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PHYSIOPATHOLOGY OF ACUTE RENAL FAILURE. NEW CLUES FOR AN OLD DILEMMA

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SUMMARY

Acute renal failure (ARF) is the term used to describe the sustained and abrupt reduction of the glomerular filtration, which causes the retention of waste products that come from the metabolism. Normally, the mechanisms potentially involved in ARF are divided into: pre-renal, parenchymatous, and post-renal. Regarding the etiology of the parenchymatous ARF, it would seem to be the sum of multiple pathogenic variables such as: tubular necrosis and apoptosis, alteration of the filtration barrier, retrodifusion of glomerular filtration, intrarenal vasoconstriction, contraction of the mesangium, intratubular obstruction, intersticial swelling, activation of proteolytic enzymes, and so on. Because of the above exposed data, only a multicausal perspective would seem to be adequate to understand and solve this syndrome.

KEY WORDS: Acute renal failure, glomerular filtration

RESUMEN

Insuficiencia renal aguda (IRA) es el término con el cual se designa a la reducción abrupta y sostenida del filtrado glomerular, de la cual resulta la retención de productos de desecho del metabolismo corporal. Clásicamente se dividen los mecanismos de la IRA en pre-renal, parenquimatoso, y obstructivo. En el caso de la IRA parenquimatosa, ésta pareciera ser el resultado de la sumatoria de las múltiples variables: necrosis y apoptosis tubular, alteración de la barrera de filtración, retrodifusión del filtrado glomerular, vasoconstricción intra-renal, contracción del mesangio, obstrucción intratubular, inflamación intersticial, activación de enzimas proteolíticas, entre otros. Por este motivo se postula que sólo una mirada de perspectiva multicausal de este síndrome pareciera ser la estrategia adecuada para conseguir su entendimiento cabal y tendiente a la resolución del mismo.

PALABRAS CLAVE: Insuficiencia renal aguda, filtrado glomerular

INTRODUCTION

Acute renal failure (ARF) is the term used to describe the sustained and abrupt reduction of the glomerular filtration, which causes the retention of waste products that come from the metabolism [1-3].

Although currently a universal definition for this syndrome has not been found, it is reasonable to take as a parameter for its detection, the documentation of a sustained and acute increase of 0.5 mg/dl in basal serum creatinine, if it is lower than 2,5 mg/dl, or an increase higher than 20%, if its basal value is higher than 2,5 mg/dl [1,2,4-].

Normally, the mechanisms potentially involved in ARF are divided into:

1. Fall of the renal flow preserving the integrity of the parenchyma (pre-renal ARF) [5-9].

2. Acute renal parenchymatous damage (intrinsec ARF) [10-14].

3. Urinary flow obstruction (post renal ARF) [15-16].

4. Mixed[15,17-18].

Regarding the etiology of the parenchymatous ARF, after more than half a century of research a central physiopathologycal mechanism has not been found, which would seem to be the sum of the multiple pathogenic variables displayed in such condition. Below we will discuss each one of these variables we know about thanks to experimental models (based on the use of ischemic or toxic agents) carried out mainly on rodents:

a) Tubular necrosis: any of the renal damaging agents can lead to the death of the tubular cells due to damage of at least one of its constitutive elements: cellular membrane, lysosomes, etc causing the condition known as *acute tubular necrosis* (ATN). However, the number of necrotic cells is not enough to justify renal failure per se which is characteristic of this syndrome [10-14].

b) Tubular Apoptosis: In recent years, some authors have stressed the importance not only of the induction of tubular necrosis inducing agents in the physiopathology of ARF, but also of the phenomenon which prematurely activates the usual programmed cellular death mechanism or apoptosis, thus adding the concept of *cellular apoptosis* to the typical ATN [15].

c) Alteration of the filtration barrier: A reduction in the length and density has been documented at the level of the endothelial pores of the glomerulus [19-21].

d) Retrodifusion of glomerular filtration: Another of the mechanisms which participates in the decrease of the renal function is the retrodifusion of glomerular filtration as a result of the alteration of the Starling´s forces around the proximal tubules. Therefore, most of the initially filtrated substances are reabsorved returning immediately to the vascular compartment, thus making the filtration ineffective [16,22].

