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Co-Administration of Albumin and Furosemide in Acute Heart Failure with Diuretic Resistance

Coadministração de Albumina e Furosemida na Insuficiência Cardíaca Aguda com Resistência aos Diuréticos

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ABSTRACT

Acute heart failure is a frequent cause of hospital admission in Portugal, and has an increasing tendency given the aging population. Although most admissions for acute heart failure are caused by congestive conditions, not all patients have a congestive phenotype, reflecting the complexity of a process with multiple pathophysiological pathways. The use of diuretics, usually loop diuretics, is the mainstay of treatment for congestion. However, many patients develop resistance, thus constituting a challenge with no consensual solution to date, despite extensive debate over the years. Despite its frequent use in clinical practice, the co-administration of albumin and furosemide remains controversial in the management of patients with acute heart failure, hypoalbuminemia, and diuretic resistance. This review addresses the pathophysiological mechanisms of congestion in patients with acute heart failure and explores the theoretical basis that supports the co-administration of albumin and furosemide in this clinical context. It is intended to clarify the potential benefit of the combined approach in this specific population and identify possible gaps in the literature that could be the subject of future studies.
Keywords: Albumins; Diuretics; Drug Resistance; Furosemide; Heart Failure; Sodium Potassium Chloride Symporter Inhibitors

RESUMO

A insuficiência cardíaca aguda é uma causa frequente de internamento hospitalar em Portugal, com tendência a aumentar devido ao envelhecimento da população. Apesar de a maioria dos internamentos por insuficiência cardíaca aguda ser motivada por quadros congestivos, nem todos os doentes apresentam um fenótipo congestivo, o que reflecte a complexidade de um processo com múltiplas vias fisiopatológicas. A utilização de diuréticos, habitualmente diuréticos de ansa, constitui a base do tratamento da congestão. No entanto, muitos doentes desenvolvem resistência, constituindo assim um desafio sem solução consensual até à data, apesar do extenso debate ao longo dos anos. Apesar da sua utilização frequente na prática clínica, a coadministração de albumina e furosemida permanece controversa na gestão de doentes com insuficiência cardíaca aguda, hipoalbuminémia e resistência aos diuréticos. Esta revisão aborda os mecanismos fisiopatológicos da congestão nesses doentes e explora a base teórica que suporta a coadministração de albumina e furosemida no respectivo contexto clínico. Pretende-se clarificar o potencial benefício da estratégia combinada nesta população específica e identificar possíveis lacunas na literatura que possam ser alvo de estudos futuros.
Palavras-chave: Albuminas; Diuréticos; Furosemida; Inibidores de Simportadores de Cloreto de Sódio e Potássio; Insuficiência Cardíaca; Resistência a Medicamentos

INTRODUCTION

Acute heart failure (AHF) is a frequent cause of hospital admission in Portugal and represents a challenge in terms of therapeutic management.[1] With no prognostic impact, diuretic therapy including loop diuretics (LD) such as furosemide, is a cornerstone in decongestive therapy.[2] However, up to one third of patients with heart failure (HF) become resistant to diuretics, which is related to poor clinical outcomes.[3–5] In these cases, a combined therapeutic approach may prevent sodium reabsorption and promote water excretion.[6] This may include sodium and water restriction, increasing doses of diuretics and the sequential blockage of the nephron. Despite this combined approach, some patients remain congestive and become resistant to diuretic therapy, with progressive deterioration of their clinical condition and quality of life, particularly if they have hypoalbuminemia.[7] The underlying mechanisms behind diuretic resistance are incompletely understood.[8] So far, there is not enough evidence to support the generalized use of a furosemide and albumin combined approach in clinical practice. This article discusses the pathophysiological mechanisms of AHF with congestion and the potential role of albumin-furosemide co-administration to address diuretic resistance.

MATERIAL AND METHODS

The authors conducted a literature search in the PubMed/Medline and Cochrane databases for articles

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including the Medical Subject Headings (MeSH) terms 'heart failure', 'albumin', 'diuretics' and/or 'diuretic resistance'. The search included articles published from 1986 until September 2021. The methodological approach applied for the selection of articles to include in the main text is summarized in Fig. 1. An initial screening was independently conducted by two authors. Duplicates and titles that did not mention at least one of the MeSH terms were excluded. The same authors independently selected the abstracts for full text assessment if they included information focusing on albumin and furosemide co-administration regardless of the index disease. Documents that did not include information about HF and/or diuretic resistance or the co-administration of albumin and furosemide were considered irrelevant and excluded. From this selection, relevant articles were included in the main text.

