



CKJ REVIEW

Focus on renal congestion in heart failure

Baris Afsar¹, Alberto Ortiz², Adrian Covic³, Yalcin Solak⁴, David Goldsmith⁵, and Mehmet Kanbay⁶

¹Department of Medicine, Division of Nephrology, Konya Numune State Hospital, Konya, Turkey, ²Nephrology and Hypertension Department, IIS-Fundacion Jimenez Diaz and School of Medicine, Madrid, Spain, ³Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. PARHON' University Hospital, and 'Grigore T. Popa' University of Medicine, Iasi, Romania, ⁴Department of Nephrology, Sakarya Training and Research Hospital, Sakarya, Turkey, ⁵Renal and Transplantation Department, Guy's and St Thomas' Hospitals, London, UK, and ⁶Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey

Correspondence to: Mehmet Kanbay; E-mail: mkanbay@ku.edu.tr, drkanbay@yahoo.com

Abstract

Hospitalizations due to heart failure are increasing steadily despite advances in medicine. Patients hospitalized for worsening heart failure have high mortality in hospital and within the months following discharge. Kidney dysfunction is associated with adverse outcomes in heart failure patients. Recent evidence suggests that both deterioration in kidney function and renal congestion are important prognostic factors in heart failure. Kidney congestion in heart failure results from low cardiac output (forward failure), tubuloglomerular feedback, increased intra-abdominal pressure or increased venous pressure. Regardless of the cause, renal congestion is associated with increased morbidity and mortality in heart failure. The impact on outcomes of renal decongestion strategies that do not compromise renal function should be explored in heart failure. These studies require novel diagnostic markers that identify early renal damage and renal congestion and allow monitoring of treatment responses in order to avoid severe worsening of renal function. In addition, there is an unmet need regarding evidence-based therapeutic management of renal congestion and worsening renal function. In the present review, we summarize the mechanisms, diagnosis, outcomes, prognostic markers and treatment options of renal congestion in heart failure.

Key words: acute kidney injury, fluid management, heart failure, hypervolemia, renal congestion

Introduction

Deterioration of renal function is common in both acute and chronic heart failure (HF) settings lately described as 'cardiorenal syndromes'. Renal congestion (RC) has become increasingly recognized as a potential contributor to cardiorenal syndromes, and adequate control of congestion with simultaneous improvement/preservation of renal function has been proposed as a central goal of patient management in HF [1]. The pathophysiological mechanisms, prognostic markers and treatment options

regarding RC and deterioration of kidney function in HF are not fully elucidated, despite significant research. In the present review, we summarize data on mechanisms, diagnosis, outcomes, prognostic markers and treatment options for RC in HF.

Renal congestion is a fairly new concept and its importance is just beginning to be realized. Congestion—either clinical or identified with echocardiography—allows stratification of HF patient prognosis [2, 3]. As part of systemic congestion, RC is of special interest due to the physiology of glomerular filtration. Indeed,

Received: August 24, 2015. Accepted: October 27, 2015

© The Author 2015. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

the kidney plays a major role in fluid overload compensation and, at the same time, **glomerular filtration, a key component of kidney function, partly depends on venous pressure, which is elevated in patients with systemic congestion** [4]. Thus, RC is more than a mandatory manifestation of systemic congestion and may *per se* have prognostic implications beyond those of systemic congestion.

The prognostic impact of renal congestion in HF

Congestion has a negative impact on clinical outcomes in patients with HF. In 2557 patients undergoing right heart catheterization, **elevated central venous pressure predicted mortality** and was associated with **low estimated glomerular filtration rate (eGFR), independent of cardiac index** [5]. In 1684 HF patients, decongestion (assessed as hemoconcentration: a $\geq 3\%$ absolute increase in hematocrit) was associated with a greater risk of in-hospital worsening renal function as defined increase in $SCr \geq 0.3$ mg/dL, worsening blood urea nitrogen (BUN) was defined as a $\geq 25\%$ increase and worsening estimated glomerular filtration rate (eGFR) was defined as a $\geq 25\%$ decrease, but this effect disappeared 4 weeks post-discharge. More importantly, after a median follow-up of 9.9 months, every 5% increase in hematocrit was associated with a 19% decreased risk of all-cause death [hazard ratio [HR] 0.81 [95% confidence interval (CI) 0.70–0.95]], after adjustment for baseline clinical risk factors. An increase in hematocrit change was also associated with decreased cardiovascular mortality or HF hospitalization at ≤ 100 days post-randomization [HR 0.73 (95% CI 0.71–0.76)] [6]. Such data were confirmed in 336 patients with acute decompensated HF, in whom hemoconcentration was associated with a lower risk of mortality, despite an increased risk for **worsening renal function (WRF)** [7]. In another study, hemoconcentration correlated with favorable prognosis despite a decrease in renal function in 1969 patients with acute decompensated HF [8]. In 6080 patients with HF after myocardial infarction enrolled in the EPHESUS trial, plasma volume decrease, which was indirectly estimated using the Strauss formula, was associated with better outcomes [9]. In patients with chronic HF enrolled in the GISSI-HF trial, increased estimated plasma volume was associated with worse clinical outcomes, independent of body weight changes [10].

Importantly, in acute decompensated HF there was a **strong association between an increased urine volume in the first 24 h and a lower incidence of WRF (defined as an increase in serum creatinine >0.3 mg/dL above baseline)** [11]. This finding is extremely relevant since it overcomes prejudice regarding the fear of decreasing renal plasma flow and deterioration of kidney function. In addition, WRF was less frequent in patients who achieved decongestion as measured by low central blood pressures [4].

