renal and cardiac injury in severe sepsis or septic shock. The purpose of this paper is to review pathophysiology and clinical aspects of septic cardiorenal syndrome in light of the actual clinical and experimental evidence.

2. Epidemiology

Incidence of sepsis in Europe is 350 new cases on 100,000 inhabitants per year [12] and its prevalence is high among all hospitalised patients (one–third) and, mostly, among those admitted to ICUs. Indeed, 10%–15% of all patients admitted to ICUs develop septic shock [13].

Moreover, numerous studies have shown septic AKI to be highly common among the critically ill, ranging from 16% to 41% [14, 15] of patients with severe sepsis and septic shock [16]. Patients with septic AKI are often older, have a higher prevalence of comorbidity and are more severely ill than those with nonseptic AKI [17].

On the other side, myocardial dysfunction may occur in up to 20% of patients with septic shock. Patients with myocardial dysfunction have significantly higher mortality (70%) compared to septic patients without cardiovascular impairment (20%) [18]. Biomarkers such as cardiac troponin T and I have been studied in sepsis. Elevations in cardiac troponin T and I correlate with the presence of left ventricular systolic dysfunction [19–21] and 30–80% of patients with severe sepsis and septic shock show NSTEMI on ECG with serum troponin values above the normal range. Furthermore, levels of cardiac troponin also correlate with duration of hypotension and intensity of vasopressor support in patients with septic shock [22, 23]. The potential role of B-type natriuretic peptide (BNP) as a biomarker has also been evaluated in septic patients. Recent studies have shown increased levels of BNP in patients with severe sepsis and septic shock [24]. Levels of BNP correlate with the degree of myocardial dysfunction and mortality [10].

More recently, echocardiography has been utilized to define heart dysfunction in severe sepsis and septic shock. In a longitudinal study with transthoracic echocardiography in septic shock patients, left ventricular ejection fraction was significantly depressed in all patients [25], resulting in severe reductions in left ventricular stroke volume. Of interest, these abnormalities were more pronounced in survivors than in nonsurvivors.

3. Hemodynamic Alterations

Type 1 cardiorenal syndrome is defined as an acute cardiac dysfunction which leads to acute renal failure, that is, acute cardiorenal syndrome [1]. Traditionally, septic AKI has been seen as the consequence of renal hypoperfusion and reduced renal blood flow, that is, an ischemic kidney injury, which occurs during severe sepsis, septic shock or multiple organ failure [26]. During early phases of septic shock, and in underresuscitated patients, systemic vasodilation and fluid shift reduce cardiac preload, thus reducing cardiac output. This may decrease renal blood flow (RBF) [27] and reduce glomerular filtration rate, leading to prerenal azotemia [26]. If renal hypoperfusion continues, ischemic injury to kidneys occurs, and AKI develops (see Figure 1).

Sepsis and septic shock are also characterized by a variable degree of myocardial dysfunction, which is linked to multiple factors. Experimental studies on laboratory animals show the role of mediators such as cytokines, endothelin [28], and nitric oxide [29] on myocardial cells and mitochondrial dysfunction [30] as possible mechanisms involved in this phenomenon [10]. Moreover, ventilation with positive end-expiratory pressure required by patients with severe
Sepsis or septic shock may contribute to intrarenal hemodynamic alterations. In a prospective experimental study on humans, Jacob et al. [31] evaluated the effects of increasing intrathoracic pressure with positive end-expiratory pressure on renal blood flow. High values of PEEP were associated to decreased mean arterial pressures, cardiac output and urinary output. PEEP-induced decrease in urinary output was correlated to renal perfusion pressure decrease. Furthermore, as demonstrated by Peng et al. [32] in bacteremic dogs, the presence of intrabdominal hypertension can adversely affect cardiac output and contribute to renal hypoperfusion (see Figure 1).

As a consequence of all these alterations, renal blood flow, and oxygen delivery decrease [33]. There is evidence that early goal directed hemodynamic optimization has positive effects on survival of septic patients, and restoring and maintaining good organ perfusion and oxygenation may account for this effect [34]. To preserve or restore renal function, a judicious, targeted use of fluids and vasopressors is recommended [35]. Recovery of renal function and diuresis herald a general improvement in systemic oxygen delivery and consumption which is of good prognostic value [26].

