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REVIEW

Reevaluating the lower limit of renal autoregulation: does one size fit all?

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Abstract

Renal autoregulation plays a crucial role in maintaining stable renal blood flow despite fluctuations in systemic arterial pressure. Existing paradigms, largely based on animal studies, suggest an autoregulation lower limit of 80 mmHg. However, the direct applicability of these findings to human physiology and clinical practice remains uncertain. Accordingly performed a comprehensive literature review to reevaluate the evidence about the lower limit of renal autoregulation. Animal and human studies were identified to assess the variability of the lower limit of renal autoregulation across different species, the influence of chronic conditions and acute interventions on this threshold, and the impact of blood pressure management strategies in critical care and anesthesia settings. We identified a broad range of lower limits of renal autoregulation, which were significantly influenced by experimental conditions and species differences. Human studies suggest that the autoregulation threshold might be lower than the traditionally mentioned 80 mmHg, with evidence indicating that renal function can be preserved at $<$80 mmHg mean arterial pressure levels. Moreover, clinical trials did not document a deterioration in renal function with blood pressure targets $<$80 mmHg. In individuals with diabetes, hypertension, or renal insufficiency the lower limit of autoregulation was increased. In humans there is insufficient evidence to state that 80 mmHg is the lower limit of renal autoregulation. This 80 mmHg threshold was also inconsistently identified in dog and mouse studies. Some human disease, however, may alter the limits of such autoregulation. Further research is warranted to define the value of the autoregulation threshold in human disease.

Keywords

Renal autoregulation; Tubuloglomerular feedback; Kidney; Blood pressure

1. Background

Renal autoregulation is a physiological phenomenon which plays a pivotal role in maintaining kidney function [1]. Renal autoregulation enables the kidneys to maintain a stable renal blood flow despite fluctuations in systemic arterial pressure [2]. This adaptive capacity is underpinned by a complex physiological response, which modulates vascular resistance in response to systemic arterial pressure changes [1]. It is believed that this autoregulatory mechanism operates effectively within specific systemic blood pressure limits [3]. Outside of these limits, renal blood flow changes according to systemic arterial pressure. These boundaries are conventionally defined within the range of 80 to 180 mmHg of renal perfusion pressure (RPP). Accordingly, ensuring systemic arterial pressure above the autoregulation's lower limit is considered important to preserve renal function, particularly in critical care and anesthesia settings [4].

Renal perfusion pressure is equal to Mean arterial pressure (MAP) − (central venous pressure + intra-abdominal pressure), making RPP lower than MAP, particularly under pathological conditions (Fig. 1) [5, 6].

Everyday clinical practice and guidelines recommendations already suggest a MAP target of 65 mmHg, which is outside the autoregulation range [7].

This literature review aims to scrutinize the foundational evidence behind the value of 80 mmHg as the lower limit of renal autoregulation. We seek to determine the consistency of this threshold across animal models and human studies, reevaluating the existing paradigms of what is considered an optimal lower limit for renal pressure management in clinical practice.

2. Methods

This narrative review was conducted following the Scale for the Assessment of Narrative Review Articles (SANRA) [8]. The review question was developed using the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research type) [9] framework: in animals and humans, is the

