

## EDITORIAL

# The renal effects of amino acids infusion

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## 1. Main text

Acute kidney injury (AKI) frequently affects surgical and critically ill patients [1–3]. AKI is associated with increased morbidity and mortality [4], as well as the requirement for additional resources [5]. Patients with severe AKI often need renal-replacement therapy (RRT), a treatment that doubles hospitalization costs [6] and has repercussions on long-term mortality and quality of life [7]. Until June 2024, the only proposed preventive measure for AKI was the adoption of the Kidney Disease: Improving Global Outcomes (KDIGO) bundle [8]. This editorial aims to summarize the evidence regarding the renal protective effect of amino acids (AA) and to highlight their possible mechanisms of action.

A large body of evidence shows that long-term high protein consumption has detrimental effects on kidney function, especially in patients with chronic kidney disease (CKD) [9]. Indeed, in these patients, since the 1950s, a low protein diet has been recommended due to the potentially detrimental effect of protein intake on long-term glomerular hyperfiltration, induced by modifications of glomerular vascular resistance, and progression to glomerulosclerosis [9]. However, the vasodilatory effect of protein on the afferent arteriole has not been taken into account in the field of acute medicine.

In 1973, a randomized trial, which included 53 AKI patients, showed, for the first time, that there was a beneficial effect of AA infusion, with a faster recovery from renal failure and improved survival [10]. Despite these provocative findings, the manuscript remained forgotten for almost fifty years, possibly due to its small sample size and other methodological issues.

Since then, animal studies have demonstrated that AA infusion can improve renal perfusion, increase glomerular filtration rate (GFR), and enhance renal cortical and medullary oxygena-

tion [11]. Additionally, early human pilot trials have suggested that a brief AA infusion (2–3 days) is safe, has positive effects on kidney function both short-term [12, 13] and long-term, and may also reduce mortality in critically ill patients [14].

Given the abovementioned promising effects, in June 2024, a large multi-national, randomized, double-blind, placebo-controlled trial [15] (PROTECTION trial) was published which investigated and confirmed the favorable effect of AA infusion in AKI prevention, by studying more than 3500 patients undergoing cardiac surgery with cardiopulmonary bypass. In this trial, postoperative AKI occurred in 474/1759 (26.9%) patients in the AA group vs. 555/1752 (31.7%) patients in the placebo group (relative risk, 0.85; 95% confidence interval (CI), 0.77 to 0.94,  $p = 0.002$ ). Furthermore, there was also a reduction in KDIGO stage 3 AKI (1.6% vs. 3.0%; relative risk, 0.56; 95% CI, 0.35 to 0.87) [16].

Since the pathophysiology of AKI remains complex and unclear, it is not easy to define all the AA mechanisms of action, but several hypotheses have been tested, involving both vascular and tubular events [17]. They have shown that AA induce the recruitment of renal functional reserve (RFR), increase renal blood flow, and improve renal oxygenation. In this regard, it is important for clinicians to understand the concept of RFR.

The GFR measures the amount of plasma ultrafiltrate passing from the glomerulus into Bowman's space within a specific timeframe. It is typically expressed in mL/min and it represents the most commonly used marker of kidney function [18]. Physicians usually consider the estimated measurement of GFR from creatinine serum concentration [19]. The ability of a normal kidney to increase its GFR in response to specific stimuli (such as a protein or AA load) is a tangible example

of the recruitment of RFR [20]. The concept of RFR was described for the first time in detail by Bosch *et al.* [20] in 1983, but many aspects and mechanisms still need to be clarified. Nonetheless, under physiological conditions, the kidneys function at around 75% of their maximum filtration capacity [21]. Hence, baseline GFR can increase by as much as 40% after being activated by a protein load (Fig. 1). When considering an AA load, it is estimated that the peak of GRF (also known as Stress GFR) is approximately obtained after 30 to 60 minutes [22].