In fact, existing data suggest that **congestion is more relevant than WRF for outcomes**. A prospective study investigated the relative impact of WRF versus the presence of congestion on post-discharge mortality and readmission in 599 patients with acute decompensated HF [12]. Congestion was defined as the persistence at discharge of one or more signs or symptoms of fluid overload (third heart sound, pulmonary rales, jugular venous stasis, hepatomegaly and peripheral edema). There was no difference with respect to outcomes between patients with WRF and no congestion and patients without WRF and no congestion. In contrast, outcomes were worse in patients with congestion alone (with or without WRF). The authors concluded that WRF alone, when detected using serial serum creatinine measurements, is

not an independent determinant of outcomes in patients with acute HF; it has an additive prognostic value only when it occurs in patients with persistent signs of congestion [12]. Taken together, these data suggest that **residual congestion is perhaps a key variable underlying prognosis in HF patients with cardiorenal syndromes**.

The pathophysiology of renal congestion and WRF in heart failure

The pathophysiology of renal congestion in HF is complex and involves multiple simultaneous pathways (Figure 1).

Ageing, hypertension and diabetes may be cofactors both in HF and in renal dysfunction. Their coexistence can accelerate atherosclerosis, myocardial pathology and chronic kidney disease (CKD) [13]. Use of iodinated radiocontrast agents or nonsteroidal anti-inflammatory drugs may predispose to renal dysfunction and renal congestion [14].

Arterial underfilling contributes to WRF during HF. When low aortic pressure results in a **renal perfusion pressure ≤ 80 mmHg, kidney autoregulation is no longer possible** [15]. Hemodynamic responses depend on **endothelial function, which is impaired in CKD and in HF**. Reduced kidney perfusion pressure **upregulates the sympathetic nervous and renin angiotensin aldosterone (RAS) systems**. Both angiotensin II and catecholamines further induce **glomerular arteriolar vasoconstriction**, decreasing renal plasma flow (RPF) [16]. However, **angiotensin II has a disproportionate vasoconstrictive effect on the efferent arteriole, preserving GFR despite reduced RPF** [17]. Thus, **initially, the filtration fraction and GFR are preserved but eventually increased angiotensin II and/or catecholamine levels become maladaptive, causing more preglomerular vasoconstriction and decreasing GFR** [18]. This in turn **activates proximal tubular sodium and water reabsorption**, leading to **more systemic and renal congestion** [19].

Elevated central venous pressure in HF promotes renal congestion (also known as **backward failure**). Indeed, classic experiments demonstrate that (i) there is a **steeply graded relationship between change in renal venous pressure and reduction in urine flow and (ii) kidney blood flow is reduced more by an increase in venous pressure than by an equivalent decrease in arterial pressure** [20]. These changes occur **independently of any reduction in cardiac output and/or mean arterial pressure**, changes that occur much later in the progression of HF [21]. In **healthy individuals without HF, a transient hypervolemic state leads to increased renal fluid and salt excretion**, which decreases both blood volume and cardiac output, returning the pressure back to normal. However, in patients with HF despite an increase in blood volume (hypervolemic state) the **elevated right atrial and central venous pressure impinge on salt excretion** by the kidney, so that a **vicious cycle of sodium retention, volume expansion and HF is initiated, leading to more renal congestion** [22].

Increased intra-abdominal pressure and abdominal congestion (i.e. splanchnic) and interstitial congestion may also have a role. Renal blood flow is inversely related to intra-abdominal pressure [23, 24]. Intra-abdominal venous hypertension can also result in systemic hypotension and low cardiac output [25]. Compromised capacitance of the splanchnic vasculature and deficient abdominal lymph flow may also contribute to elevated cardiac filling pressures [26], which initiates/adds to the cascade of events causing WRF and renal congestion. In addition, recent evidence suggests that **alteration of gut flora during HF may play an important role in WRF and renal congestion**. Indeed, it has been suggested that the **entrance of bowel toxins** into the