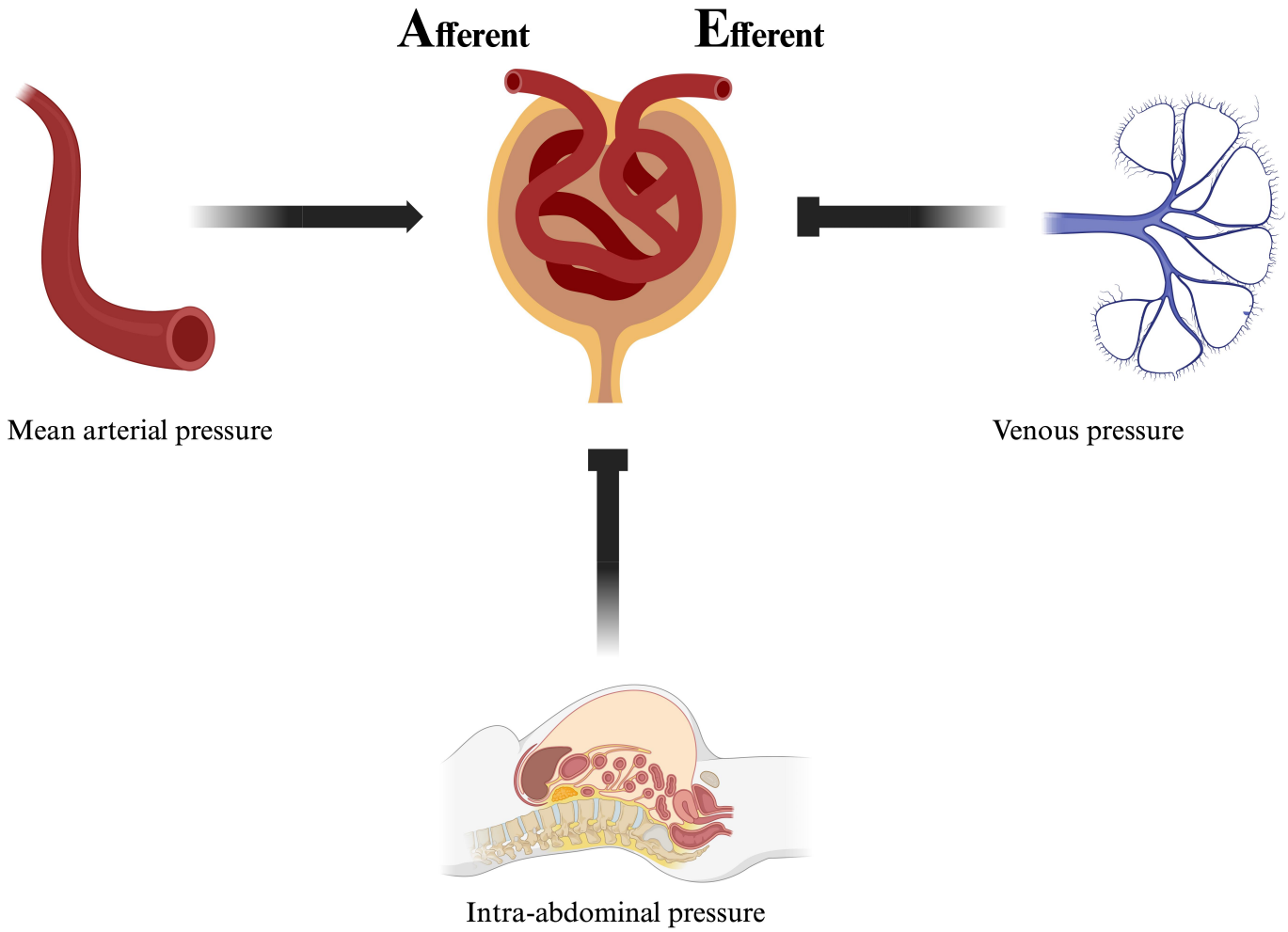

FIGURE 1. Hemodynamic interactions regulating renal flow. Perfusion pressure is directly derived from mean arterial pressure (MAP), which is opposed by intra-abdominal pressure and venous pressure, exerting opposing forces on incoming flow. This relationship is described by the equation: perfusion pressure = MAP − (intra-abdominal pressure + venous pressure). Pathological conditions such as ascites, which increase intra-abdominal pressure, or right ventricular dysfunction, which raises venous pressure, can decrease perfusion pressure. Flow enters through the afferent arteriole and exits via the efferent arteriole. The mechanisms that maintain constant flow despite a decrease in perfusion pressure include efferent arteriole constriction or afferent arteriole dilation. This ensures a stable flow despite the decrease in pressure. When compensatory mechanisms are maximized, flow decreases as pressure decreases: this marks the lower limit of renal autoregulation.

lower limit of 80 mmHg for renal autoregulation a constant value, or does it vary based on species differences, assessment techniques or underlying pathological conditions?

