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REVIEW

Physiopathology of acute renal failure during sepsis☆

T. Regueira[a,*], M. Andresen[a], M. Mercado[a], P. Downey[b]

[a] *Departamento de Medicina Intensiva, Hospital Clínico Universidad Católica de Chile, Pontificia Universidad Católica de Chile, Santiago, Chile*
[b] *Departamento de Nefrología, Hospital Clínico Universidad Católica de Chile, Pontificia Universidad Católica de Chile, Santiago, Chile*

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Abstract Acute renal failure (ARF) is an independent risk factor associated with increased mortality during sepsis. Recent consensus definitions have allowed the standardization of research on the subject. The understanding of the physiopathology of ARF during sepsis is limited by the scarcity of histological studies and the inability to measure renal microcirculatory flows. Historically, ARF during sepsis has been considered to be a consequence of diminished renal blood flow (RBF). Indeed, in early stages of sepsis or in sepsis associated to cardiogenic shock, RBF may decrease. However, recent studies have shown that in resuscitated sepsis, in which cardiac output is characteristically normal or even elevated and there is systemic vasodilatation, RBF is normal or even increased, with no associated histological evidence of significant tubular necrosis. Thus, other factors may participate in the genesis of ARF in sepsis. These include apoptosis, glomerular and medullary microcirculatory disorders, cell changes in response to the pro-inflammatory cascade characteristic of sepsis, oxidative stress, mitochondrial dysfunction and damage induced by mechanical ventilation, among others. Sepsis-associated ARF treatment is supportive. In general, renal replacement therapies can be grouped as intermittent or continuous, and as those whose primary objective is the replacement of impaired renal function, versus those whose main objective is to secure hemodynamic stability through the clearing of pro-inflammatory mediators.

PALABRAS CLAVE
Sepsis;
Insuficiencia renal aguda;
Flujo sanguíneo renal

Fisiopatología de la insuficiencia renal aguda durante la sepsis

Resumen La insuficiencia renal aguda (IRA) es un factor de riesgo independiente asociado a mayor mortalidad durante la sepsis. Definiciones de consenso recientes han permitido estandarizar los trabajos de investigación en el tema. La comprensión de la fisiopatología de la IRA durante la sepsis está limitada por la escasez de estudios histológicos y por la

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* Corresponding author.
E-mail address: regueira@med.puc.cl (T. Regueira).

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imposibilidad de medir los flujos microcirculatorios renales. Históricamente se ha considerado a la IRA séptica como una patología dependiente de la caída del flujo sanguíneo renal (FSR). Efectivamente, en las etapas precoces de la sepsis o en la sepsis acompañada de shock cardiogénico existe compromiso del FSR; sin embargo, estudios recientes han demostrado que en la sepsis reanimada, aquella en que característicamente se observa un gasto cardiaco normal o alto y vasodilatación sistémica, el FSR es normal o incluso aumentado y no existe evidencia histológica significativa de necrosis tubular. Otros factores, distintos al puramente hemodinámico, participan en la génesis de la IRA en la sepsis. Entre éstos están la apoptosis celular, los trastornos microcirculatorios glomerulares y medulares, los cambios celulares en respuestas a la cascada proinflamatoria propia de la sepsis, el estrés oxidativo, la disfunción mitocondrial y el daño a distancia inducido por ventilación mecánica, entre otros. En la actualidad, el tratamiento de la IRA en la sepsis es de soporte. En general, las terapias de reemplazo renal pueden ser clasificadas como intermitentes o continuas, y en las que buscan primariamente el reemplazo de la función renal deteriorada, frente a aquellas cuyo objetivo principal es lograr la estabilidad hemodinámica de los pacientes mediante la remoción de mediadores proinflamatorios.

Epidemiology

The incidence of acute renal failure (ARF) in critical patients is variable, depending on the definition used and the population studied, but ranges from 30 to 50%.[1] Sepsis and its most severe presentation, septic shock, are the main causes of ARF in the Intensive Care Unit (ICU), accounting for up to 50% of all cases.[2] Mortality due to sepsis remains high, particularly when associated to organ dysfunction such as ARF (with mortality rates of 20–35%) or in the presence of hemodynamic alterations (mean mortality 60%). The development of ARF during sepsis is an independent risk factor associated to increased patient mortality[2]; in this context, the FRAMI study, involving 43 Spanish ICUs, showed the appearance of ARF in critical patients to be independently associated to increased mortality, with an odds ratio (OR) of 2.51.[3]

Definition

Until recently there was no clear consensus-based definition of ARF in sepsis. The ADQI (Acute Dialysis Quality Initiative) group has proposed a consensus-based diagnostic classification that has been favorably viewed by clinicians, and has made it possible to standardize research work in this field.[4] The mentioned classification is known as the RIFLE (in reference to Risk, Injury, Failure, Loss, and End-stage renal failure) (Table 1). Patients are classified according to the loss of glomerular filtration (GF) (with respect to the baseline reference of each patient) and/or urinary flow (UF) into 5 categories (selecting the criterion yielding the poorest classification): risk (R), injury (I), failure (F), loss (L) or end-stage renal failure (E). ARF in sepsis is diagnosed in all patients meeting the criteria of sepsis,[5] meeting some of the RIFLE criteria, and lacking other conditions or causes capable of accounting for ARF, such as the use of contrast media or nephrotoxic drugs.

The RIFLE classification has been validated by a number of studies. In a study involving 20,126 patients admitted to a university hospital, 10%, 5% and 3.5% of the subjects reached the maximum R, I and F scores in the RIFLE classification, respectively. Mortality among the patients increased linearly with the severity of the RIFLE score, making it possible to independently predict mortality.[6] Another study involving 41,972 patients admitted to the ICU reported an ARF incidence of 35.8%. The mortality in the group without ARF was 8.4%, versus 20.9%, 45.6% and 56.8% in those with class R, I and F acute renal failure, respectively. The presence of ARF of any category was found to be an independent mortality risk factor.

With the purpose of improving sensitivity, the RIFLE criteria were modified by the Acute Kidney Injury Network (AKIN) group, which defined ARF as an increase in serum creatinine of $\geq$0.3 mg/dl or a percentage increase of $\geq$1.5 times from baseline as recorded in the previous 48 h (Table 2).[7] Urine output as a criterion of ARF was maintained, though the glomerular filtration rate and RIFLE L and E scores were excluded. AKIN, in contrast to RIFLE, requires two creatinine measurements spaced 48 h apart in order to establish a diagnosis of ARF.

Some authors have compared RIFLE versus AKIN in patients subjected to heart surgery[8] or admitted to the ICU.[9] In general, mortality is comparable with both methods and tends to increase with the severity of ARF–thus confirming that acute renal damage is correlated to patient mortality.

Pathogenesis

The study of the mechanisms involved in the development of ARF in sepsis is limited by the few histological studies in humans, due to the risk involved in the process and its frequently irreversible nature, and by the impossibility of measuring renal microcirculatory flow values.

Renal blood flow in sepsis

The classical position in septic patients is that the principal mechanism underlying ARF is ischemia or hypoperfusion–suggesting that the decrease in renal blood flow (RBF) and renal vasoconstriction are the characteristic events of sepsis. Furthermore, the main interventions for the management of ARF in sepsis have been volume replacement in already resuscitated patients,[10] and the use of renal