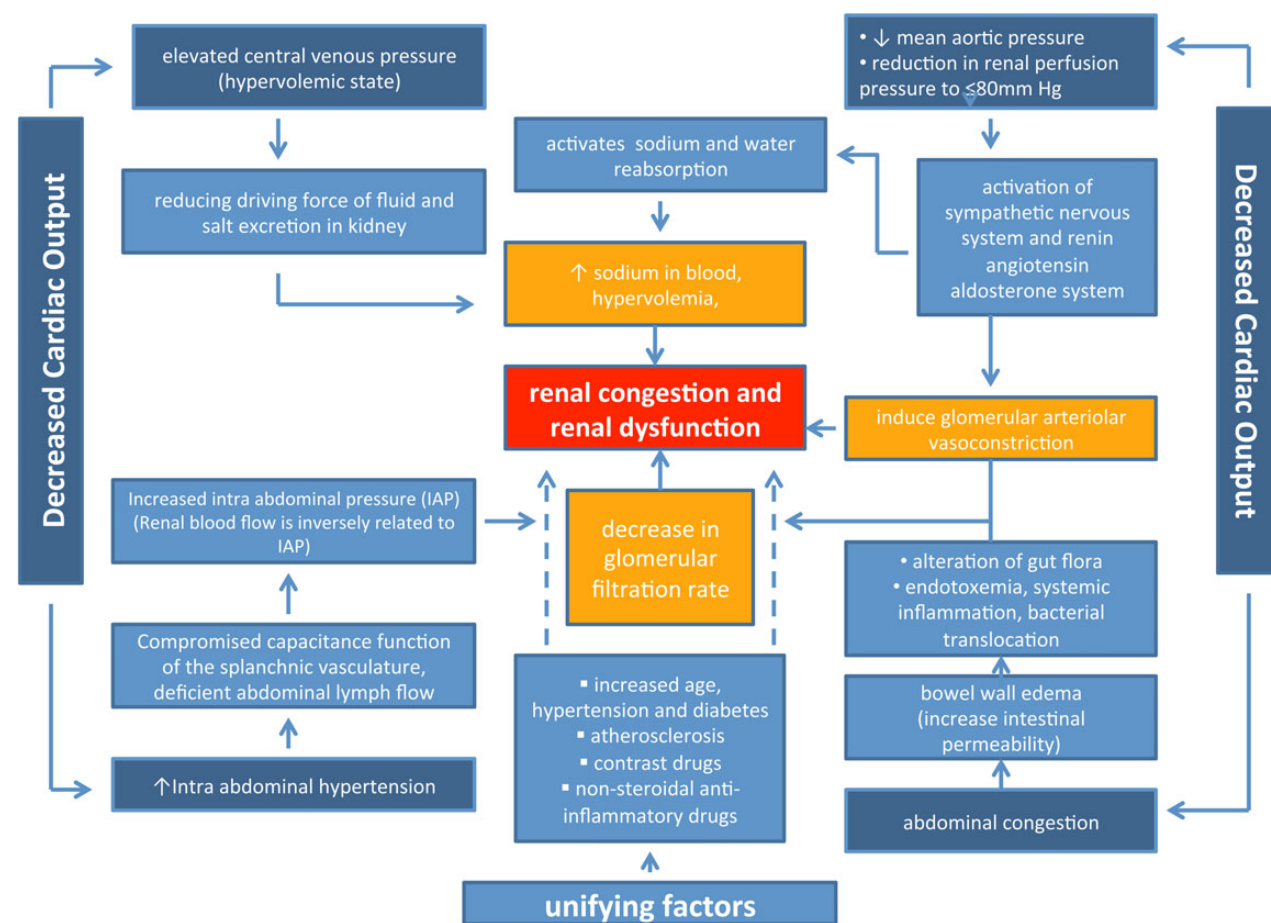


Fig. 1. Mechanisms involved in renal congestion in heart failure.

circulatory system—as a result of **impaired intestinal barrier function secondary to congestion**—may cause a further **depression of cardiac and renal function**. These toxins are mainly produced by microorganisms in the gut lumen and are altered in advanced HF, **especially when there is congestion** [27].

What are the **consequences of renal congestion?**

Renal congestion leads to increased renal interstitial pressure that affects the entire capillary bed and the tubules, possibly also inducing local hypoxia. Tubular compression raises the luminal pressure, further attenuating the transglomerular pressure gradient, and lowering the GFR. It is important to appreciate that an **increase in renal interstitial pressure due to venous congestion is physiologically different from that caused by elevations in arterial pressure, which is associated with natriuresis** [28].

Inflammation may also promote and be a consequence of renal congestion [29]. Inflammation may cause vascular dysfunction via endothelial activation and enhanced arterial stiffness, reduce myocardial contractility through functional suppression of contractility and increased myocardial cell death, contribute to progressive renal dysfunction and **fibrosis** and increase endothelial permeability, thus facilitating fluid extravasation into lung alveoli and absorption of **pro-inflammatory endotoxin from the bowel** [29]. Conversely, in HF and venous congestion, activation of the RAS and sympathetic system promotes/enhances

the inflammatory response. In addition, accumulating evidence suggests that **volume overload per se and venous congestion independent of RAS and sympathetic system activation promote the expression of inflammatory mediators** [29].

A very recent study evaluated the role of peripheral venous congestion, induced by the venous stress test, on inflammation and endothelial activation. **Venous arm pressure was increased to 30 mmHg above baseline by inflating a cuff around the dominant arm (test arm)**. Plasma interleukin-6 (IL-6), endothelin-1 (ET-1), angiotensin II, vascular cell adhesion molecule-1 (VCAM-1) and chemokine (C-X-C motif) ligand 2 (CXCL2) were **significantly increased in the congested arm as compared with the control (no cuff) arm** (Figure 2) [30]. In HF, bacterial endotoxin production and **bacterial translocation from the bowel lumen may increase** [31, 32]. Indeed, in a recent prospective study, **endotoxin levels were higher in CKD patients with fluid overload than in those without fluid overload** [33].

Endothelial cells may become activated during venous congestion to a pro-oxidant, pro-inflammatory and vasoconstricting state. Once 'activated', the endothelium can promote additional congestion through humoral, renal and cardiac mechanisms, resulting in a deleterious positive feedback loop [20]. Venous stretch increased the release of ET-1, IL-6 and tumor necrosis factor α (TNF- α) [34] and endothelial reactive oxygen species (ROS) production [35]. ROS and cytokines may also trigger an inflammatory response through activation of nuclear factor κ B [36].