2.1 Eligibility criteria

We included studies published in peer-reviewed journals that analyzed the lower limit of renal autoregulation. Both animal studies and human studies, including observational and randomized controlled trials, were considered. No restrictions were applied regarding language, and studies from all geographical regions were eligible for inclusion. Research focusing on the effects of species differences, assessment techniques and pathological conditions on renal autoregulation were prioritized.

2.2 Search methods

We conducted a comprehensive search targeting both animal studies and human observational and randomized controlled trials. PubMed, Cochrane Library, and Embase were searched up to March 2024 to gather literature. Additionally, we identified further sources by manually reviewing the reference lists of key articles and consulting experts in the field. The search strategy employed relevant keywords, including “renal autoregulation”, “lower limit of autoregulation”, “perfusion pressure” and “blood flow”, combined with terms such as “kidney” and “renal”. No restrictions were applied concerning language or publication status, ensuring a thorough and unbiased capture of all relevant materials.

2.3 Study selection

Two authors independently screened all identified studies for eligibility using a standardized form based on predefined in-

clusion criteria. Any disagreement was resolved through discussion or by consulting a third author when necessary.

2.4 Qualitative analysis

A qualitative synthesis was conducted to integrate findings from the included studies [10]. The studies were divided into two main categories: those focusing on animal models and those involving human subjects. Key themes and patterns related to the lower limit of renal autoregulation were identified, with particular attention to species differences, assessment techniques, and the impact of pathological conditions. Divergent findings were carefully examined and contextualized within the broader literature to explore potential sources of variability. The synthesis aimed to provide a comprehensive narrative that highlights both consistent trends and areas of uncertainty in the current body of evidence.

3. Kidney autoregulation in animal studies

In his pioneering work with dog kidneys in 1946, Selkurt EE charted a pressure-flow relationship from 14 mmHg (the point of zero flow) to 120 mmHg, uncovering that renal blood flow (RBF) remained stable and largely unaffected by arterial blood pressure changes beyond the limit of 80 mmHg [11]. After this study, teaching about the concept and value of the lower limit of autoregulation has remained unaltered to this day.

Diverse methodologies are deployed to explore the lower limits of renal autoregulation in animal studies. In rodents, a common approach involves decreasing RPP by affixing and inflating a cuff around the abdominal aorta (or directly on the renal artery in larger animals) (Fig. 2).

While the conventional lower autoregulation limit is now recognized to be around 75 mmHg in dogs and 85 mmHg in rats [12], contrasting evidence exists. Arendshorst *et al.* [13], using electromagnetic flow meter recordings in anesthetized rats, determined the lower limit of renal autoregulation to fall between 95 and 105 mmHg. Persson *et al.* [14], directly measuring RBF in conscious dogs, found the lower limit to be 60 mmHg, which increased to 91 mmHg amidst sympathetic activation. Similarly, McNay *et al.* [15] identified the lower limit to be 100 mmHg in dogs, noting that autoregulatory mechanisms are influenced by the administration of vasoactive drugs. Turkstra *et al.* [16] observed that the lower limit varied calculating it at 78 mmHg, manually measuring it at 95 mmHg, and finding significant differences in hypertensive mice.

Further investigations by Silene L *et al.* [17], employing a sigmoid equation, pinpointed the lower limit at approximately 90 mmHg, which shifted to around 100 mmHg following furosemide infusion. Isolated, pump-perfused kidney evaluations indicated that the lower limit of autoregulation ranges from 90 to 120 mmHg in dogs and 80 to 100 mmHg in rats [18–21]. Utilizing Doppler to examine perfusion across different kidney regions introduced additional complexity, unveiling variable lower autoregulation limits with distinct characteristics in rats, dogs and rabbits [22–26].

In their systematic review including studies of sepsis and septic acute renal failure in which RBF was measured, Langenberg *et al.* [27] found that RBF findings in experimental sepsis depend on the model used. This regulation also possesses a dynamic aspect, as renal vascular resistance adapts to changes in RPP [1].

Our comprehension of the lower limit of renal autoregulation is deeply rooted in these animal experiments. Nevertheless, the variability observed across different animal models and investigative techniques complicates the straightforward application of these findings to human physiology [1, 4, 12].

