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Ultrafiltration Tolerance: A Phenotype That We Need to Recognize

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Abstract

Background: The evaluation and management of fluid balance are key challenges in critical care patients who require renal replacement therapies because cumulative fluid balance is an independent factor that increases morbidity and mortality in different clinical scenarios. ***Summary:*** One of the strategies when fluid overload is refractory to diuretics is extracorporeal fluid removal (i.e., net ultrafiltration [UF_{NET}] during kidney replacement therapy). However, problems with UF_{NET} without individualized assessment are cardiovascular events and intradialytic hypotension, events that contribute to decreasing organ perfusion and sympathetic stress. Therefore, we must consider and try to predict the best timing for the start of ultrafiltration and find the point where the patient is most tolerant to ultrafiltration, making a simile to the concept of fluid tolerance. ***Key Messages:*** UF_{NET} is a continuous and dynamic process, going through moments of tolerance and intolerance to ultrafiltration; as nephrologists, we must take the necessary measures to move through this period.

Introduction

The evaluation and management of fluid balance are key challenges in critical care patients who require renal replacement therapies. In the scenario of de-resuscitation, this fluid accumulation results from resuscitation, maintenance infusions, medications, nutrition and blood products, being accentuated if it is concomitant with acute kidney injury (AKI), and diminished urine output [1].

The cumulative fluid balance is an independent factor that increases mortality in clinical scenarios such as ARDS, septic shock, AKI and is also associated with prolonged mechanical ventilation, impaired recovery from AKI, impaired wound healing, abdominal compartment syndrome, and discharge to a healthcare facility [2–5]. One of the strategies when fluid overload is refractory to diuretics is extracorporeal fluid removal (i.e., net ultrafiltration [UF_{NET}] during kidney replacement therapy). Ultrafiltration has been used in the treatment of patients with fluid overload more than 70 years ago [6]. However, the prescription of UF_{NET} requires careful consideration of the fluid balance and overload, the total amount of fluid to be removed to achieve euvolemia, and the appropriate rate because rapid fluid removal through ultrafiltration involves the risk of iatrogenic hypotension, which has also been associated with adverse

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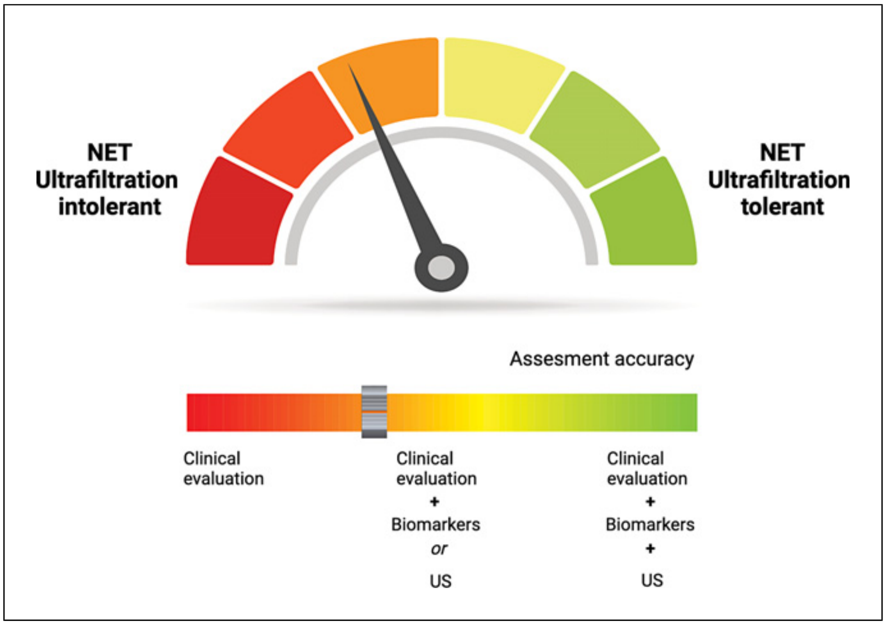

Fig. 1. Ultrafiltration tolerance continuum. The evaluation of UF_{NET} must be constant because during the session the patient may begin being tolerant to ultrafiltration and move to the extreme of intolerance to ultrafiltration, requiring modifications to avoid complications, so it should not be a dichotomous variable. Diagnostic precision should try to be as high as possible with the proposed tools, however, different scenarios and/or centers, we will not be able to use the 3 proposed tools affecting diagnostic accuracy.

outcomes [7–10]. Intradialytic hypotension complicates 17–70% of acute hemodialysis [11]. Currently, there is no consensus between intensivists and nephrologists regarding the maximal ultrafiltration rate considered safe, with a target removal variability per day between 0.5 and 2.0 L. In addition, there is a high variability between countries regarding the UF_{NET} rate (e.g., between 101 and 193 mL/h in European countries) [12, 13]. Concomitantly, a different approach while prescribing ultrafiltration was reported. Intensivists are more willing to incorporate hemodynamic monitoring and ultrasound, while nephrologists are more "reactive" with interventions to improve tolerance to ultrafiltration [12]. As critical care nephrologists, we must incorporate both experiences, trying to avoid complications in the de-resuscitation process. Therefore, individualized hemodynamic assessment together with a standard protocol becomes extremely necessary for safe and effective fluid removal in critical care patients.