4. Microvascular Alterations

Sepsis-induced alterations of microcirculation are ubiquitous and are linked to both cardiovascular and renal failure [36]. Several studies [37–39] suggest that systemic vasodilation leads to reduced tissue oxygen delivery (DO₂), with progressive mitochondrial dysfunction/disruption and cytopathic hypoxia, which can cause organ failure [40]. In early phases of severe sepsis/septic shock, reduction in renal blood flow is associated to arterial hypotension, fluid shift, hypovolemia, and low cardiac output, that is, ischemic AKI (see above). Old experimental studies showed that renal blood flow was reduced in endotoxemic rats [41]. However, in fluid-resuscitated septic patients with AKI, cardiac output is normal or high and glomerular filtration rate can be low despite normal or high renal blood flow [26] (see Figure 2). This is because glomerular filtration rate is related to glomerular filtration pressure, which relies on the balance between afferent and efferent arteriolar tone. During sepsis glomerular efferent arteriola dilates more than afferent, thus reducing glomerular filtration pressure [42] (see Figure 2). Vasopressors, such norepinephrine, are employed to treat arterial hypotension during septic shock [3]. Besides increasing renal blood flow through a restored renal perfusion pressure, norepinephrine increases glomerular filtration rate acting on the afferent-efferent arteriolar tone, with a more intense vasoconstrictive effect on afferent arteriola [43]. In experimental models of septic shock in ewes, Langenberg at al. suggest that recovery from AKI has been associated to an increase in renal vascular resistance [44]. While a judicious use of vasopressors may contribute to restore glomerular filtration pressure and renal function, overzealous use of norepinephrine may also lead to afferent arteriolar vasoconstriction which reduces glomerular blood flow and filtration pressure. Moreover, the increased circulating level of catecholamines, which is part of the neurohormonal stress response to sepsis, results in sustained angiotensin II release, which can adversely affect renal perfusion [45]. All these effects contribute to cause and maintain renal dysfunction.

5. Organ “Crosstalk”

Type 3 cardiorenal syndrome is defined as AKI leading to acute cardiac dysfunction, that is, acute renocardiac syndrome [1]. Indeed, a marked left ventricular dilatation has been shown in experimental models of bilateral renal ischemia in mouse [46]. Three mechanisms may be involved, that is, fluid overload, myocardial inflammation, and reduced cytokines clearance.

During sepsis, renal hypoperfusion brings to progressive worsening fluid accumulation which can adversely impact on myocardial function, further decreasing cardiac output and renal blood flow, and initiating a vicious cycle between renal and cardiovascular dysfunction. Cardiac filling pressures increase, as does myocardial work load and oxygen consumption [27]. Sympathetic burden on cardiovascular system can be already high due to neurohormonal stress response to stress and use of vasopressors. Thus, acute cardiac dysfunction can precipitate, with further reduction in renal blood flow (see Figure 3).

The ischemic injury to kidneys may contribute to “long distance” organ damage in sepsis [47]. During ischemic renal injury in mouse, Kelly demonstrated increased myocardial levels of mRNA for TNF-alpha, IL-1, and ICAM-1, resulting in increased leukocyte infiltration and activation [46]. The same inflammatory damage could occur during sepsis-induced ischemic renal injury and lead to myocardial cells apoptosis and fibrosis [46], with progressive myocardial dysfunction. Indeed, sepsis-associated myocardial dysfunction can be prevented by anti-TNF-alpha antibodies or receptor antagonists [46] and cytokines removal by the mean of high volume hemofiltration has shown beneficial effects on cardiac function and hemodynamics in septic patients [48]. Knoet et al. showed the effect of TNF neutralization on renal function by a TNF-soluble receptor in the endotoxemic mice,
demonstrating the role of TNF in the early renal dysfunction (16 h) [49].

Finally, AKI itself can result in reduced clearance of systemic, circulating cytokines, which can worsen myocardial inflammatory injury. Expressions of cytokines and leukocyte adhesion molecules, and expression of membrane ion and water-channel protein in distant organs, including the cardiovascular systems, are altered during AKI [50].