4. Kidney autoregulation in human

Investigating the mechanisms of renal autoregulation in humans is notably challenging due to the absence of non-invasive techniques to directly measure renal blood flow [27].

Christensen *et al.* [28]. embarked on a series of randomized controlled trials (RCTs) to assess the effects of acute blood pressure reductions on renal function in both healthy subjects and those with underlying conditions. Their initial study evaluated the impact of blood pressure reduction on renal autoregulation in diabetic patients, administering clonidine to participants with and without renal insufficiency. Intriguingly, those without renal insufficiency maintained their renal function independently from blood pressure [28]. Conversely, a subset of patients with nephropathy exhibited a direct, passive relationship between glomerular filtration rate (GFR) and arterial blood pressure.

A subsequent double-blind RCT focusing on hypertensive patients with type 2 diabetes, who were not exhibiting clear signs of nephropathy and were under angiotensin II receptor blocker treatment, showed that GFR autoregulation remained intact during therapy with candesartan at 16 mg daily. This finding was significant even though some patients treated with candesartan had MAP values beneath the established autoregulation threshold of 80 mmHg [29].

In another randomized, single-blinded case-control study changes in GFR induced by acute MAP lowering revealed a wide variation in autoregulation concluding that “Our results suggest that the lower normal limit of the autoregulation of the kidney in normoalbuminuric nondiabetic human beings may be below the lower normal limit of autoregulation, that is, 80 mmHg found in animal studies” [30, 31].

Bourgoin *et al.* [32] conducted a randomized study on 28 septic shock patients, targeting MAP to 65 mmHg versus 85 mmHg (through elevated doses of norepinephrine). The study found no significant differences in renal function outcomes between the two groups [32]. Similarly, LeDoux *et al.* [33] observed no substantial variation in urine output when increasing MAP from 60 mmHg to 65, 75 and 85 mmHg in septic shock patients.

Asfar *et al.* [34], in their randomized trial involving patients with septic shock undergoing resuscitation, compared mean arterial pressure targets of either 80 to 85 mmHg versus 65 to 70 mmHg. They found no difference in the incidence of renal failure between the two pressure targets. However, in the subgroup with chronic hypertension, patients in the lower target group exhibited a significantly higher incidence of renal failure and required renal replacement therapy. This suggests that patients with hypertension might experience a rightward

