Heart failure and renal insufficiency often coexist in the same patient. Customarily, this condition is described as ‘cardio-renal syndrome’. In this situation mortality increases significantly as the renal dysfunction worsen. Treating these patients is challenging, due to their instability (congestion needs to be controlled, while maintaining, or not worsening, organ perfusion), making in-hospital and mid-term mortality hard to improve. Congestion represent the key characteristic of this syndrome, and its treatment is far from been standardized, considering that the condition represent, still, the first cause of re-hospitalization for these patients. Present treatment should be modified, because barely accounts for renal physiology and is responsible for ‘resistance to diuretics’, which eventually becomes iatrogenic, and non ‘sodium-dependent’ hyponatraemia. It is then important to emphasize the importance of the ‘sequential nephron blockade’, to decrease the number of ‘non-responder’ to diuretics, and the possible role of the ‘acquaretics’. 

Heart failure (HF) and renal insufficiency (RI) often coexist in the same patient. Customarily, this condition is described as ‘cardio-renal syndrome’. In this situation mortality increases significantly as the renal dysfunction worsen. In a meta-analysis evaluation more than 80 000 patients admitted to the hospital for HF, Smith et al., pointed out that the presence of RI increased mortality 1.5 times over the control group. When RI became severe (glomerular filtration rate < 30 mL/min/1.73 m²) mortality tripeled. It is relevant that not only an impaired renal function at hospital admission for HF has an impact on mortality, but also and foremost the worsening renal failure in a patients with initial normal kidney function. Worsening renal failure is clearly the most common clinical form of kidney dysfunction, often difficult to diagnose and grasp (there is no ‘troponin’ for the kidney), because the diagnosis still relies, essentially, on clinical evaluation. Treating these patients is challenging, due to their instability (congestion needs to be controlled, while maintaining, or not worsening, organ perfusion), making in-hospital and mid-term mortality hard to improve. Furthermore, the drugs routinely used in for this condition (diuretics, vaso-dilators, inotropes, etc.) improve the haemodynamic state, but worsen prognosis. This is an important concept, well known for inotropes, but often disregarded for diuretics. The latter, regardless the infusion modality (bolus or continuous infusion), requires progressively increasing dosages to treat the patients. Unfortunately, this practice further decreases renal perfusion, thus activating the renin-angiotensin-aldosterone system (RAAS), therefore, inciting more reabsorption of water and salt in an already over-loaded and congested patient.

Congestion and fluid overload are the defining features of this syndrome, and diuretic treatment is essential (Figure 1). The first-line and most popular drugs are certainly the loop diuretics. It is customary to follow the initial bolus dose with incremental quantities of the same molecule. Regrettably this practice, albeit well established, is flawed, and responsible for a ‘resistance’, which eventually becomes iatrogenic, and non ‘sodium dependent’ hyponatraemia.

Loop diuretics and congestion

The loop diuretics act directly on the ionic exchange, through structures called ‘sodium-potassium-2chloride channels’ within the thick portion of the ascending loop of glomerulus.
These are endoluminal structures, and the diuretic activity is not dependent on the plasma levels of the drug, but on the peritubular fluid levels, which is in the lumen. This detail is responsible for the decrease efficacy of the drug when renal perfusion is reduced for low cardiac output. The mechanism of action of these compounds also explains their limitations. When we compare the dose/effect curves in the cardio-renal patients vs. normal individuals (Figure 2), the curve shifts low and to the right,11,12 representing that: at the same dose the diuretic effect is lower; a progressively incremental dose is necessary to maintain or increase the diuretic effect (‘S’ shaped curve); and eventually a ‘plateau’ is reached where even massive doses of the drug are ineffective. This point is defined as ‘diuretic resistance’ and is dreaded by physicians for its negative impact on mortality.13 Diuretic resistance has many ‘actors’, but only one ‘director’: the RAAS, which excessively and inappropriately activated, acts on all the functional sites of the kidney, progressively decreasing its function, till anuria. Accordingly ‘diuretics resistance’, largely regarded as an adverse event, is, instead, the ‘normal’ physiologic response of the kidney in HF when ‘strained’ by loop diuretics alone. In fact, in HF, the reduced perfusion activates all renal functional sites, essentially through RAAS, to absorb water and salt to support an adequate blood volume. It is then a survival mechanism! Stimulating the kidney with loop diuretics alone, albeit with the appropriate doses and timing, triggers, through feed-back mechanisms, all the other functional sites responding to different diuretics, thus not blocked by the loop diuretics, and are activated either by increasing their velocity of action or with hyper-expression, where not present (such is the case of aquaporin), thus progressively negating the natriuretic effect, till anuria. As a consequence an appropriate management of the fluid overload in HF will require, from the beginning, an association of different diuretics, acting on different sites and with synergetic effects. This concept is conventionally referred as ‘sequential nephron blockade’ (Figure 3).