### 6. Organ Inflammation

Type 5 cardiorenal syndrome is defined as a systemic insult which leads to concomitant renal and cardiac dysfunction [1]. An inflammatory pathogenesis can be a common key feature for both the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction [47, 51]. In a prospective observational study on 1836 hospitalized patients with community-acquired pneumonia, Murugan et al. demonstrated that renal injury and AKI associated to pneumonia recognize an inflammatory pathogenesis [52]. In this paper, outcome of renal injured patients was strictly related to IL-6 plasma concentration [52]. Endotoxin mediated release of TNF-α may affect simultaneously kidneys and cardiovascular system [53]. In the endotoxemic mice, Knutek et al. suggested that TNF-alpha can be also released by glomerular mesangial cells in response to Gram-negative endotoxin and act promoting leukocyte migration and activation in renal tissue, thus inducing septic AKI [49]. In an experimental model of cultured human proximal tubular cells, Jo et al. demonstrated that endotoxin, TNF-α and other pro-inflammatory cytokines induced apoptosis of renal tubular cells [54].

Inflammation has a well-defined role in inducing hypotension in septic patients [55]. Prolinflammatory cytokines, such as TNF-α, IL-1 and IL-6, may also induce myocardial inhibition [28–30]. Sepsis-induced release of nitric oxide and increased production of peroxynitrite also depress myocardial function. Tavernier et al. studied contractile function of cardiac myocytes isolated 12 h after induction of endotoxemia in rats. Authors demonstrated that cardiomyocytes from LPS-injected rats had depressed twitch shortening compared with control cells and that contractile depression was unaffected by inhibitors of nitric oxide synthase [56]. Moreover, in a retrospective analysis of human autopic specimens, Kooy et al. demonstrated the formation of peroxynitrite within the myocardium during sepsis, suggesting a role for peroxynitrite in inflammation-associated myocardial dysfunction [57]. On the other hand, renal hypoperfusion during sepsis-induced low cardiac output state leads to myocardial inflammation, apoptosis, and fibrosis (see above) [46].

### 7. Changes in Microvascular Permeability

Sepsis induced inflammatory response causes diffuse alteration in microcirculation [58]. Microcirculatory dysfunction contributes to altered tissue perfusion and oxygen delivery/consumption, thus contributing to septic shock and renal failure, that is, type 5 CRS [2]. Enhanced endothelial expression of leukocyte adhesion molecules and alteration of endothelial cells contacts can increase microvascular permeability, thus leading to extravascular fluid shift, fluid overload, hypovolemia, reduced venous return, and low cardiac output. Interstitial edema further reduces oxygen delivery to tissues, and fluid overload is an independent risk factor for mortality among septic patients with AKI [59]. At renal level, increased expression of adhesion molecules is associated to enhanced leukocytes migration, which may lead to endothelial cells injury and detachment, as shown by Paller during experimental renal ischemic injury in rats [60]. Altered glomerular permeability results in microalbuminuria [61].

Glycocalix is a thin (0.5–1.2 μm) molecular structure which lies beneath capillary endothelial cells and regulates capillary flow, leukocytes adhesion and migration, platelets adhesion and coagulation [62]. It is important in regulating capillary permeability. Several studies suggest that glycocalix disruption may contribute to increased permeability, both in systemic and renal microcirculation [63, 64], increasing leukostasis, microthrombosis, fluid shift, and interstitial edema. This leads to reduced oxygen delivery to tissues and organ failure [65].

### 8. Clinical Features

Septic cardiorenal syndrome is a clinical diagnosis. Its definition implies concomitant presence of acute hemodynamic and renal dysfunction in a patient with sepsis. Sepsis is defined by two or more signs among tachycardia, tachypnea, leukocytosis/leukopenia, and fever/hypothermia [3]. In severe sepsis one acute organ dysfunction is present, usually cardiovascular or renal. Arterial hypotension, an arterial systolic pressure below 95 mmHg, or 40 mmHg below the usual in previously hypertensive patients, is typically observed when hemodynamic dysfunction becomes manifest [3]. Myocardial dysfunction may be present as well, with reduced myocardial contractility and left ventricular ejection fraction [66]. Serum cardiac troponins and B-type natriuretic peptide may be elevated as they are sensitive and specific biomarkers of myocardial damage [67]. As suggested by Ammann et al.,
in septic, critically ill patients, serum troponin I levels may increase in absence of coronary artery disease, as a marker of myocardial dysfunction, and its levels correlate with mortality rates [68, 69]. However, when AKI is present, serum troponin may be elevated due to underlying renal dysfunction [70], as demonstrated by Musso and Colleagues in patients with chronic renal failure [71].