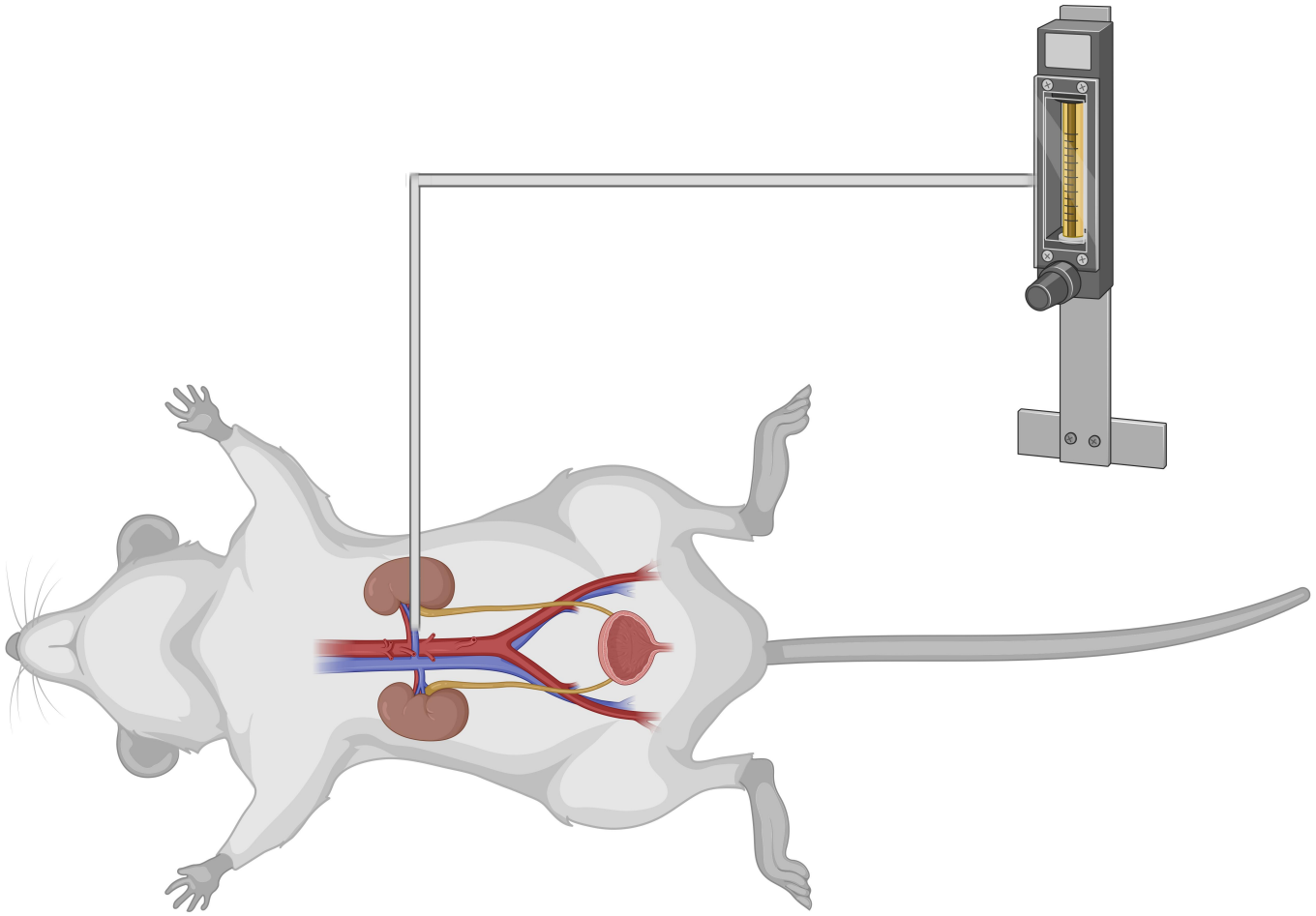

FIGURE 2. Assessment of autoregulation of blood flow in an animal model. A mouse, previously anesthetized, undergoes a surgical procedure to expose its left kidney via a surgical incision. The left renal artery is cannulated, and a flowmeter is attached to continuously measure the blood flow. Blood pressure variations are induced by progressively tightening a clamp on the suprarenal aorta.

shift in their range of autoregulation.

In another study, Lamontagne *et al*. [35] conducted a randomized clinical trial including 2600 patients aged 65 years or older with vasodilatory hypotension, randomized to permissive hypotension (65 mmHg) or standard care. The results showed that lower pressure exposure did not increase the risk of acute kidney injury, even in patients with chronic hypotension. Similarly, in cardiac surgery settings where pressure can be effectively maintained within a predefined range during cardiopulmonary bypass, studies comparing high versus low arterial pressure targets with primary outcomes of kidney injury found no difference in terms of acute kidney injury, glomerular filtration rate (GFR), or the need for renal replacement therapy [36, 37]. The same was observed in non-cardiac surgery settings [38].

Recent meta-analyses of RCTs showed that targeting blood pressure below the traditionally defined lower limit of autoregulation is not associated with a deterioration in renal function in intensive care and perioperative setting [39, 40]. Moreover, in prospective studies that assessed RPP and its correlation with renal damage, the observed pressures were <80 mmHg, irrespectively of the presence or absence of renal damage [41, 42].

These findings collectively suggest that the kidney's autoregulation threshold might indeed be lower than the traditionally cited 80 mmHg. This body of evidence underscores the complexity of renal autoregulation in humans and the necessity for a revised understanding that accounts for individual variability and underlying health conditions.

5. Effects of diseases on renal autoregulation

Renal autoregulation is a vital mechanism that ensures stable RBF and GFR despite fluctuations in systemic blood pressure. This ability to maintain homeostasis is crucial for preventing kidney damage. However, several metabolic diseases and systemic conditions—such as obesity, hypertension, diabetes (type 1 and type 2), metabolic and hormonal imbalances, anemia, and coagulopathies—can impair renal autoregulation.