e) Intrarenal vasoconstriction: This mechanism is to some extent responsible for the decrease of glomerular filtration characteristic of the parenchymatous ARF, but it is not its main cause since the magnitude of the decrease is lower than the filtration one, and even re-establishing the renal perfusion is usually not only accompanied by the persistance of the decrease in glomerular filtration but also of a more serious damage [23-28].

f) Contraction of the mesangium: Mesangial cells are contracted generating a reduction of the Kf (ultrafiltration coefficient), which helps reducing the filtration surface [29].

g) Disbalance between vasoconstrictor and vasodilator substances: The arteriolar vasoconstriction and mesangial contraction mechanisms already mentioned are stimulated by a local of vasoconstrictor substances (angiotensin II, platelet activating factor (PAF), adenosine, endothelin 1,A2 thromboxane, etc) and a reduction of the vasodilators (prostaglandine E2, nitric oxide, etc) which occurs during ARF [23-28, 30].

h) Intratubular obstruction: In parenchymatous ARF, the tubular cells redistribute their integrins (adhesion molecules

of the cellular membrane) which move away from its usual position (capillary pole) and relocate in the apical pole. This phenomenon contributes to the intratubular obstruction phenomenon because the tubular cells, not so adhered now to the basal membrane, fall towards the tubular light where despite its integrins, they adhere among them, as well as to the apical face of those which are still adhered to the basal membrane. Generally the Tam-Horsfall tubular protein is added to this conglomerate, which increases the volume of these cellular plugs thus increasing its obstructive power [22].

i) Intersticial swelling: The inflammatory cells would be recruited at the renal intersticial level due to the local release of cytokines (e.g. alfa TNF, etc) via a hypoxic or toxic stimulus. Such infiltration would generate an edema and compromise of the local microcirculation [15].

j) Activation of proteolytic enzymes: Tissue ischemia leads to an increase in the levels of intracellular calcium, which would have a bad effect in the tubular cells. Intracellular calcium triggers the activation of enzymes which damage sub-cellular structures: For example, this is how calpain is activated, a protease which damages the tubular cytoskeleton. This observation has made some authors propose the use of calcium blockers in parenchymatous ARF[15].

k) Oxidative stress: The damaging agents which can produce parenchymatous ARF are also exciters of histotoxic metabolites derived from oxygen [31].

l) Tissue growth factors: Cellular damage stimulates several growth factors which contribute to the regeneration of necrotic tubular cells, even some of them, such as IGF or EGF have demonstrated its effectiveness when used exogenously in animal models of ARF. Nevertheless, the activity of some of these factors can contribute to the generation of excessive fibrosis during the repairing processes [32-33].

From what was discussed above we can obtain two main conclusions:

- **The three physiopathological mechanisms proposed to interpret the generation of an ARF: decreased flow, tissue damage and obstruction appear, to some extent, together in parenchymatous ARF.**
- **Definitely, a monocausal physiopathological model, as it was thought in the past century, cannot cause a complex phenomena such as acute renal failure [34-35]. Only a multicausal perspective would seem to be adequate to understand and solve this syndrome.**

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Acute renal failure is a syndrome which have been defined as a rapid (in hours or days) renal function reduction. Since this syndrome can be caused by several sort of diseases, there are many physiopathologic mechanisms involved in its installation.

Several hypothesis have been proposed to explain acute renal failure etiology which are based on information obtained from experimental models: hemodynamic alterations (Kf reduction, vasoconstriction, medulla congestion), tubular injury (back-filtration, intratubular obstruction), and those proposed by molecular biology such as cytoskeleton damage or cellular polarity alteration[1-2]. The above review of Musso et al, lists the changes which have been described in these pilot studies.

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In this article Musso et al. deliver in an academic, clear and brief way an up to date of the physiopathologic mechanisms involved in acute renal failure development and perpetuation.

The delivered information is based on data which comes from basic and clinical reaserch.

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