Invited review article

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Unloading therapy by intravenous diuretic in chronic heart failure: a double-edged weapon?

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A well established part of therapeutic approaches applying to cases of chronic heart failure (CHF) with extreme fluid retention is represented by intensive intravenous (i.v.) therapy with loop diuretics. This kind of therapy, if appropriately modulated according to the individual clinical picture and biohumoral pattern, is able to decrease the abnormally high ventricular filling pressures, thereby relieving the breathlessness while being able to retrieve a suitable urine output, so as to propitiate regression or disappearance of edema without unfavorable influences on renal clearance of nitrogenous compounds. Nevertheless, the intensive i.v. diuretic therapy should be tailored on the basis of a close assessment of baseline hemodynamic data and hemodynamic response to the medications, in addition to the careful diuretic dose titration and cautious evaluation of risk/benefit ratio. Actually, by using this kind of therapy, there is a risk that a tubular or glomerular injury can be generated and that a frequently preexisting renal dysfunction can be aggravated, especially when excessive doses of loop diuretics are being erroneously administered, so as to cause hypotension, hypoperfusion and/or relative dehydration in patients with decompensated CHF who could have expressly benefitted from intensive unloading therapy. Recently, the genesis of CHF-related progressive renal deterioration has been highlighted by affirming that a major role may be played rather by neurovegetative disorders, that is, by increase in sympathetic tone and abnormalities in kidney's vasomotility than by cardiac inotropism deficiency. The measures, thought to be able to prevent renal arterial constriction and to impede deterioration of glomerular filtration rate (GFR) due to the ischemic–necrotic tubular injury, as occurring in the set of intensive unloading therapy with i.v. furosemide or other loop diuretic, are represented by application of inotropic and renal vasodilator support by dopamine i.v. infusion at low doses or by other inotropic agents provided with recognized renal vasodilator properties and/or by addition to i.v. furosemide of osmotic agents able to expand the hematic volume, so counteracting or minimizing the reflex renal vasoconstriction induced by furosemide-related reduction in intravascular circulating volume: i.v. infusion of small volumes of hypertonic saline solution, as well as administration of albumin, mannitol and/or plasma expanders. Because renal impairment, as developing in the setting of CHF, has proven to represent a very important indicator of adverse outcome, every effort should be addressed to prevent any significant (>25% of basal value) rise in serum creatinine consequent to diuretic unloading therapy or to other procedures (paracentesis of tense ascites, ultrafiltration) aimed at rapid fluid removal in edematous or ascitic CHF or cardiogenetic anasarca. Ultrafiltration, even though a promising technique highly valued for its acknowledged property to obtain a more rapid fluid and weight loss in CHF patients with marked fluid retention, has been demonstrated so far to produce neurohumoral activation, creatinine abnormalities and symptomatic hypotensions similar to those due to i.v. loop diuretics; thus, the hypothesized advantages of this technique remain to be further clarified and confirmed, with regard to its safety profile and cost-effectiveness.
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Intensive unloading therapy with loop diuretics in chronic heart failure patients with extreme fluid retention: light and shade

In chronic heart failure (CHF) patients with extreme fluid retention, the therapeutic weapon largely recognized as effective and useful, and most frequently applied, is represented by diuretics, particularly potent loop diuretics such as furosemide, torasemide, bumetanide and so on [1,2]. However, their use is burdened with many important side-effects and limitations, as is effectively highlighted by the review of Brandimarte *et al.* [3] reported in this issue. First of all, a lack of response to oral loop diuretics is known to be a common event [4], particularly in elderly patients with advanced CHF. Against this complication, the consequent therapeutic option usually lies in administering high doses of loop diuretics as intravenous (i.v) boluses or i.v. continuous infusion [5]. This therapy, in cases where it has been

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appropriately modulated according to the individual clinical picture and biohumoral pattern, is able to decrease the abnormally high ventricular filling pressures, so relieving the breathlessness while being able to retrieve a suitable urine output, so as to propitiate the regression or disappearance of edema without unfavorable influences on renal clearance of nitrogenous compounds.