Obesity has a profound impact on renal autoregulation due to the complex interplay between adipose tissue, the renin-angiotensin-aldosterone system (RAAS), and renal hemodynamics. Excess adipose tissue is associated with increased sympathetic nervous system activity, hyperfiltration, and elevated RAAS activity, all of which lead to impaired autoregula-

tion [43, 44]. This state of hyperfiltration and increased intraglomerular pressure eventually damages the glomerular filtration barrier, contributing to glomerulosclerosis [45]. Obesity-related inflammation, marked by elevated levels of proinflammatory cytokines such as Tumor necrosis factor (TNF-α) and Interleukin 6 (IL-6), also plays a role in disrupting renal blood flow regulation [46, 47]. Studies have shown that weight loss, particularly through bariatric surgery, can improve renal autoregulatory function by reducing RAAS activity and restoring normal sympathetic regulation [48].

Hypertension is both a major cause and a consequence of impaired renal autoregulation. Chronic high blood pressure leads to damage of the renal microvasculature, particularly the afferent arterioles, which are crucial for the myogenic response [49, 50]. Over time, this damage results in a rightward shift of the lower limit of autoregulation, meaning that the kidneys require higher perfusion pressures to maintain normal function [1].

Diabetes, severely impairs renal autoregulation. In diabetic nephropathy, hyperglycemia induces thickening of the glomerular basement membrane and expansion of the mesangial matrix, which leads to loss of the autoregulatory response [51]. Studies have shown that in diabetic patients, the afferent arteriole fails to constrict in response to increased blood pressure, resulting in glomerular hyperfiltration and progressive kidney damage [52].

Metabolic and hormonal imbalances, such as hyperlipidemia and hyperaldosteronism, also impair renal autoregulation. Hyperlipidemia promotes atherosclerosis in the renal vasculature, reducing blood flow and altering the myogenic response [53]. Meanwhile, hyperaldosteronism, often associated with metabolic syndrome, increases sodium retention and blood volume, contributing to elevated renal perfusion pressures that can overwhelm the autoregulatory mechanisms [54].

Anemia, common in chronic kidney disease, exacerbates the disruption of renal autoregulation through multiple mechanisms. Reduced oxygen delivery to the renal tissue triggers hypoxic injury, which in turn affects the myogenic and tubuloglomerular feedback mechanisms, leading to altered RBF [55].

Coagulopathies can also affect renal autoregulation, particularly in conditions associated with hypercoagulability or bleeding disorders. Hypercoagulable states, increase the risk of renal thrombosis, which can impair blood flow and reduce the kidneys' ability to regulate GFR [56].

Overall, common metabolic and systemic diseases such as obesity, hypertension, diabetes, metabolic and hormonal imbalances, anemia, and coagulopathies have profound effects on renal autoregulation. These conditions either shift the lower limit of autoregulation or impair the ability of the kidneys to regulate blood flow.

6. Further prospective: angiotensin II, amino acids and protective hemodynamics

Current therapies like angiotensin II (ANG II) and amino acids have the potential to modify the lower limit of renal autoregulation. The lower limit of autoregulation not only varies between individuals but also fluctuates within the same individual based on the treatments and conditions to which they are subjected [57]. Renal autoregulation appears governed by mechanisms like tubuloglomerular feedback and the myogenic response [58]. Tubuloglomerular feedback (TGF) and the myogenic response (MR) are the two primary mechanisms that regulate renal blood flow and GFR to maintain kidney function despite fluctuations in systemic blood pressure. TGF is a feedback mechanism that links the function of the nephron's tubular system to the afferent arteriole's resistance. It is primarily mediated by the macula densa, a group of specialized cells located at the junction of the thick ascending limb and the distal convoluted tubule. When the macula densa detects an increase in sodium chloride concentration in the tubular fluid, it signals the afferent arteriole to constrict, reducing glomerular filtration and renal blood flow to maintain a stable GFR [59–62]. Conversely, when sodium chloride (NaCl) concentration is low, the afferent arteriole dilates, increasing GFR [63].