One of the problems with UF_{NET} without individualized assessment are cardiovascular events and intradialytic hypotension, events that contribute to decreasing organ perfusion and sympathetic stress [14–16]. Cardiac output (CO) is not routinely monitored, and RRT hemodynamic monitoring is currently limited to intermittent noninvasive or invasive blood pressure, being an insensitive marker of decreased CO because intradialytic hypotension occurs only when CO is markedly decreased and when the vasoconstrictive reserve is exhausted [17–19].

Therefore, we must consider and try to predict the best timing for the start of ultrafiltration and find the point where the patient is most tolerant to ultrafiltration, making a simile to the concept of fluid tolerance (Fig. 1) [20]. Different approaches must be considered; a proposal would be the use of biomarkers, point-of-care ultrasound (POCUS), and evaluation of the clinical condition and context of the patient (Fig. 2). This multi-parametric evaluation is necessary because different mechanisms affect CO such as inflammation and redistribution of volume, myocardial injury, and sympathetic system changes secondary to neurological events, and the use of clinical evaluation only to diagnose hypervolemia does not predict hemodynamic tolerance [17, 21–24].

Biomarkers and Ultrafiltration Tolerance

The plasma refilling rate to the intravascular compartment is favored by the resulting rise in oncotic pressure. If the UF rate exceeds the refill rate, the reduction in preload induces a fall in stroke volume that predisposes to hemodynamic instability. Serum albumin is a good predictor of hypotension during dialysis [25]. In patients with hypoalbuminemia (<3 g/dL), the use of albumin before starting therapy showed a 74.2% reduction in hypotensive events [11]. In this line, albumin would have a fundamental role in the tolerance of ultrafiltration. When performing a therapy with only dialysis, ultrafiltration will remove water and sodium due to the sodium gradient generated between the plasma and the dialysate. On the other hand, when using convection, as in hemodiafiltration, albumin is concentrated