RESULTS

Four hundred and ninety titles were selected from the database search and, based on their relevance, 91 titles were selected for abstract screening. A second selection excluded 34 records: two due to repetition and 32 due to irrelevance (Fig.1). From the 57 articles selected, 38 were literature reviews (1 - 7, 10 - 16, 44, 45, 48 - 50, 17 - 33, 35 - 37), five were prospective studies (9, 46, 38, 52, 54), six were retrospective studies (8, 51, 36, 39, 43, 55) and eight

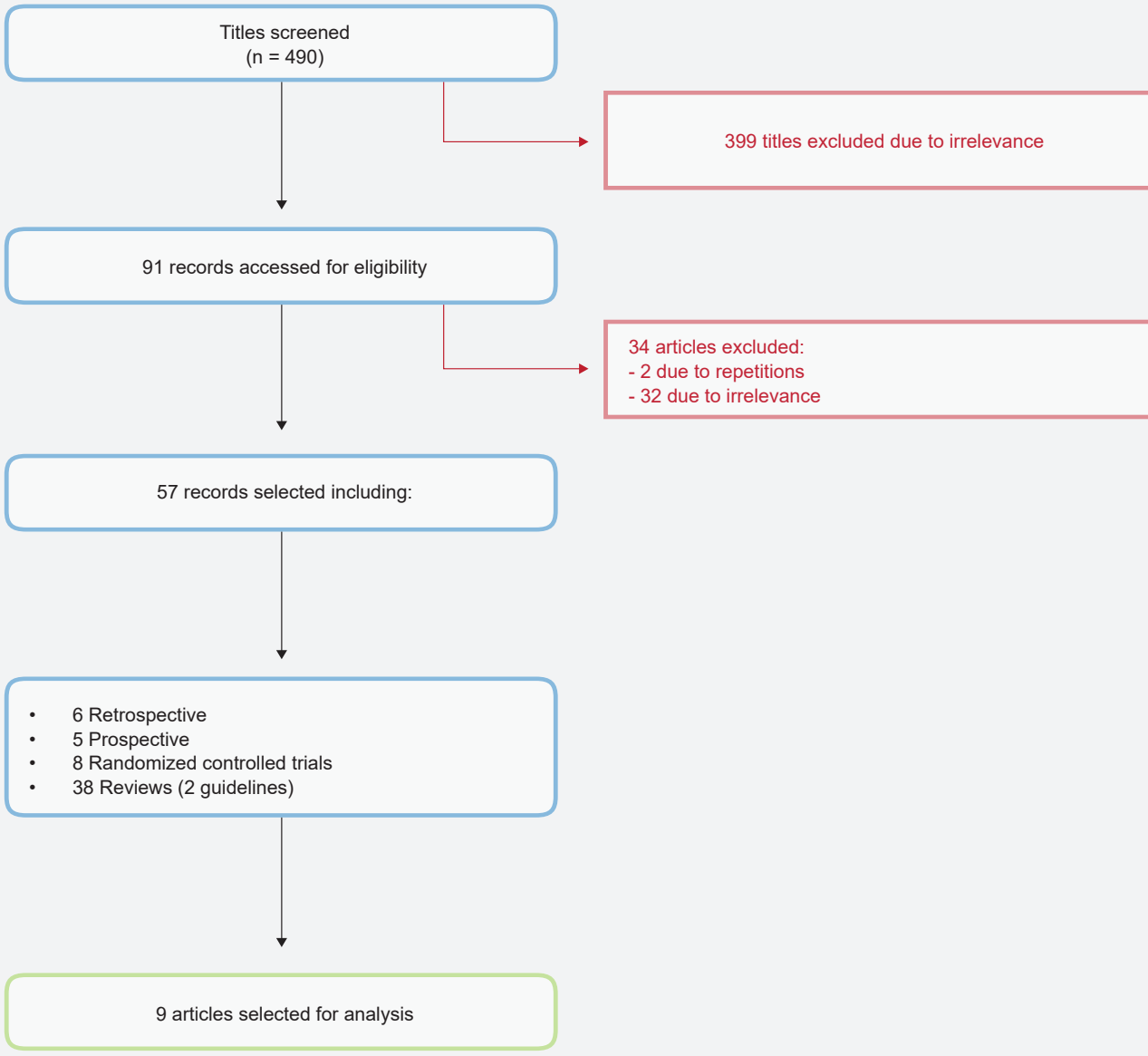

Figure 1 – Results. Included and excluded articles according to predefined criteria.