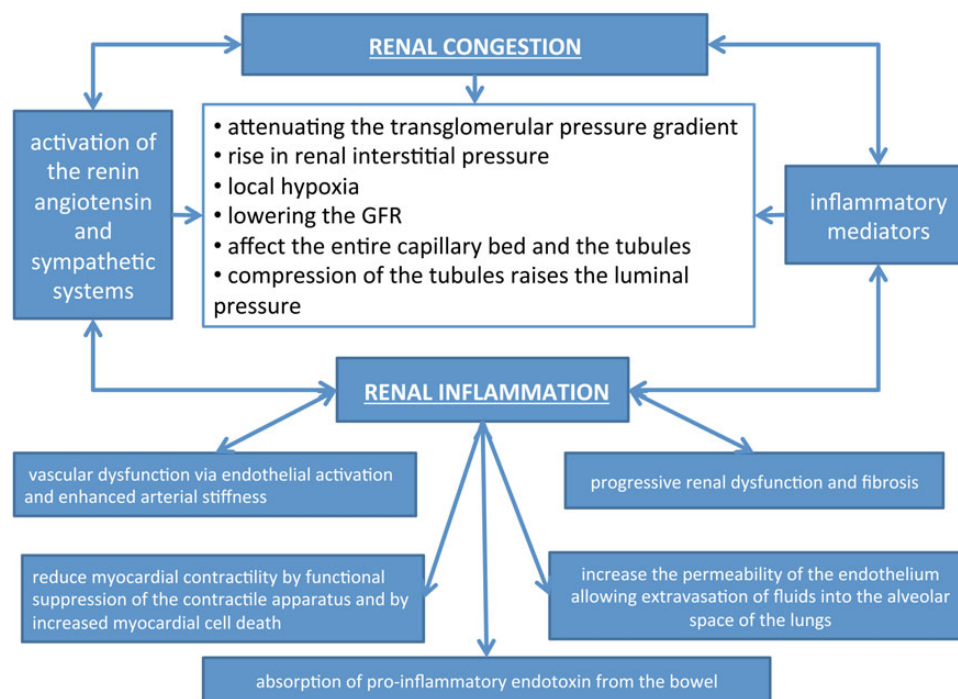


Fig. 2. Mechanisms of increased inflammation during venous congestion.

How to assess renal congestion?

Unfortunately there is no direct method to assess renal congestion. This is in contrast to the several possibilities for evaluating lung congestion. Indeed, visualization of B lines by lung ultrasound is now accepted as a valid method to assess pulmonary congestion in HF [37, 38]. Traditional markers such as eGFR and emerging markers such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1) and natriuretic peptides offer prognostic information in HF and renal dysfunction. However, none of these markers are specific for renal congestion. **Natriuretic peptides** are now routinely used and high values [**>600 pg/ml B-type natriuretic peptide (BNP)** or **>6000 pg/ml N-terminal pro-BNP**] are associated with **high filling pressures** secondary to volume overload [39]. BNP levels correlate with capillary wedge pressure and can also serve as an indirect marker for deterioration of kidney function during treatment of acute decompensated HF [40]. However, natriuretic peptides are not specific for renal congestion and can reflect congestion specifically related to HF. Echo/Doppler should be explored as a means to assess renal veins congestion. Thus, research is needed to find direct ways to measure renal congestion in HF.

Treatment of renal congestion and decongestion strategies in heart failure

There are various treatment options for renal congestion in HF that are beyond the scope of this review and will only be briefly mentioned (Table 1). Therapeutic strategies aim at eliminating excess fluid without compromising renal function.

Salt and water restriction

Salt and water restriction for routine management of HF is usually based on expert opinion rather than evidence-based proof [57]. Fluid restriction (1000 mL/day) in hyponatremic (serum sodium <137 mmol/dL) patients with HF improved the quality of life at

60 days after discharge [58]. In HF patients with preserved ejection fraction, sodium restriction was associated with favorable changes in ventricular diastolic function, arterial elastance and ventricular–arterial coupling [59]. A randomized trial (trial number NCT01896908) will investigate the effects of sodium and fluid restriction on neurohormonal activation in HF patients with preserved ejection fraction. However, another study failed to observe a clear benefit of sodium and fluid restriction in HF patients with preserved ejection fraction [60]. Likewise in another randomized trial, patients admitted for worsening HF did not benefit from aggressive fluid and sodium restriction [61]. The different findings may be due to patient characteristics, study design or not enough fluid and sodium restriction. On the other hand, sodium restriction may have a direct effect on extracellular volume, improving endothelial function and arterial stiffness [62, 63].

The effect of sodium and fluid restriction may differ in older and younger patients [64]. In elderly people, dietary sodium restriction might even cause harm through hypovolemia and increased neurohormonal activation, causing falls and their associated morbidity. Dietary sodium intake should be individually tailored based on HF severity and the physiologic response to sodium loading [57]. Thus, future clinical studies are needed to assess the effectiveness of sodium and fluid restriction in different stages and clinically divergent HF patients.

Loop diuretics, ultrafiltration and dialysis strategies

Loop diuretics are commonly used in patients with HF. In HF, the dose–response curve shifts downward and to the right. Thus, a **higher dose is required** to achieve the **same therapeutic effect** [65]. However, **higher loop diuretic dosages** in HF were associated with **worse clinical outcomes**, including WRF [66]. These studies were **criticized** since patients with more severe HF and preexisting renal disease require higher diuretic doses [41]. Indeed, in another trial involving 308 patients, after adjusting for cardiovascular risk

Table 1. Treatment strategies for venous congestion in heart failure

Loop diuretics	Use intravenous route Bolus dosing may be as effective as continuous infusion Start the initial dose at 2–2.5 times the home oral dose Increase the dose until the adequate symptom relief is achieved Avoid single dosing Consider adding thiazide diuretics or ACE-I and ARB in case of resistance
Ultrafiltration	Peripheral venovenous ultrafiltration Peritoneal dialysis
V2R antagonists	Increase free water excretion and improvement in sodium level Experimental evidence suggests an increase in survival Augment the diuretic and the natriuretic response to furosemide
Adenosine receptor blockers	Dilatation of afferent arteriole and preservation of GFR No effect on worsening renal function Had a favorable effect on dyspnea as well as short-term mortality May be associated with higher rates of seizures and stroke
Dopamine	Improve renal blood flow and diuresis at low doses In acute HF, use with caution
Natriuretic peptides	No clear effect on mortality, rehospitalizations or prevention of renal damage Decrease cardiac filling pressure, increase cardiac output, promote diuresis and decrease RAS and release of norepinephrine Borderline effect on dyspnea May have hypotensive effect
Novel therapies	Spliced BNPs Hypertonic saline with furosemide Relaxin
Left ventricular assist device	Was used refractory HF and cardiorenal syndrome Studies have demonstrated that creatinine levels decrease fast initially, then decrease gradually Early postoperative mortality correlates with the severity of preoperative renal dysfunction