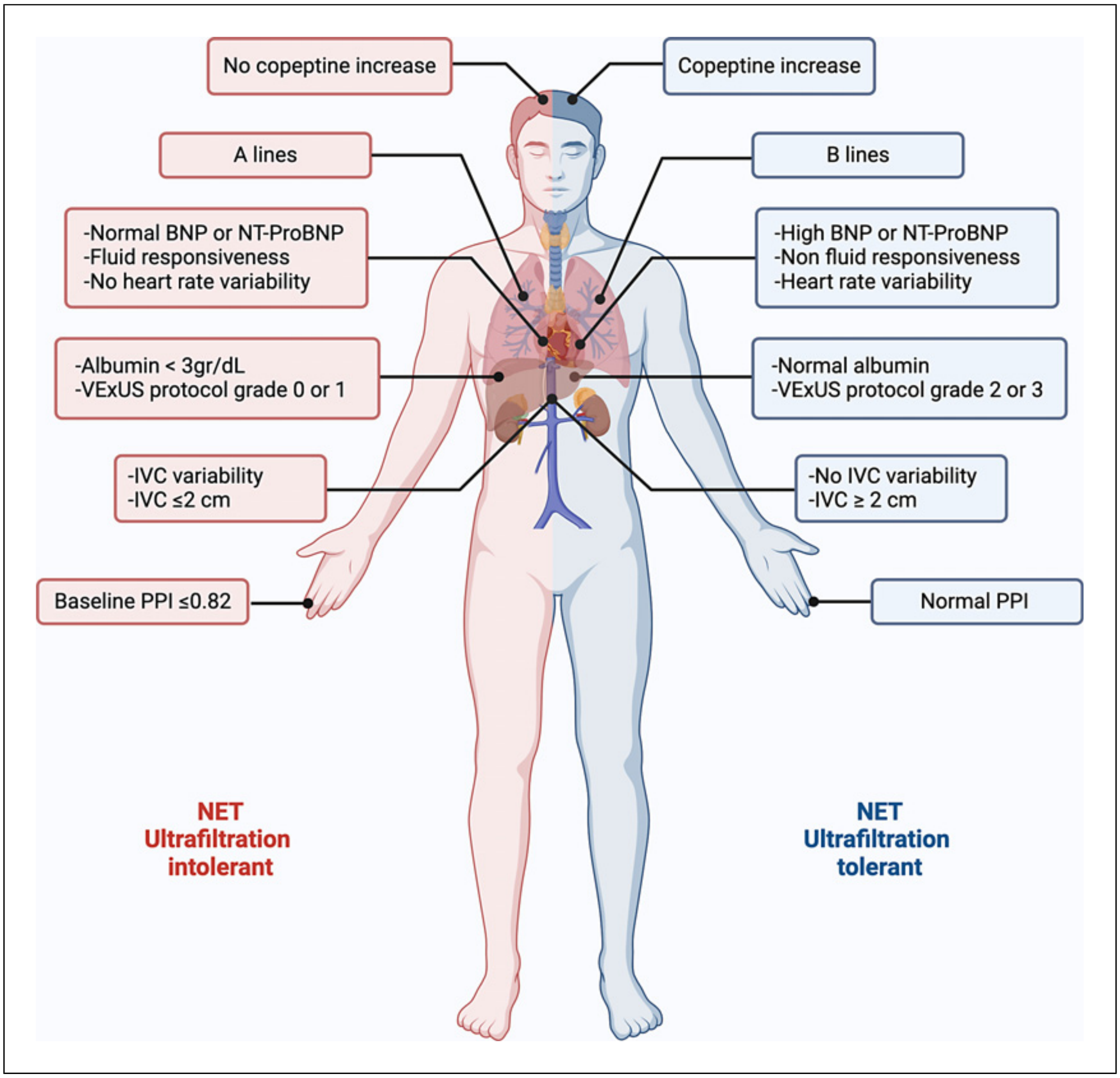

Fig. 2. Elements to define ultrafiltration tolerance. IVC, inferior vena cava; PPI, peripheral perfusion index.

on the blood side, favoring sodium retention "Gibbs-Donnan effect." This increase in osmolarity will facilitate refilling from the interstitial compartment [26, 27].

B-type natriuretic peptide (BNP) and NT-proBNP are cardiac biomarkers secreted by the ventricular cardiomyocytes in response to increased wall stress. The levels of this biomarker before weaning from mechanical ventilation can predict weaning failure and death [28, 29]. A protocol based on BNP-guided therapy results in a significantly more negative fluid balance during the weaning period with diuretics [30]. Elevated levels of pre-dialysis and post-dialysis BNP have been associated with overhydration in maintenance hemodialysis patients, and it was associated with less intradialytic systolic blood pressure decline and lower risk of intradialytic hypotension [31].

Hypocalcemia is common at the initiation of continuous renal replacement therapy (CRRT) and may increase the risk of CRRT-associated hypotension mainly due to its effects on systemic vasodilation and depression of left ventricular function. A post hoc analysis of the ATN trial showed that a serum-ionized calcium <1.02 mmol/L was associated with a significant increase in the risk of hypotension during CRRT [32].

Inflammation might also contribute to fluid overload by increasing capillary permeability, producing fluid extravasation, volume overload, and edema formation, a phenomenon called capillary leak syndrome. Angiopoietin-2 plays an important role in regulating the vascular barrier and is a marker of vascular permeability. Angiopoietin-2 correlates with endothelial injury, inflammation, glycocalyx shedding, fluid overload complications, and a higher chance of vasopressor requirement [33]. In another group, serum TNF-α and IL-1β were predictors of IDH [34].

Copeptin levels (a marker of arginine vasopressin) are found to rise during hemodialysis sessions accompanying ultrafiltration. The group of Korucu et al. [35] reported that patients with IDH had a significantly lower increase in copeptin levels throughout the hemodialysis session, suggesting that the response to an acute fall in arterial blood pressure is blunted in these patients, regardless of whether they maintained epinephrine and norepinephrine levels similar to the non-IDH group.

POCUS and Ultrafiltration Tolerance

POCUS is a noninvasive tool that allows us to perform hemodynamic monitoring in the late fluid removal stage after resuscitation and is an option to detect patients likely to tolerate UF_{NET}. The images to be obtained for a volumetric evaluation of congestion correspond to lung ultrasound, inferior vena cava (IVC), VExUS protocol, and echocardiographic estimation of stroke volume [36]. A multisegment and dynamic evaluation, taking into account variation over the respiratory/ventilatory cycle, is essential for a better prediction of tolerance and to understand the physiological process of the patient. Using only one option may limit the results [37].