were randomized controlled trials (RCT) (46, 47, 40 - 42, 53, 57, 58). Nine studies focused on the co-administration of albumin and furosemide and were included in the analysis: five concluded in favour of co-administration strategy (7, 41, 42, 47, 53) but one did not focus on diuretic resistant patients (47); four articles concluded against the co-administration strategy (4, 40, 46, 55). From these nine studies, only one clearly included HF patients (46). The articles focusing on the co-administration of albumin and furosemide are listed in Tables 1 and 2.

DISCUSSION

Acute heart failure, congestion, and diuretic resistance

Several mechanisms may be involved in AHF, and congestion appears to be the consequence of a complex, multi-pathophysiological process. This process leads to increased intra-cardiac filling pressures which appears to be the starting point for the congestive state. Trends in weight and volume status act as surrogate markers for congestion which is one of the main targets of the current strategies for HF management. However, fluid retention is not evident in all patients and this heterogeneity in clinical presentation suggests that other mechanisms may increase cardiac filling pressures and subsequently trigger AHF.[9] Blood volume redistribution between different vascular compartments may be one contributing mechanism.[10]

Diuretic resistance suggests impaired sensitivity to diuretics and results in reduced sodium and water excretion, limiting the possibility to achieve an euvolemic state.[11] There is not a universal definition for diuretic resistance, but

Table 1 – Articles that favor the co-administration of furosemide and albumin (regardless of the index disease) by order of appearance in the main text

Study	Design	Cohort	Findings
Duffy *et al*, 2015[7]	Review	Nephrotic syndrome patients	Combination therapy should be considered in patients with diuretic resistance.
Martin *et al*, 2005[47]	Crossover, prospective	40 patients with acute lung injury/ acute respiratory distress syndrome and albumin < 6g/dL	Combination therapy in patients with hypoproteinemia significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability.
Fliser *et al*, 1999[41]	Crossover, prospective	9 patients with nephrotic syndrome	Co-administration of human albumin potentiates the action of furosemide, but only modestly.
Phakdeekitcharoen *et al*, 2012[42]	Crossover, prospective	24 patients with CKD and hypoalbuminemia	Combination therapy has a superior short-term efficacy over furosemide alone in enhancing water and sodium diuresis.
Inoue *et al*, 1987[53]	Crossover	20 patients with hypoalbuminemia (diverse aetiologies)	Combination therapy allowed effective diuresis in patients with diuretic resistance.

NA: non-applicable; CKD: chronic kidney disease

Table 2 – Articles that do not support the co-administration of furosemide and albumin (regardless of the index disease) by order of appearance in the main text

Study	Design	Cohort	Findings
Ellison *et al*, 2019[4]	Review	NA	Did not support the use of combination therapy in diuretic resistant patients.
Makhoul *et al*, 1997[46]	Observational, prospective	30 patients with acute respiratory failure due to cardiogenic pulmonary oedema	Combining continuous furosemide infusion with albumin offers no advantage over the use of continuous furosemide alone.
Chalasani *et al*, 2001[40]	Crossover, prospective	13 patients with cirrhosis (variable causes)	Combination therapy did not enhance diuretic effects in patients with cirrhosis and ascites. In addition, the administration of albumin did not alter the pharmacokinetics or pharmacodynamics of furosemide.
Doungngern *et al*, 2012[55]	Retrospective	31 ICU patients (variable causes)	Addition of albumin to a furosemide infusion did not enhance diuresis obtained with furosemide alone in critically ill patients.