The myogenic response is an intrinsic mechanism in vascular smooth muscle that reacts to changes in blood pressure. When the afferent arteriole experiences an increase in blood pressure, the smooth muscle cells constrict to prevent an excessive rise in glomerular pressure, thereby protecting the delicate glomerular capillaries [64–66]. The third mechanism (3M) response is primarily mediated by angiotensin, with pre- and post-glomerular vasoconstriction being a significant factor behind the hypotensive resetting of RBF autoregulation [67–70]. Cupples *et al.* [71] indicated that slow adaptations in autoregulation are disrupted by inhibiting ANG II receptors, highlighting the central role of ANG II. Reductions in RBF lasting for 20–30 minutes lead to a lowering of the baseline level of RBF, over which autoregulation is exercised. This adjustment of the autoregulatory set point is predominantly driven by pressure-dependent stimulation of the renin-angiotensin system, and is blocked by angiotensin-converting enzyme (ACE)-inhibition, ANG II receptor antagonism, or by stabilizing ANG II levels [71–79]. This mechanism suggests that externally administered angiotensin II could significantly lower the renal autoregulatory threshold, influencing clinical outcomes in the management of renal function under varying blood pressure conditions [80, 81].

Similarly, amino acids are responsible for an increase in renal blood flow through various mechanisms [82]. RBF and GFR increase for several hours after consuming a meal containing meat [83]. These responses are believed to result from elevated plasma amino acid levels, as comparable changes in renal hemodynamics are observed during the intravenous infusion of amino acids [84–87]. Various mechanisms have been proposed to explain this amino acid-stimulated hyperperfusion, including vasodilation of the afferent arterioles, stimulate glomerular functional reserve, effects on the macula densa, and sodium reabsorption (Fig. 3) [88, 89].

Therefore, regardless of pressure levels, amino acids can promote adequate flow even at low pressure levels, enhancing renal function and potentially modifying the dynamics of renal autoregulation. Furthermore, the need to tailor this target based on individual patient histories is apparent, underscoring the importance of a personalized approach in clinical practice.