Nevertheless, the intensive i.v. diuretic therapy should be tailored on the basis of a close assessment of baseline hemodynamic data and hemodynamic response to the medications, in addition to the careful diuretic dose titration and cautious evaluation of risk/benefit ratio. Actually, by using this kind of therapy, there is a risk that a tubular or glomerular injury can be generated and that a frequently preexisting renal dysfunction can be aggravated, especially when excessive doses of loop diuretics are erroneously administered, so as to cause hypotension, hypoperfusion and/or relative dehydration in patients with decompensated CHF who could have expressly benefitted from intensive unloading therapy [6]. Deterioration of renal function during i.v. furosemide-intensive regimen is believed to occur as a consequence of an abrupt or sharp drop in effective circulating hematic volume, in turn arising from both a direct venodilatory effect – especially on thoracic great veins – and rapid intravascular volume depletion, loop diuretic-related. The combined final result of these actions may be an important falling-off of cardiac output – due to more difficult recruitment of adequate preload – and a significant decrease in arterial systemic pressure. This, in turn, may elicit vasoconstriction and hypoperfusion of the renal arterial bed – even if the clinical picture of shock has not been attained – due to visceral and peripheral vasoconstrictor reaction, mediated via aortocarotid baroreceptors, as well as selective enhancement in vasoconstrictor drive of the renal afferent arterioles, mediated via juxta-glomerular and macula densa baroreceptor apparatus [7]. In addition, the combination, even though rather popular, of angiotensin-converting enzyme (ACE) inhibitors and high i.v. doses of loop diuretics seems to further decrease glomerular intracapillary pressure and glomerular filtration rate (GFR) [3] as a consequence of both reactive vasoconstriction, hypovolemia-related, of the afferent glomerular arterioles and simultaneous occurrence of impaired constrictive tone produced by angiotensin II inhibition on the glomerular efferent arterioles [7].

With regard to the studies [8,9] mentioned by Brandimarte *et al*. it is manifest that the safety of usual i.v. dosing regimens of loop diuretics has been questioned, mainly due to their potential, depending on dosage employed, for harmful hyperactivation of both renin–angiotensin–aldosterone system (RAAS) and sympatoadrenergic system (SAS), that is, just the undesirable compensatory neurohormonal reactions that should be mitigated or restrained, according to the contemporary guidelines for CHF therapy, by means of ACE inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists (concerning RAAS) or beta-blockers (as for SAS). Such a discrepancy could be alternatively interpreted by admitting the need for more cautious assignment and more careful modulation of loop diuretic dosage rather than by suggesting the idea of giving up the intensive i.v. diuretic therapy for edematous CHF patients and to routinely prefer, instead, the mechanical removal of interstitial excess of fluids (by means of conventional ultrafiltration or other techniques). Actually, to date, no trial is known to have demonstrated that ultrafiltration ensures a prolongation in the life expectancy of a CHF patient [9]. However, there are some studies that emphasize the capacity of obtaining greater weight and fluid loss by ultrafiltration compared with i.v. diuretics [8,9]; in spite of this, in the UNLOAD [9] trial, the evidence for a more rapid fluid loss by ultrafiltration was not associated with any demonstration of better response relative to safety end points, including renal function, electrolytes and blood pressure. Thus, as the main handicap of unloading intensive therapy with loop diuretic is represented by the frequent occurrence of renal functional impairment, treatment-related, as ascertained by a rise in serum creatinine (>0.3 mg/dl or $>25\%$, depending on the adopted algorithm, compared with basal levels), the similar incidence of renal worsening as found by comparing the edematous CHF patients undergoing ultrafiltration with those treated with i.v. diuretics does not make an attractive proposal for routine adoption of ultrafiltration instead of infusion of furosemide.

Why is it mandatory to prevent new-onset or aggravated mild-to-moderate renal dysfunction superimposed on chronic heart failure as a consequence of drastic or inappropriate intensive diuretic therapy?

Another issue that would merit particular emphasis is the reason for which any significant (≥ 0.3 mg/dl) rise in serum creatinine should be feared and, if possible, prevented, even though not so pronounced as to itself indicate the need for hemodialysis. The increase in serum creatinine in response to high dosages of i.v. loop diuretic reflects an acute decline in glomerular perfusion and filtration (so-called prerenal hyperazotemia) due to reduction in effective circulating hematic volume, diuretic-related. This depicts a kidney's homeostatic reaction, which strikingly resembles that seen in response to hemorrhage. Nevertheless, the general rule of offering a suitable rehydration to patients with shrinkage in fluid circulating volume (hemorrhagic, burned, dehydrated patients) does not seem to apply in cases where the reduction in circulating volume has been classified as spurious, that is related to a shift of large fluid volumes into the extravascular space rather than due to true losses of water and electrolytes from their total body pool; so, in most cases, the CHF patients with severe widespread

edema are considered and treated as hypervolemic patients, in spite of their state of impaired effective circulating volume.