Typically, reduced urine output and increased serum creatinine are considered as clinical signs of acute renal failure in clinical practice [72], and they were included in RIFLE criteria [6, 7]. However, serum creatinine lacks of sensitivity since its plasma levels rise only after half of the renal function is lost [73]. Alternative biomarkers for AKI include serum interleukin-18 and urinary kidney injury molecule-1, cystatin-C, and beta-2 microglobulin [74]. In an observational cohort study, Soni et al. demonstrated that neutrophil gelatinase associated lipocartin (NGAL) acted as a sensitive biomarker for AKI, particularly for septic AKI [72]. In a series of 143 critically ill children, serum NGAL was a sensitive marker for AKI during systemic inflammatory response syndrome (SIRS) and septic shock [75]. Its plasma level correlated with severity of the syndrome and showed some specificity for septic shock [75]. Recently, Bagshaw et al., in a prospective observational study, demonstrated that patients with septic AKI had higher levels of plasma and urine NGAL compared to those with nonseptic AKI [76]. Interestingly, NGAL, with interleukin-1 receptor antagonist and protein C, was recently included among plasma biomarkers which could allow an early diagnosis of septic shock and multiple organ failure in patients admitted to emergency department with suspected sepsis [77].

9. Treatment

Removal of infective source, antibiotic therapy and supportive care are all indicated in presence of sepsis-associated cardiovascular and renal dysfunction [3]. Early hemodynamic optimization was efficacious in reducing mortality among critically ill septic patients [34]. Fluids are administered to restore intravascular volume and vasopressors or inotropic drugs are infused to restore systemic vasodilation and myocardial depression. Their use should be targeted to specific and clinical end points, such as mean arterial pressure or central venous oxygen saturation [78]. Increased venous return and increased myocardial contractility lead to increased cardiac output. This may contribute to improved renal blood perfusion and glomerular filtration, thus restoring urinary output [79]. Loop diuretics, such furosemide, are often used to increase and/or maintain urinary output during septic AKI, but their efficacy has been questioned and their use may be detrimental on renal function [76]. If oliguria is present, fluid administration should be judicious as volume overload and tissue edema may develop, contributing to impaired lung function and tissue oxygenation [79]. Once systemic cardiovascular optimization has been obtained, a shift towards more restrictive fluid administration strategies has been advocated to reduce AKI associated complications [76]. When renal function is persistently reduced despite hemodynamic optimization, continuous renal replacement therapy (CRRT) is indicated [80]. Worsening serum creatinine levels, volume overload, metabolic acidosis, and electrolytic alterations usually mandate CRRT. CRRT, and particularly high volume venovenous hemofiltration, may also modulate inflammatory response during sepsis, acting through cytokine removal or adsorption, even though the exact mechanism is still debated [81]. However, definite evidence of CRRT for nonrenal indications is still lacking, venovenous hemofiltration can improve hemodynamics and revert sepsis-associated hypotension [82]. Thus, in patients with septic cardiorenal syndrome, CRRT may not be only supportive, but also contribute to reverse common causative factors.

10. Conclusions

Cardiorenal syndrome is common among patients with severe sepsis and septic shock. Pathogenesis is related to multiple factors affecting both the heart and kidneys, including shock related renal hypoperfusion, systemic and intrarenal vasodilation, ubiquitous inflammatory injury to tissues, endothelial dysfunction, and altered capillary permeability. Injured kidneys can further impair myocardial function, thus contributing to maintain shock and organ hypoperfusion. Early and targeted optimization of hemodynamics is indicated to reverse systemic hypotension and to restore urinary output. In case of persistent renal impairment, venousous hemofiltration may be used to remove cytokines and restore renal function.

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