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; V2R, vasopressin type 2 receptor; GFR, glomerular filtration rate; RAS, renin angiotensin aldosterone system; BNP, B-type natriuretic peptide.

and clinical stability, diuretic dose was not associated with increased risk [41]. The frequency of dosing of loop diuretics is another issue. A single dose of furosemide elicits transient natriuresis [67, 68] and loop diuretics may be given two or more times per day or continuously. However, continuous dosing was not more effective than an optimally prescribed bolus regimen, as proven in the Diuretic Optimization Strategies Evaluation (DOSE) trial [41]. The addition of nonloop diuretics (i.e. thiazide or potassium-sparing diuretic) may overcome the escape phenomenon due to activation of the RAS and sympathetic system and sodium reabsorption by more distal sodium transporters [65].

Several guidelines state that ultrafiltration is another reasonable approach for patients with refractory congestion not responding to diuretic therapy [69, 70]. It is currently unclear which strategy is safer and more effective [71]. Some important differences are obvious. First, the amount of urine produced in response to intravenous (i.v.) diuretics is not predictable, whereas fluid removal by ultrafiltration is completely controllable and adjustable. Second, the ultrafiltrate is isotonic, removing more sodium than loop diuretics, which induces hypotonic urinary output [72]. Third, since ultrafiltration can be controlled by machines and the amount of fluid removal is strictly controlled, excess fluid removal and neurohumoral activation can be prevented [73]. Also, the adequacy of intravascular refill during ultrafiltration can be assessed by continuous monitoring of the hematocrit. Finally, elimination of pro-inflammatory cytokines [74] or sodium-retaining vasoconstrictive agents may occur during ultrafiltration, theoretically leading to an improvement in urinary output or restoration of diuretic responsiveness during ultrafiltration [75].

Bearing all issues in mind, one may think that ultrafiltration is superior to diuretics, albeit it is an invasive procedure. However, there are no strict recommendations regarding the preferential use of diuretics, ultrafiltration or in combination, as stated earlier. In fact, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial showed that the use of a stepped pharmacologic therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 h. While a similar amount of weight loss was achieved with the two approaches, ultrafiltration was associated with a higher rate of adverse events [76]. The AVOID-HF randomized study was designed to determine whether ultrafiltration as an initial strategy reduces hospitalizations for acute HF before the onset of worsening renal function as compared with i.v. diuretics [77]. Unfortunately, it was recently prematurely terminated due to patient recruitment challenges ('No interim analyses were completed; study closure was not related to any concerns about safety or futility, as stated by the sponsor'; ClinicalTrials.gov NCT01474200).

Peritoneal dialysis is another option in HF [78] and improves quality of life in HF [79]. However, these studies must be interpreted with caution due to the small number of patients, lack of a control group and advanced renal failure. Furthermore, there are no studies available comparing head-to-head peritoneal dialysis, diuretic therapy and salt restriction in congestive HF [80] and peritoneal dialysis has adverse effects such as peritonitis, increased intra-abdominal pressure and hyperlipidemia. In a very recent review, Lu et al. [81] suggested that peritoneal dialysis decreased hospitalization days and improved heart function in patients with congestive HF [81].

Continuous ultrafiltration strategies [48, 43] may also have a potential beneficial role in HF. It was suggested that cardiovascular tolerability is better with continuous venovenous hemodiafiltration in patients with acute HF [48]. However, there are no large-scale head-to-head comparison studies with regard to diuretics, conventional dialysis and continuous therapies. This is the reason that ultrafiltration should not be used as a quicker way to achieve a sort of mechanical diuresis nor as a remedy for inadequately prescribed and administered diuretic therapy. Instead, it should be reserved for selected patients with advanced HF and true diuretic resistance, as part of a more complex strategy aimed at adequate control of fluid retention [42].

Vasopressin type 2 receptor antagonists

Vaptans are recently marketed drugs. Since vaptans increase free water excretion and increase serum sodium levels (which are usually low in advanced HF), they may have potential benefits in HF [44, 45]. In animal models of HF, tolvaptan increased urine volume, decreased lung congestion and improved survival but did not modify blood pressure. Additionally, renal histopathologic damage, including tubular fibrosis and glomerulosclerosis, was ameliorated [46].

There are also human studies. In the EVEREST trial, tolvaptan caused an early and sustained reduction in body weight and improved serum sodium but did not improve mortality or morbidity [46].

In another study, conivaptan and loop diuretics (either alone or combined with conivaptan) were compared in stable HF patients. There were no differences with regard to hemodynamics, neurohormonal activation, renal blood flow and GFR. Conivaptan and furosemide similarly increased urine volumes, but only furosemide increased urinary sodium excretion. Conivaptan significantly augmented both the diuretic and the natriuretic response to furosemide when both were combined [47].

Adenosine receptor blockers

Adenosine is secreted by juxtaglomerular cells in response to increased distal sodium load and is usually increased in HF. Intensive diuretic treatment increases distal sodium load, leading to increased adenosine secretion. This in turn may cause decreased GFR by constricting afferent arterioles [82].