**Sequential nephron blockade**

The diuretic drugs combination should take into account the patients’ characteristics, grouping the various classes according to the stage of congestion, the rapidity the intervention requires, and the presence of comorbidities. In the acute setting and for patients with severe congestion, our protocol for diuretic treatment includes at least three diuretics of three different classes from the beginning.

To the continuous infusion of loop diuretics (e.g. furosemide 40-60 mg/h), which follows the bolus injection (e.g. 60-80 mg), we immediately add a thiazide diuretic, usually metolazone (5-20 mg/day orally), titrated to at least 10 mg/day for 3 or 4 days.14 A prolonged use is not recommended for the possibility of hyponatraemia. The drug has a long half-life which can be helpful. The third class of diuretics is the anti-aldosterone drugs, which should be used in all patients with advanced HF.15 We prefer canrenon (200 mg i.v. 2-3 times a day) with close monitoring of the serum potassium levels. Besides the strict diuretic effect, the pathophysiologic base for the use of this class of drugs is the secondary hyperaldosteronism distinctive of these patients. A valid alternative in patients with hyperkalaemia is the carbonic anhydrase inhibitor, usually acetazolamide (250-500 mg orally).16 This is an undervalued diuretic, mostly used in the treatment of glaucoma, that when used in combination with other diuretics could offer invaluable advantages. The acid-base balance should be carefully monitored for the possible acidosis associated with this
drug. A further opportunity is offered by a specific class of drugs, particularly effective: the acquaretics. Tolvaptan is the only drug in this class presently available for clinical use. In the ambulatory patients the same conceptual approach is followed, and the dosages are obviously adjusted according to the severity of congestion. This therapeutic plan is designed to decrease the incidence of 'non-responders', and allowed us to reconsider the parameters defining the ‘true’ diuretic resistance (Table 1, Figure 4).

Considering the renal mechanisms involved in HF, clarifies the notion reiterated in the Scientific Literature correlating incremental loop diuretics doses with the occurrence of ‘resistance’, which is eventually iatrogenic. Hyponatraemia, regularly associated with increased mortality, and burdened by a confusing definition, is, in the majority of cases, a disorder due to excess of water, rather than a sodium deficiency in need of correction. Data in the Literature are consistent, but the interpretation is only partially convincing. Diuretic resistance has been considered as predictable consequence of the disease and not an after-effect of a treatment dictated more by habit than attention to renal physiology.
The aquaretics

The aquaretics are non-peptide antagonists of vasopressin receptor. An increase blood level of vasopressin is often present in patients with HF and is proportional to the progression of the disease, contributing to water retention and hyponatraemia, both correlating to a worst prognosis.

Vasopressin is formed in the hypothalamus and acts on two types of receptors: V1, located in the heart and vascular system, increases peripheral resistances contraction through a rise in intracellular calcium, stimulates proliferation of vascular smooth muscle and increases platelet aggregation; V2, located in the renal collecting tubule where specifically increases the reabsorption of free water and exerts antidiuretic effect. These latter actions are key features of HF. None of the diuretics in the other classes commonly utilized can affect this mechanism of water reabsorption.

Several molecules have been developed able to bind with vasopressin receptors thus inhibiting their action and facilitate diuresis. The only one presently available for clinical use is Tolvaptan. Its selective action on V2 receptors establishes a very significant free water elimination, hence the name ‘aquaretics’. The increased diuresis is not combined with electrolytes loss, at variance form the traditional diuretics defined as ‘salt-losing diuretics’. The reference trial in HF is the EVEREST (The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), study which demonstrated a significant effect in alleviating congestion and other haemodynamic parameters, but no significant modification of the outcomes. Accordingly, the drug did not receive approval in Italy for treatment in HF, but only for treatment of hyponatraemia in syndrome of inappropriate secretion of antidiuretic hormone. Although the results of the trial with Tolvaptan have been disappointing, the very effective diuretic action would suggest further research efforts, probably addressing different endpoints.

Conclusions

Renal insufficiency is the most common complication of HF. Congestion and fluid overload are typical of this syndrome, but the treatment is presently based more on ‘habits’ than on solid physiology concepts. The interaction between the heart and the kidney in HF should generate a rational therapeutic approach, and an ongoing constructive debate.

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