NA: non-applicable; ICU: intensive care unit

clinical and laboratory markers of poor diuretic response have been described.[12] The 'reference diuretic dose' is consistently determined as 40 mg of furosemide or equivalent among studies. Accordingly, clinical surrogates of poor diuretic response may include diuresis below 1400 ml or a net weight change of 0 to 2.7 kg. Laboratory markers for poor diuretic response include fractional excretion of sodium at baseline < 0.2%, lower chloride levels at baseline (97 to 103 mEq/L) and/or a urinary sodium and urinary furosemide concentration ratio below 2 mmol/mg.[12–16]

The splanchnic circulation and 'effective blood volume'

The 'effective circulatory volume' is one of the main determinants of preload to the heart and refers to blood in the arterial system and in non-splanchnic venous vessels.[17] In a similar manner, the highly compliant venous system acts as a reservoir for blood and is actively involved in the regulation of preload to the heart and cardiac output.

The splanchnic vascular compartment is a major reservoir for blood and can accommodate or release most of the volume change in circulating blood.[10,18] It has an abundance of adrenergic receptors, with an asymmetrical distribution, with higher density of adrenergic terminals on veins.[19] This causes a stronger venous vasomotor response compared to other vascular regions and makes the splanchnic circulation an important component of effective circulatory volume regulation.

In healthy individuals, the baroreflex prevents fluid shift from the splanchnic reservoir by providing a sympathetic-inhibitory influence on this vascular bed.[20] Increases in sympathetic tone should recruit blood from the splanchnic and peripheral compartment to the heart, which increases filling pressures. In HF patients, a decreased baroreflex function inhibits the capacity to buffer eventual rises of effective circulatory volume, especially in acute disease states.[21,22] In HF, a 'fast track' for decompensation stems from autonomic imbalance with overactivity of the sympathetic nervous system (SNS), resulting in increased preload and extravascular edema. A slower mechanism, also mediated by the SNS, causes sodium retention resulting in splanchnic congestion. Finally, in HF, the storage capacity of splanchnic vasculature may be impaired *per se*, reducing its ability to buffer extra fluid. This fluid redistribution mechanism accelerates the increase in central filling pressures and might play a significant role in the pathophysiology of AHF.[23]

The cardiorenal interaction and 'renal congestion'

The cardiorenal interaction in AHF remains poorly understood. Coexistent renal dysfunction may complicate the treatment of HF and the use of LD to treat congestion may worsen renal function.[24] Renal dysfunction in HF patients is traditionally associated with decreased renal perfusion and altered neural-hormonal feedback mechanisms. New findings point to a major role of venous congestion in the pathophysiology of renal dysfunction in AHF. In fact, persistent venous congestion explains several changes observed in HF: hormonal and endothelial activation, increased intra-abdominal pressure, excessive tubular sodium reabsorption and volume overload. Among others, these mechanisms lead to further renal dysfunction and increased cardiac filling pressures.[24–26] Moreover, irreversible renal dysfunction due to persistent renal hypoperfusion or venous congestion may lead to inefficient decongestion. Addressing and solving the reversible causes of renal dysfunction, should facilitate effective decongestion.[27]

Glycocalyx loss and albumin

The glycocalyx is a complex layer of membrane-bound proteins that lines the luminal surface of the endothelium. Among other functions, it regulates vascular permeability, contributing to the vascular homeostasis.[28] Albumin integrates the structure and stabilizes the glycocalyx. Under physiological conditions, the glycocalyx inhibits the shift of albumin across the endothelium and plays a major role in the regulation of hydrostatic and oncotic pressure gradients through the capillary beds.[29,30] Moreover, changes in capillary pressure may impose changes in the composition of the fluid under the glycocalyx. In contrast, the interstitial fluid composition may take longer to adjust to changes in vascular pressure.[31] Glycocalyx loss can occur in any vascular bed, but it can be easily detected in the kidneys since albuminuria is measured in the urine.[30] This process is normally reversible and may occur in the absence of glomerular structural injury. Detecting glycocalyx loss is important as it may constitute a reversible cause of albuminuria and renal dysfunction, and due to its influence in fluid shift across compartments.