The PROTECT trial (a placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute HF and volume overload to assess treatment effect on congestion and renal function) randomized 2033 patients admitted for acute HF to rolofylline or placebo. Rolofoylline had a favorable effect on dyspnea and short-term mortality, but no beneficial effect on WRF was observed [82]. However, rolofylline was associated with higher rates of seizures and stroke and drug development was stopped [49].

Dopamine

Renal dose dopamine has been traditionally used to increase urine volume [50, 51]. The recent Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial randomized 60 acute HF patients to high-dose furosemide or low-dose furosemide plus low-dose dopamine. Although the 60-days outcomes were similar in both groups, deterioration of kidney function and hypokalemia were more frequent with high-dose furosemide. The major limitation of the study was small sample size [51]. Thus, there is no evidence to recommend dopamine administration for the

protection of renal function in HF patients with fluid overload and the need of diuretic treatment [83].

Natriuretic peptides

Recombinant human BNP (nesiritide) decreases cardiac filling pressure, RAS activity and norepinephrine release while increasing diuresis and cardiac output [84]. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial in patients with acute HF, nesiritide had a borderline effect on dyspnea but no effect on outcomes when compared with placebo [52]. Also, concerns have been raised regarding untoward effects on renal function and mortality with nesiritide infusion [85]. Alternatively, spliced BNPs such as ASBNP and ASBNP.1 lack the hypotensive side effects of nesiritide and increased GFR, suppressed plasma renin and angiotensin and induced natriuresis and diuresis [53]. Randomized trials are warranted for these new agents in HF.

Nepriylsin is a neutral endopeptidase that degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin and adrenomedullin. Inhibition of nepriylsin increases the levels of these peptides, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention and maladaptive remodeling. A recent trial comparing the angiotensin receptor-nepriylsin inhibitor LCZ696 with enalapril in HF patients with reduced ejection fraction was stopped early due to the obvious superiority of LCZ696 with respect to the primary outcome, a composite of death from cardiovascular causes or hospitalization for HF, as well as to cardiovascular death, symptoms and physical limitations of HF [54].

Novel therapies

A combination of hypertonic saline and furosemide was thought to prevent rebound sodium reabsorption and promote effective diuresis. Indeed, a combination of high-dose furosemide with bolus hypertonic saline infusion in patients with New York Heart Association class IV HF resulted in improved diuresis, shortened hospital stay, decreased BNP levels and reduced readmissions compared with i.v. diuretic therapy alone [86].

Relaxin induces systemic and renal vasodilatation through actions on nitric oxide and endothelin B receptors. In a phase II trial (pre RELAX), relaxin was associated with relief of dyspnea and a tendency to greater weight loss with smaller doses of diuretics and nitrates [87]. The RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute HF) trial compared serelaxin with placebo, with a primary endpoint of dyspnea relief [55, 56]. In 1161 patients with acute HF, serelaxin was associated with decreased other (non-HF, non-sudden death) cardiovascular deaths [hazard ratio (HR) 0.29 (95% CI 0.12–0.73), P = 0.005] and sudden death [HR 0.46 (95% CI 0.20–1.07), P = 0.065], but did not impact HF deaths or non-CV deaths. There was no specific comment on renal function and renal congestion [56].

Implantation of a left ventricular assist device for refractory HF and cardiorenal syndrome was associated with an initial fast decrease in creatinine levels, followed by a more gradual decrease. However, it is interesting to note that early postoperative mortality correlated with the severity of preoperative renal dysfunction, implying the importance of renal function [88, 89].

Conclusions

Renal congestion is now acknowledged as a major contributing factor for worse outcomes in HF patients. The management of

renal congestion in cardiac failure remains an important but unresolved clinical challenge. Among existing hurdles, renal congestion cannot be directly measured. In addition, the pathophysiology of renal congestion is still incompletely understood. Several pathways may be involved, but there may be interpatient variability in activation of the involved systems and companion diagnostics to individualize the management of HF are needed, with a focus on preventing renal injury and decreasing renal congestion. Various treatment strategies alone or in combination can be used for this purpose. More randomized clinical trials are needed to investigate imaging strategies, therapeutic options and individualization of therapy strategies for renal congestion in HF.

Ethical approval

This is a review and thus there was no need for ethical approval. This article does not contain any studies with human participants or animals performed by any of the authors.

Acknowledgements

A.O. was supported by FIS PI13/00047, PIE13/00051, ISCIII-RETIC REDinREN RD12/0021, Comunidad de Madrid S2010/BMD-2378, CYTED IBERERC, Programa Intensificación Actividad Investigadora (ISCIII).

Conflict of interest statement

None declared.