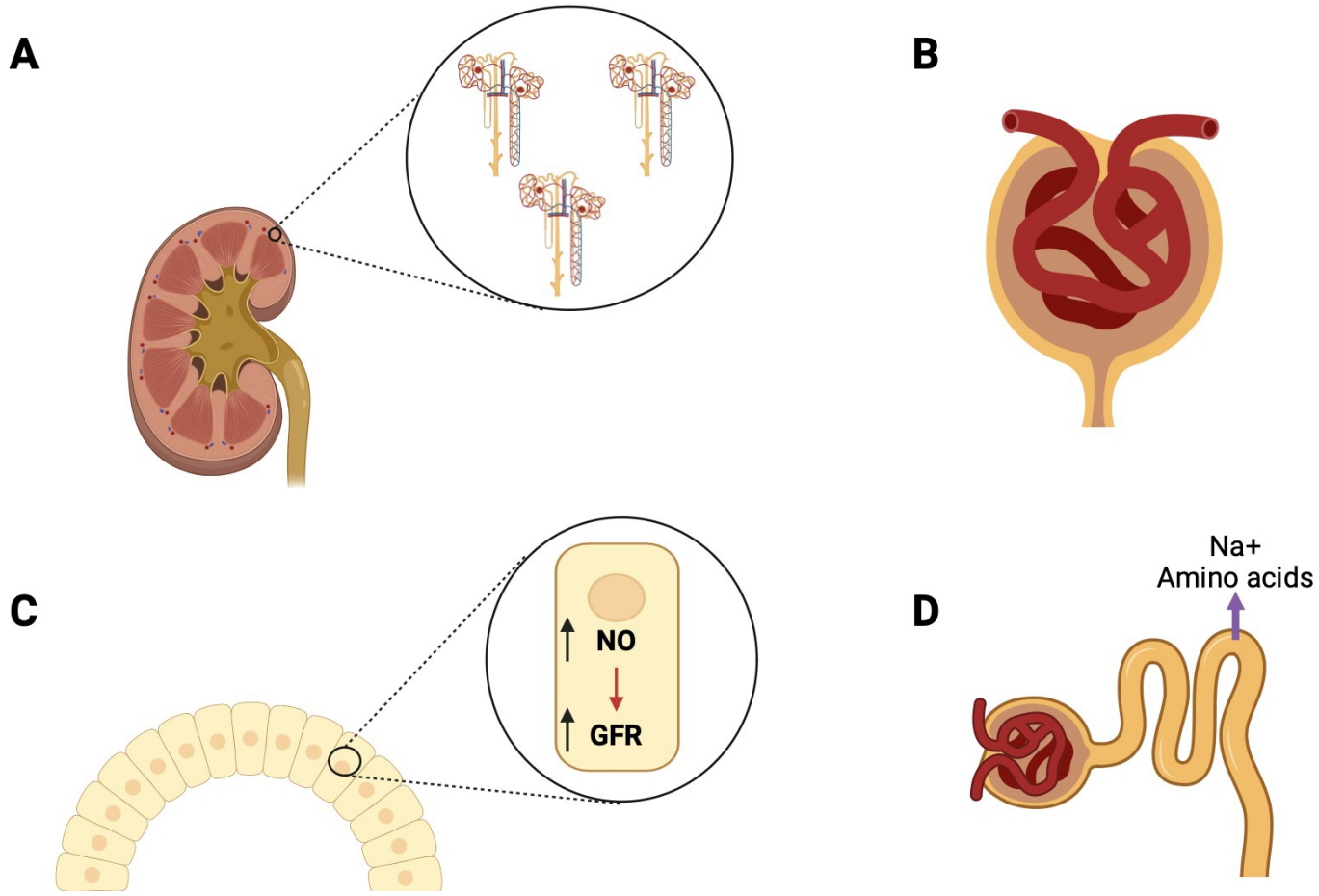

FIGURE 3. Mechanisms of amino acids induced glomerular filtration enhancement. (A) Amino acids activate normally silent cortical glomeruli, especially in the cortical region. (B) They cause vasodilation of the afferent arteriole, increasing blood flow. (C) Amino acids have a direct effect on the macula densa, stimulating the production of nitric oxide (NO) and thereby increasing the glomerular filtration rate (GFR). (D) Amino acids are co-transported with sodium via a sodium-amino acid transporter, leading to increased sodium reabsorption in the proximal tubule.

We previously introduced the term "protective hemodynamics" as a nuanced approach to hemodynamic management that emphasizes safeguarding blood flow rather than solely focusing on achieving target MAP values [39, 40]. This concept also critically considers the iatrogenic risks associated with vasopressor use [90], advocating for a more balanced and patient-centric approach to hemodynamic management [91]. Indeed, vasopressors which are commonly used to manage hypotension in critical care settings, can introduce several iatrogenic risks. Prolonged use or excessive doses of vasopressors such as norepinephrine can lead to excessive vasoconstriction, reducing blood flow to vital organs like the kidneys and intestines. This can result in ischemia, organ dysfunction, and increased risk of acute kidney injury [92, 93]. Additionally, vasopressors may impair microcirculatory blood flow, exacerbating tissue hypoxia despite improvements in systemic blood pressure [94].

7. Conclusions

In conclusion, the findings from this literature analysis suggest that the minimum level of renal autoregulation remains undefined. Results from animal studies cannot be straightforwardly applied to human physiology. While direct evidence pinpointing the minimum threshold of autoregulation in humans remains elusive, the collective data at our disposal suggest that this threshold likely falls below the conventionally selected 80 mmHg mark. Studies that explore renal autoregulation in diverse clinical scenarios, to better define and optimize blood pressure management strategies that safeguard renal function are needed.

AVAILABILITY OF DATA AND MATERIALS

The data used to support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

FD, GL and RL—designed the research study; MB, MC, YK, FR and FP—performed the research; FD, RL, MB, MC, FR, YK and FP—analyzed the data; FD and GL—wrote 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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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, and Yuki Kotani is serving as the Editorial Board member of this journal. We declare that Giovanni Landoni and Yuki Kotani had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to NB.

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