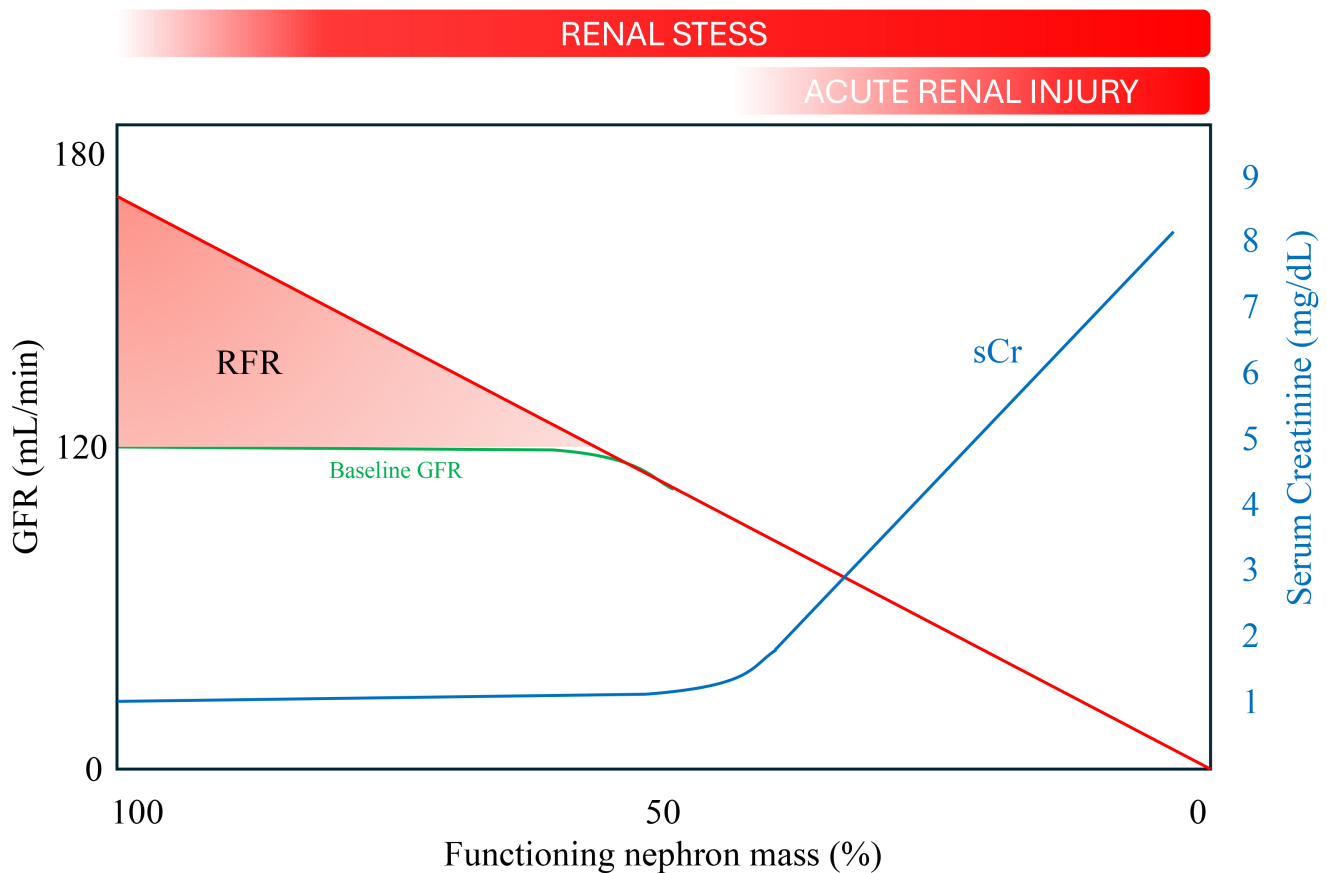
One of the first hypotheses formulated regarding the possible AA mechanisms of action on renal function was that the kidney could increase its activity directly through renal AA metabolism [23]. According to it, an increase in renal metabolism of AA would lead to vasodilation, as physiologically occurs in other body regions. Surprisingly, a similar vasodilatory effect on the afferent renal arterioles was observed even following the infusion of specific AA (*e.g.*, alpha-aminoisobutyric acid), which cannot be metabolized by the kidney, due to the lack of relevant enzymes [24].

What we know in addition today is that in the proximal tubule, AA and sodium are co-transported; thus, a higher protein or AA intake stimulates the absorption of sodium and chloride. As a consequence, the tubular fluid entering the macula densa has a lower salt concentration, leading to a

decreased signal for the initiation of tubuloglomerular feedback activation, as well as triggering a reduction of afferent arteriolar resistance [25]. Moreover, *glycine* seems to have a vasodilatory effect since it is a co-agonist to the N-methyl-D-aspartate (NMDA) receptors of the proximal tubule membranes [26]. All these aspects culminate in the improvement of renal perfusion and increased GFR.

Furthermore, several studies have demonstrated that the expression of renal cortical nitric oxide synthase [27] and cyclooxygenase-2 [28] correlates with dietary protein intake. The increased activity of these enzymes in the renal cortex leads to the production of nitric oxide and prostaglandins, which may facilitate the reduction in afferent arteriolar resistance through their vasodilatory effect. Additionally, *L-arginine* is a substrate for nitric oxide synthase, so its role could further enhance such pathways.

Not only paracrine but also endocrine factors could be involved. For example, both pancreatectomized animals and humans have a limited ability to recruit RFR [29, 30]. In this sense, glucagon could play a key role, functioning as a mediator in the AA-induced improvement of GFR [31]. Moreover, a high-protein diet has been also shown to acutely enlarge glomerular dimensions by stimulating the release of endothelial growth factor [32]. Again, these combined effects enhance renal perfusion and increase the GFR.



**FIGURE 1. Recruitment of renal functional reserve (RFR).** Typical increases in baseline glomerular filtration rate (GFR) occur, for example, in response to amino acids infusion. Changes in GFR may correspond to different serum creatinine (sCr) levels. Due to the renal ability to recruit RFR, acute kidney injury does not usually immediately result from initial renal stress. This figure was modified from Ronco *et al.* [22].

There are therefore many hypotheses regarding the possible mechanisms through which an AA load could increase GFR, finally recruiting RFR. Renal protection, however, must take into account a final fundamental aspect, which may be considered a mechanism of action or the common pathway effect, which is related to renal tissue oxygenation. In this regard, a recent animal study has shown that AA infusion improves both cortical and medullary oxygenation by more than 20% [11].

## 2. Conclusion

In conclusion, the role of AA in preserving kidney function under situations of pathophysiological renal stress is now a new open and interesting field of clinical research for the medical and scientific community. The PROTECTION trial [16] has, for the first time, identified an effective measure to prevent AKI, testing it in a relevant model of “planned AKI”, as is the case for cardiac surgery with cardiopulmonary bypass. Future research should focus on further different settings in order to generalize this significant (and potentially widely applicable) finding.

## ABBREVIATIONS

AA, amino acids; AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RFR, renal functional reserve; RRT, renal-replacement therapy.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## AUTHOR CONTRIBUTIONS

RL, GL and RB—designed the research study and wrote the first draft of the manuscript. MBR and AP—performed the research, analyzed the data, reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as the Editor-in-Chief of this journal.

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