An objective of POCUS is an assessment of fluid responsiveness (FR), defined as an increase of >10–15% in stroke volume or CO following fluid administration. Lack of FR may identify patients likely to tolerate fluid removal with renal replacement therapy [38]. Using fluid response predictors, such as an increase in the cardiac index after a passive leg raising, can predict intradialytic hypotension [39]. Other groups showed that a dynamic variation of IVC is a significant predictor of achieving the UF_{NET} target using different IVC variation cutoffs (e.g., <23% or <40%) and suggesting that patients with low IVC variability most likely have relative intravascular volume overload and have a higher likelihood of achieving the UF_{NET} [40, 41]. Incorporating lung ultrasound to detect pulmonary congestion with IVC variation allows for the identification of two profiles to predict the risk of IDH (patients with pulmonary congestion with or without intravascular depletion) [41]. Implementing these tools in patients with pulmonary congestion allows us to temporarily pause ultrafiltration when we observe an increase in IVC variability. This protocol has demonstrated early and more fluid removal in the ultrasound group, unlike just a clinical evaluation [42].

Clinical Assessment and Ultrafiltration Tolerance

An evaluation of the patient's global context and medical history is essential. Along with this, knowing if the triggering event is resolved or on the way to resolution, together with some tools, might help us predict the risk of IDH.

One of the mechanisms that generates IDH is autonomic dysfunction (a prevalent comorbidity in diabetic patients), leading to an inadequate sympathetic response to the hypovolemia developed during hemodialysis. Tolerance to fluid removal during hemodialysis depends on compensatory cardiovascular reflexes which need an intact autonomic nervous system. Thus, autonomic dysfunction has been considered an important risk factor for intradialytic hypotension [43, 44]. One method to evaluate the autonomic nervous system function is through heart rate variability because heart rate variability reflects the balance between sympathetic and parasympathetic nervous systems [45]. Different groups have shown that non-variability of heart rate during the session is a predictor of IDH, reflecting a state of an exhausted autonomic system, with a sympathetic system exerting its maximum effort to maintain arterial pressure and peripheral perfusion [46–48].

Peripheral perfusion index (PPI) is defined as "the ratio of pulsatile blood flow to the nonpulsatile blood flow." PPI reflects changes in peripheral vasomotor tone, with a median normal value of 1.4 arbitrary unit, and is measured from the photoelectric plethysmographic signal of the pulse oximeter. PPI has been reported to be a useful predictor of hypotension during continuous venovenous hemofiltration and intermittent hemodialysis when the baseline PPI is ≤0.82 arbitrary unit [49, 50].

Regarding measures widely used to evaluate the response to fluid (pulse pressure variation and stroke volume variation), experts mention its use as part of a general evaluation to define the start of de-resuscitation (absence of FR). However, less than 50% of intensivists/nephrologists in Europe use these variables to prescribe UF_{NET} [13, 51].

Another option to integrate and obtain information at the patient's bedside is the use of relative blood volume monitor (BVM) measurement, thus indirectly evaluating the possible discrepancy between the ultrafiltration rate and the refilling rate in real time [52]. The use of BVM dates back to the early 1990s when Crit-Line® technology was implemented to measure hematocrit changes during hemodialysis by connecting an additional monitor to the membrane inflow line set-up [53]. This technology has continued to evolve with biofeedback to optimize the ultrafiltration rate during the treatment automatically. When the rate of change in blood volume decreases between −3 and −6.5% per hour, it indicates a suitable compromise between a high ultrafiltration rate and the prevention of intradialytic symptoms. However, when the rate of change in blood volume is greater than −6.5% per hour, a higher risk for IDH exists [54].

A technical aspect of the BVM is the best place for the blood chamber sensor, awarding placement before administering fluids to reduce alteration of Hct value by any fluids blended with the blood. An elegant option is to place the Hct sensor chamber at the outflow lumen of the dual-lumen access catheter. This approach will improve the precision of the data [55]. Despite controversial results in patients on maintenance dialysis, this technology has reduced IDH episodes by 29% in patients undergoing UF_{NET} in the ICU, maintaining the balance between ultrafiltration and vascular refilling [56–58].

Conclusion

It is important to understand that the intravascular volume status in ICU is a moving target. As nephrologists, we must adapt and understand this process as a continuum, going through moments of tolerance and intolerance to ultrafiltration and taking the necessary measures to move through this period. These new tools will allow us to detect which phase our patients are in and thus adjust therapies to their needs.

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Conflict of Interest Statement

C.R. has received funding for lectures and been a consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioMérieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. G.R.-G. declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The authors alone are responsible for the content and writing of this article.

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Author Contributions

G.R.-G. designed the work and collected and analyzed the data. G.R.-G. and C.R. drafted the work or substantively revised it, and all authors read and approved the final manuscript.

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