Loop diuretics

To be effective, LD must transit to the kidney via the circulation, undergo secretion by the proximal tubule, be delivered to the luminal surface of thick ascending limb cells, and bind to and inhibit the Na-K-2Cl cotransporter. More than 95% of the absorbed LD circulate bound to albumin and are transported in its inactive form. In their active site, they inhibit sodium reabsorption promoting natriuresis and water excretion.[4,32]

The natriuretic effect of LD may be modified by processes upstream or downstream from their active site. Hepatorenal or cardiorenal syndromes, occur frequently in HF patients and may promote fluid overload and poor response to diuretic therapy. Moreover, conditions such as liver cirrhosis or nephrotic syndrome may cause protein deficiency

or loss impacting LD pharmacokinetics and challenging the evaluation of its true diuretic effect.[4,32] Knowing which of these conditions plays the dominant role, could change the treatment approach.

Hypoalbuminemia and diuretic response to LD in HF patients

Albumin is a major player in maintaining cardiovascular homeostasis due to its oncotic properties and seems to be a powerful risk predictor, even within normal ranges.[33] It is also a marker of inflammation, arterial stiffness, liver and kidney disease, which may occur in HF patients. Hypoalbuminemia is a frequent condition in HF patients and is associated with the malnutrition-inflammation complex syndrome, which translates the relation between malnutrition, inflammation and atherosclerosis-related cardiovascular disease.[34] Other conditions that may increase the severity of hypoalbuminemia in the elderly, comorbid patient include: hemodilution; altered albumin synthesis in liver disease; vascular dysfunction with increased transcapillary escape rate; kidney disease (mainly end-stage kidney disease) with reduced synthesis and increased albumin degradation; and enteral loss.[35–37] Hypoalbuminemia induces a low plasma oncotic pressure, which facilitates transcapillary fluid shift causing pulmonary edema, even in patients without increase in pulmonary capillary hydrostatic pressures. It also favors myocardial edema, volume overload, diuretic resistance and exacerbation of oxidative stress and inflammation, contributing to the progression of HF.[35] In fact, hypoalbuminemia is considered a risk factor for the development of HF and is predictive of mortality in patients with acute and chronic HF.[38,39] Evidence is growing that hypoalbuminemia independently predicts incident HF in patients with end-stage renal disease and elderly patients, as well as mortality in patients with HF regardless of left ventricular ejection fraction and clinical presentation.[35]

Theoretically, hypoalbuminemia should affect LD pharmacokinetics by indirectly increasing the volume of distribution, increasing the odds of resistance. Also, an excess of albumin in the renal tubules may act as a scavenger for the unbound LD forcing its excretion, thus contributing to diuretic resistance.[40] On the other hand, administration of albumin should positively impact renal hemodynamics, increasing oncotic pressure in the circulatory system and improving the glomerular filtration rate and effective renal plasma flow.[41,42] In patients with AHF receiving intravenous diuretics, moderate/severe hypoalbuminemia as determined by the nadir (not necessarily serum albumin level at admission) is associated with a greater risk of acute worsening of renal function and the need for intravenous vasoactive therapy. Therefore, the timing of serum albumin level assessment may influence the utility of albumin as a biomarker of short-term clinical outcomes in patients with AHF.[39]

The discussion regarding the impact of albumin concentration on the mechanism of action of LD makes sense. However, its clinical relevance, particularly in the range of values routinely found in clinical practice, has not yet been proven in patients with HF.[8,36,43]

Co-administration of albumin and furosemide throughout the decades

Numerous strategies for the management of HF with congestion and diuretic resistance have been investigated.[44,45] One of them consists in the intravenous co-administration of albumin and furosemide in patients with HF and hypoalbuminemia. Although there is a rationale for the addition of colloids to diuretic therapy, only a few studies addressed this problem in AHF and none proved its beneficial role.[46–49] Presently, there are no evidence-based recommendations for this combined therapy in diuretic resistant AHF patients with hypoalbuminemia.[50,51]

Monzo *et al*, confirmed a strong correlation between congestion and hypoalbuminemia.[9] Peterson *et al*, found a trend toward greater diuresis in patients with normal albumin levels versus hypoalbuminemia.[39] A trial carried out by Phakdeekitcharoen *et al*, concluded that the combination of furosemide and albumin had superior short-term efficacy over furosemide alone in enhancing water and sodium diuresis in hypoalbuminemic patients with chronic kidney disease.[42] In another way, a pre-clinical study showed that proteinuria may compromise the benefit of albumin and furosemide in hypoalbuminemic patients with nephrotic syndrome.[52] Inoe *et al* tested a small subset of hypoalbuminemic patients (mean serum albumin concentration of 2.0 g/dL), in which the furosemide-albumin complex effectively increased the urine volume.[53]