References

- Aronson D. Cardiorenal syndrome in acute decompensated heart failure. *Expert Rev Cardiovasc Ther* 2012; 10: 177–189
- Ambrosy AP, Pang PS, Khan S et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013; 34: 835–843
- Pellicori P, Carubelli V, Zhang J et al. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. *JACC Cardiovasc Imaging* 2013; 6: 16–28
- Mullens W, Abrahams Z, Francis GS et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; 53: 589–596
- Damman K, van Deursen VM, Navis G et al. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; 53: 582–588
- Greene SJ, Gheorghiane M, Vaduganathan M et al. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. *Eur J Heart Fail* 2013; 15: 1401–1411
- Testani JM, Chen J, McCauley BD et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010; 122: 265–272
- van der Meer P, Postmus D, Ponikowski P et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol* 2013; 61: 1973–1981
- Rossignol P, Menard J, Fay R et al. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHEUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) sub-study. *J Am Coll Cardiol* 2011; 58: 1958–1966
- Rossignol P, Masson S, Barlera S et al. Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. *Eur J Heart Fail* 2015; 17: 424–433
- Aronson D, Abassi Z, Allon E et al. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. *Eur J Heart Fail* 2013; 15: 637–643
- Metra M, Davison B, Bettari L et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012; 5: 54–62
- Giamouzis G, Butler J, Triposkiadis F. Renal function in advanced heart failure. *Congest Heart Fail* 2011; 17: 180–188
- Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012; 60: 1031–1042
- Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. *Drugs* 1990; 39(Suppl 4): 10–21; discussion 22–24
- Blankstein R, Bakris GL. Renal hemodynamic changes in heart failure. *Heart Fail Clin* 2008; 4: 411–423
- Sambandam KK. Effective use of loop diuretics in heart failure exacerbation: a nephrologist's view. *Am J Med Sci* 2014; 347: 139–145
- Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. *Eur Heart J* 2011; 32: 2476–2478
- Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006; 47: 1–8
- Ganda A, Onat D, Demmer RT et al. Venous congestion and endothelial cell activation in acute decompensated heart failure. *Curr Heart Fail Rep* 2010; 7: 66–74
- Blake WD, Wegria R, Keating RP et al. Effect of increased renal venous pressure on renal function. *Am J Physiol* 1949; 157: 1–13
- Guazzi M, Gatto P, Giusti G et al. Pathophysiology of cardiorenal syndrome in decompensated heart failure: role of lung-right heart-kidney interaction. *Int J Cardiol* 2013; 169: 379–384
- Cheatham ML, White MW, Sagraves SG et al. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma* 2000; 49: 621–626; discussion 626–627
- Bloomfield GL, Blocher CR, Fakhry IF et al. Elevated intra-abdominal pressure increases plasma renin activity and aldosterone levels. *J Trauma* 1997; 42: 997–1004; discussion 1004–1005
- Harman PK, Kron IL, McLachlan HD et al. Elevated intra-abdominal pressure and renal function. *Ann Surg* 1982; 196: 594–597
- Verbrugge FH, Dupont M, Steels P et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013; 62: 485–495
- Karayannis G, Triposkiadis F, Skoularigis J et al. The emerging role of galectin-3 and ST2 in heart failure: practical considerations and pitfalls using novel biomarkers. *Curr Heart Fail Rep* 2013; 10: 441–449

28. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. *J Card Fail* 2012; 18: 930–938
29. Colombo PC, Ganda A, Lin J et al. Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. *Heart Fail Rev* 2012; 17: 177–190
30. Colombo PC, Onat D, Harxhi A et al. Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation. *Eur Heart J* 2014; 35: 448–454
31. Peschel T, Schonauer M, Thiele H et al. Invasive assessment of bacterial endotoxin and inflammatory cytokines in patients with acute heart failure. *Eur J Heart Fail* 2003; 5: 609–614
32. Niebauer J, Volk HD, Kemp M et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 1999; 353: 1838–1842
33. Goncalves S, Pecoits-Filho R, Perreto S et al. Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients. *Nephrol Dial Transplant* 2006; 21: 2788–2794
34. Colombo PC, Banchs JE, Celaj S et al. Endothelial cell activation in patients with decompensated heart failure. *Circulation* 2005; 111: 58–62
35. Harrison DG, Widder J, Grumbach I et al. Endothelial mechanotransduction, nitric oxide and vascular inflammation. *J Intern Med* 2006; 259: 351–363
36. Canty TG Jr, Boyle EM Jr, Farr A et al. Oxidative stress induces NF- κ B nuclear translocation without degradation of I κ B α . *Circulation* 1999; 100: II361–4
37. Facchini C, Malfatto G, Giglio A et al. Lung ultrasound and transthoracic impedance for noninvasive evaluation of pulmonary congestion in heart failure. *J Cardiovasc Med* 2015
38. Miglioranza MH, Gargani L, Sant'Anna RT et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging* 2013; 6: 1141–1151
39. Maisel A, Mueller C, Adams K Jr et al. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail* 2008; 10: 824–839
40. Pfister R, Muller-Ehmsen J, Hagemester J et al. NT-pro-BNP predicts worsening renal function in patients with chronic systolic heart failure. *Intern Med J* 2011; 41: 467–472
41. Felker GM, Lee KL, Bull DA et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; 364: 797–805
42. Fiaccadori E, Regolisti G, Maggiore U et al. Ultrafiltration in heart failure. *Am Heart J* 2011; 161: 439–449
43. Shiomi H, Matsubara K, Ariyoshi M et al. Efficacy and safety of continuous hemodiafiltration for acute decompensated heart failure. *Int Heart J* 2010; 51: 247–251
44. Schrier RW, Gross P, Gheorghide M et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; 355: 2099–2112
45. Morooka H, Iwanaga Y, Tamaki Y et al. Chronic administration of oral vasopressin type 2 receptor antagonist tolvaptan exerts both myocardial and renal protective effects in rats with hypertensive heart failure. *Circ Heart Fail* 2012; 5: 484–492
46. Gheorghide M, Konstam MA, Burnett JC Jr et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007; 297: 1332–1343
47. Goldsmith SR, Gilbertson DT, Mackedanz SA et al. Renal effects of conivaptan, furosemide, and the combination in patients with chronic heart failure. *J Card Fail* 2011; 17: 982–989
48. Badawy SS, Fahmy A. Efficacy and cardiovascular tolerability of continuous veno-venous hemodiafiltration in acute decompensated heart failure: a randomized comparative study. *J Crit Care* 2012; 27: 106.e7–106.e13
49. Massie BM, O'Connor CM, Metra M et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010; 363: 1419–1428
50. Elkayam U, Ng TM, Hatamizadeh P et al. Renal vasodilatory action of dopamine in patients with heart failure: magnitude of effect and site of action. *Circulation* 2008; 117: 200–205
51. Giamouzis G, Butler J, Starling RC et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. *J Card Fail* 2010; 16: 922–930
52. O'Connor CM, Starling RC, Hernandez AF et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; 365: 32–43
53. Pan S, Chen HH, Dickey DM et al. Biodesign of a renal-protective peptide based on alternative splicing of B-type natriuretic peptide. *Proc Natl Acad Sci USA* 2009; 106: 11282–11287
54. McMurray JJ, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004
55. Ponikowski P, Metra M, Teerlink JR et al. Design of the RELAXin in Acute Heart Failure Study. *Am Heart J* 2012; 163: 149–155.e1
56. Felker GM, Teerlink JR, Butler J et al. Effect of serelaxin on mode of death in acute heart failure: results from the RELAX-AHF study. *J Am Coll Cardiol* 2014; 64: 1591–1598
57. Konerman MC, Hummel SL. Sodium restriction in heart failure: benefit or harm? *Curr Treat Options Cardiovasc Med* 2014; 16: 286
58. Albert NM, Nutter B, Forney J et al. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *J Card Fail* 2013; 19: 1–9
59. Hummel SL, Seymour EM, Brook RD et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail* 2013; 6: 1165–1171
60. d'Almeida KS, Rabelo-Silva ER, Souza GC et al. Effect of fluid and dietary sodium restriction in the management of patients with heart failure and preserved ejection fraction: study protocol for a randomized controlled trial. *Trials* 2014; 15: 347
61. Aliti GB, Rabelo ER, Clausell N et al. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. *JAMA Intern Med* 2013; 173: 1058–1064
62. Gates PE, Tanaka H, Hiatt WR et al. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 2004; 44: 35–41
63. Jablonski KL, Racine ML, Geolfos CJ et al. Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. *J Am Coll Cardiol* 2013; 61: 335–343
64. Wessler JD, Hummel SL, Maurer MS. Dietary interventions for heart failure in older adults: re-emergence of the hedonic shift. *Prog Cardiovasc Dis* 2014; 57: 160–167
65. Michael Felker G. Diuretic management in heart failure. *Congest Heart Fail* 2010; 16(Suppl 1): S68–S72