Indeed, we agree with Brandimarte *et al.* [3] by sharing their fears concerning i.v. diuretic therapy at high doses – especially when not supplemented by osmotic agents [10,11] or dopamine at low doses [12,13] – to be able to entail the risk of starting a vicious cycle in which the recurrent courses of i.v. diuretic infusion are taking shape as a series of repeated threats against integrity and function of proximal renal tubules, known to be particularly vulnerable, differently from distal tubules [7], to ischemic hypoxia. The more the renal function declines – as a consequence, in the first instance, of sustained, reactive constriction of afferent arterioles and, subsequently, as a result of repeated episodes of acute and subacute tubular micronecrosis – the more unfavorable cardiac repercussions originate that are able to negatively influence the life expectancy of the CHF patient.

In truth, the underlying mechanisms, through which the CHF clinical picture and prognosis are worsened by new-onset mild-to-moderate renal insufficiency, have not so far been completely nor exhaustively explained and are likely to be numerous. On the basis of several studies [6,14], it is reasonable to gather that renal insufficiency may be more than a predictor of heart failure severity and instead may play a causative role in the progression of heart failure. So, a finding of renal impairment developing in the setting of CHF is considered to represent a very important indicator of adverse outcome, as 1% increase in mortality has been demonstrated to parallel each 1 ml/min decrease in creatinine clearance [14]. Actually, renal insufficiency is associated with multiple changes in vascular pathobiology that may worsen cardiovascular outcomes, including abnormalities in the coagulation/fibrinolytic systems, abnormal vascular calcification (due to elevated calcium–phosphorus products), endothelial dysfunction, hyperhomocystinemia, insulin resistance, elevated levels of C-reactive protein, disruptions in the endothelin/nitric oxide balance, electrolyte perturbations predisposing to arrhythmias and hyperactivation of the sympathetic nervous and renin–angiotensin systems [14]. Remarkably, the rule stating that doses of cardiotropic drugs have to be methodically undersized in the presence of chronic renal insufficiency does not apply just in case the dosage titration of furosemide for any CHF patient with renal function should be required. Actually, it is decreed – in this regard, see Ascend-HF protocol [15] and its suggested dosing schedule for the furosemide, as reported (Table 2) by Brandimarte *et al.* – to be greater (double at least) in CHF coupled with or complicated by chronic renal dysfunction (creatinine clearance $<60\,\text{ml}/(\text{min}\times 1.73\,\text{m}^2)$ compared with CHF without serious chronic renal damage (creatinine clearance $\geq 60\,\text{ml}/(\text{min}\times 1.73\,\text{m}^2)$. In fact, in the former, the augmented diuretic dosing is thought to be justified as aimed at compensating for a lesser amount of vital, recruitable loop diuretic-sensitive nephrons, as expected in the presence of organic renal damage. However, the existence of previous chronic renal insufficiency would deserve to be always carefully assessed and a hypovolemic state responsible for functional acute renal insufficiency and responsive to volume expansion – by saline solution, albumin or plasma expanders – should be accurately investigated before deciding which doses of furosemide or torasemide have to be employed for edematous CHF patients proposed for intensive i.v. diuretic administration. In this regard, the ADHERE [8] results represent an impressive warning, indicating the need to re-think our overall strategy for the management of CHF patients with copious fluid retention.

In conclusion, the study by Brandimarte *et al.* [3] appears not to disclaim the importance of loop diuretic i.v. therapy in the management of CHF with evidence of hydrosaline retention. Actually, according to them, the reported unfavorable effects of i.v. diuretic therapy in CHF patients could be impressively minimized by using lower doses of loop diuretic, by more accurately selecting the cases worthy of intensive i.v. therapy and by supplementing the diuretic i.v. drips by suitable measures able to attenuate the diuretic-related neurohormonal activation and volume depletion. As a renal impairment, developing in the setting of CHF, has to be considered a very important indicator of adverse outcome, every effort should be addressed to prevent any significant ($>25\%$ of basal value) rise in serum creatinine as a result of diuretic unloading therapy or other procedures (paracentesis, ultrafiltration) aimed at rapid fluid removal in edematous or ascitic CHF. Finally, according to them, as well as in our opinion, ultrafiltration, even though a promising technique highly valued for its acknowledged property to obtain a more rapid fluid removal and weight loss in CHF patients with marked fluid retention, has been demonstrated so far to produce neurohumoral activation and incidence of abnormal rise in creatinine and symptomatic hypotension similar to those due to i.v. loop diuretics; thus, the hypothesized advantages of this technique remain to be further clarified and confirmed with regard to its safety profile and cost-effectiveness.

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