More recently, Charokopos *et al* showed an association of hypoalbuminemia with poor diuretic efficiency but failed to maintain this correlation when the effects of inflammation on serum albumin concentration were addressed after adjustment for IL-6 levels.[54] Doungngern *et al* conducted a retrospective study on 31 intensive care patients who received furosemide as a continuous infusion with and without 25% albumin for more than six hours.[55] The authors concluded that the addition of albumin to a furosemide infusion did not enhance diuresis compared with furosemide alone in critically ill patients. However, the previous level of albumin was not considered.

In 2014, Kitsios *et al* conducted a meta-analysis focusing the co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia.[56] The studies considered included mainly patients with nephrotic syndrome and cirrhosis and none of them mentioned HF patients and diuretic resistance.

A statistically significant increase in the amount of urine volume and sodium excreted at eight hours was found, favoring the combined therapy but these differences were no longer statistically significant at 24 hours. A subgroup analysis with nephrotic syndrome as the index disease, demonstrated an increase in urinary volume, both at eight hours and 24 hours after albumin-furosemide administration compared with furosemide alone, with an absolute magnitude larger than in the main analysis. Of note, the furosemide daily dose ranged from 30 to 220 mg per day across studies, which is probably considered a low dose in the context of HF and diuretic resistance. Finally, despite the potential beneficial effect of albumin on diuresis no significant effects on natriuresis were found.[56]

Kitsios *et al* mentioned the large heterogeneity between studies as a limitation, with some including patients with cirrhosis and kidney disease with or without nephrotic syndrome.[56] Regarding methods, there were several differences between studies: only some measured serum creatinine, proteins in 24 hours urine and urinary sodium; the definition of hypoalbuminemia differed (cut-off from 1.1 to 3.1 g/dL); and doses of furosemide and albumin in individual studies were remarkably variable. Nonetheless, it was noted that a significant diuretic effect from albumin administration was detected only when associated with smaller doses of furosemide (60 mg or less in the studies with statistically significant results on the outcome of urinary volume). The authors also mentioned the possible relation between the severity of hypoalbuminemia and the extension of diuretic resistance, which could impact the effect of co-administration of albumin and furosemide.[56] They concluded that effects of the combined therapy in patients with hypoalbuminemia were modest and transient (in the first eight hours after administration of albumin) and none of the results would support a change in clinical practice.[56]

Bleske *et al* studied a cohort of 162 patients with AHF treated with continuous diuretic infusion to compare diuretic response (measured as urine output) between two groups: one with hypoalbuminemia defined as albumin ≤ 3 g/dL); and a control group without hypoalbuminemia. Unlike what has been observed in nephrotic syndrome, this study did not demonstrate that hypoalbuminemia decreased diuretic effectiveness.[43] The authors stated that diuretic effectiveness could be related with the type and degree of hypoalbuminemia and hyperalbuminuria in patients with AHF when compared with patients with nephrotic syndrome. In patients with nephrotic syndrome, a decrease in serum albumin is more probably related with albuminuria. However, in patients with HF, hypoalbuminemia may stem from hemodilution, although malnutrition, cachexia, and inflammation can also contribute. Another factor positively affecting diuresis may be the aggressive diuretic approach employed to treat patients with congestive AHF. Aggressive diuresis may overcome any effect hypoalbuminemia may have on diuretic efficacy by increasing the amount of drug at the site of action. Finally, the authors proposed that continuous infusion of furosemide, especially in higher doses, provided a continuous level of diuretic therapy above the threshold and less rebound effect, possibly increasing the diuretic effect of furosemide.[43]