66. Hasselblad V, Gattis Stough W, Shah MR et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007; 9: 1064–1069
67. Wilcox CS, Guzman NJ, Mitch WE et al. Na⁺, K⁺, and BP homeostasis in man during furosemide: effects of prazosin and captopril. *Kidney Int* 1987; 31: 135–141
68. Francis GS, Siegel RM, Goldsmith SR et al. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985; 103: 1–6
69. Jessup M, Abraham WT, Casey DE et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016
70. Dickstein K, Cohen-Solal A, Filippatos G et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29: 2388–2442
71. Shin JT, Dec GW. Ultrafiltration should not replace diuretics for the initial treatment of acute decompensated heart failure. *Circ Heart Fail* 2009; 2: 505–511
72. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. *J Am Coll Cardiol* 2012; 59: 2145–2153
73. Marenzi G, Grazi S, Giraldi F et al. Interrelation of humoral factors, hemodynamics, and fluid and salt metabolism in congestive heart failure: effects of extracorporeal ultrafiltration. *Am J Med* 1993; 94: 49–56
74. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; 121: 2592–2600
75. Rossignol P, Zannad F. Loop diuretics and ultrafiltration in heart failure. *Expert Opin Pharmacother* 2013; 14: 1641–1648
76. Bart BA, Goldsmith SR, Lee KL et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012; 367: 2296–2304
77. Costanzo MR, Fonarow GC, Filippatos GS. Ultrafiltration in heart failure with cardiorenal syndrome. *N Engl J Med* 2013; 368: 1158–1159
78. Sanchez JE, Ortega T, Rodriguez C et al. Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure. *Nephrol Dial Transplant* 2010; 25: 605–610
79. Nunez J, Gonzalez M, Minana G et al. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. *Eur J Heart Fail* 2012; 14: 540–548
80. Broekman KE, Sinkeler SJ, Waanders F et al. Volume control in treatment-resistant congestive heart failure: role for peritoneal dialysis. *Heart Fail Rev* 2014; 19: 709–716
81. Lu R, Mucino-Bermejo MJ, Ribeiro LC et al. Peritoneal dialysis in patients with refractory congestive heart failure: a systematic review. *Cardiorenal Med* 2015; 5: 145–156
82. Metra M, O'Connor CM, Davison BA et al. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. *Eur Heart J* 2011; 32: 1519–1534
83. Kellum JA, M Decker J. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; 29: 1526–1531
84. Cheng JW. Nesiritide: review of clinical pharmacology and role in heart failure management. *Heart Dis* 2002; 4: 199–203
85. Sackner-Bernstein JD, Kowalski M, Fox M et al. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; 293: 1900–1905
86. Paterna S, Di Pasquale P, Parrinello G et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. *J Am Coll Cardiol* 2005; 45: 1997–2003
87. Teerlink JR, Metra M, Felker GM et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009; 373: 1429–1439
88. Hanna EB, Hanna Deschamps E. Acute heart failure: acute cardiorenal syndrome and role of aggressive decongestion. *Clin Cardiol* 2014; 37: 773–778
89. Russell SD, Rogers JG, Milano CA et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. *Circulation* 2009; 120: 2352–2357