The DOSE trial compared the method and dose of administration of furosemide in patients with AHF. The groups were assigned to receive furosemide administered intravenously either by bolus or continuous infusion and at a low dose (previous oral dose) or high dose (2.5 times the previous oral dose). Despite the high-dose strategy association with greater relief of dyspnea, greater fluid and weight loss and fewer serious adverse events, there was no statistically significant difference regarding the primary efficacy end point (the patient's global assessment of symptoms) and safety end points. The same was found in the bolus versus continuous infusion groups, concerning the primary efficacy endpoint.[57] Both the DOSE-AHF and the ROSE-AHF trials also provided a well-characterized cohort regarding albumin concentrations and diuretic response. In these trials, an unequivocal relationship between a lower baseline albumin level (hypoalbuminemia defined as serum levels < 3 - 3.5 g/L) and decreased response to decongestive therapies was not found, which does not support the use of albumin in hypoalbuminemia.[57,58]

Co-administration of albumin and furosemide in HF patients with hypoalbuminemia and diuretic resistance: the present and the future

Clinical experience seems to support the use of albumin as a therapeutical strategy to mobilize edema fluid in dialysis patients with hypoalbuminemia and decreased effective arterial volume. In AHF patients with hypoalbuminemia and diuretic resistance, the access to the extravascular compartment is difficult. Raising the vascular oncotic pressure may allow the mobilization of excessive extravascular fluid and promote ultrafiltration by pulling extravascular fluid into the intravascular compartment.[37] Nevertheless, this beneficial role of albumin-furosemide co-administration needs to be proven in a large RCT.

Several considerations should be made regarding studies focusing on the correlation between albumin administration and LD effectiveness in HF: there are few studies including patients with AHF; cohorts included are usually of small size, have heterogenous populations and endpoints are somewhat variable across studies; the general approach to AHF is heterogeneous and may include the use of vasoactive drugs or diuretics other than furosemide, which contributes to the heterogeneity among studies.

All these considerations make it difficult to compare results and find generalizable assumptions.

Additionally, the definition of hypoalbuminemia is variable among studies, and it seems that severe hypoalbuminemia may favor the use of albumin to overcome diuretic resistance. Albumin levels should be measured in several time points and the nadir should be considered to define hypoalbuminemia. Ideally, studies should be performed in HF patients without nephrotic syndrome, cirrhosis, or any kind of other inflammatory or infectious disease, in order to reduce possible confounding factors. Hypovolemia should be identified and excluded, and other pathophysiologic mechanisms should be explored to gauge poor diuretic response.

Ultimately, a standardized definition of diuretic resistance is mandatory. Urine output and sodium excretion are specific endpoints that have demonstrated the beneficial role of albumin-furosemide administration in patients with conditions other than HF. Such specific endpoints should also be chosen over less specific ones in future studies regarding HF patients. Future RCTs should evaluate the efficacy of albumin-furosemide administration for different degrees of hypoalbuminemia, since there is just a generalized assumption that albumin is more effective in severe hypoalbuminemia, a term that also lacks definition. The timing of albumin administration (generally prior to furosemide) should also be addressed since it is known that higher doses of furosemide could make the addition of albumin less effective and that the maximal effect of albumin in expanding intravascular volume occurs in the first hour after administration.[7] For this reason, drug doses, methods and timing of administration should also be defined.

The large heterogeneity between concepts and the lack of RCTs in AHF are major limitations of this review. The consequence is that there are more questions than answers being raised, which, in another way, may be possible starting points for future studies.

CONCLUSION

Congestion in acute heart failure arises from a complex interaction between multiple pathophysiological pathways and compensatory mechanisms. The resulting increased sympathetic activity, excessive volume overload, and dysfunctional fluid redistribution ultimately lead to increased intra-cardiac filling pressures which appear to be the starting point for congestion. The specific physiologic mechanisms of diuresis enhancement and hemodynamic improvement after the co-administration of albumin and furosemide remain unclear but this combined approach seems to overcome diuretic resistance in selected patients with acute heart failure. This strategy seems to be reasonable on pathophysiological grounds and has been supported by clinical experience. However, its beneficial role in this specific population has not yet been proven and remains controversial. The variability in selection criteria, experimental design, and clinical endpoints may justify this controversy. A standardized measurable definition for congestion, diuretic resistance and hypoalbuminemia would allow for a more accurate selection of patients who could benefit from this combined approach. Large-scale randomized controlled trials are therefore needed to make recommendations regarding the use of albumin and furosemide in acute heart failure patients with diuretic resistance.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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