Chapter 6
Responsiveness to loop diuretics in heart failure

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This editorial refers to Chapter 5, ‘Diuretic response in acute heart failure: clinical characteristics and prognostic significance’, by M.A.E. Valente et al.

Loop diuretics are the most commonly used drugs in the management of pulmonary and systemic congestion in patients with acute decompensated heart failure (ADHF), as well as chronic congestive HF. The diuresis results from blockade of the Na–K–Cl cotransporter in the ascending limb of the loop of Henle. The pharmacodynamics of loop diuretics are illustrated in Figure 1, and are best described as an S-shaped curve. The first few i.v. administrations to patients with HF and congestion cause a brisk diuresis with accompanying weight loss. Although loop diuretics may be life saving in patients with ADHF and pulmonary oedema, they have not been shown definitively to extend survival in patients with chronic HF, although they do play a critically important role in the reduction of oedema and dyspnoea.

![Figure 1 Dose–response curves for loop diuretics.](image)

Patients with chronic kidney disease (CKD) exhibit a rightward shift consequent to a reduction in the secretion of the diuretic. Patients with heart failure (HF) who have received multiple doses of a loop diuretic exhibit both a rightward shift and depression of the peak (maximal response reduced). Not shown is the elevation of the natriuretic threshold which further limits the response to orally administered diuretics. Reprinted with permission from Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132–143. S. Karger AG.
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Unfortunately, drug resistance develops frequently with repeated administration of loop diuretics\(^2,3\) and, as a consequence, fluid retention and congestion recur. Loop diuretic resistance is likely to be due to the operation of several counter-regulatory processes, which cause fluid retention. These include: (i) activation of the renin–angiotensin–aldosterone system (RAAS); (ii) activation of the sympathetic nervous system (SNS), which reduces renal blood flow and the quantities of Na\(^+\) and of the diuretic reaching the loop of Henle; and (iii) hypertrophy of the epithelial cells in the distal nephron, causing increased Na\(^+\) reabsorption.\(^1\) As a consequence, the diuretic concentration–Na\(^+\) excretion curve is displaced downward and to the right (Figure 1), the threshold concentration of drug required to achieve any diuretic effect rises, and the maximal diuresis that can be achieved declines. In addition, the presence of chronic kidney disease (CKD) contributes to the pathogenesis of diuretic resistance (Figure 1). In a meta-analysis including > 1 million patients with HF enrolled into 57 trials, Damman et al. found that one-third exhibited CKD during hospitalization, and one-fourth exhibited worsening renal function (WRF).\(^4\) Both CKD and WRF were independent predictors of mortality.\(^4\) Other investigators have also reported that WRF is an independent predictor of mortality, but only in patients with persistent congestion.\(^5\)

It is not clear whether the progression of HF and the accompanying activation of the RAAS and SNS combined with the reduction of renal blood flow is responsible for diuretic resistance and/or whether diuretic resistance plays a role in the poor outcome of patients with advanced HF. Most probably there is a vicious circle, in which impaired cardiac function, as well as excessive activation of both the RAAS and the SNS, augment Na\(^+\) retention. The reduction of renal perfusion, sometimes superimposed on CKD, leads to diuretic resistance. The latter, in turn, is responsible for the need for progressively escalating doses of loop diuretic, which cause further activation of the neurohormonal axes and of renal dysfunction culminating, in some patients, in the development of the cardiorenal syndrome,\(^6\) as well as in an increasing risk of adverse clinical outcomes. The latter include prolonged hospitalization, and/or rehospitalization for failure to relieve congestion, and shortened survival. In this vicious circle it is not clear whether diuretic resistance is only a risk marker for future adverse clinical outcomes, or whether it plays a causal role. I think that it is likely that diuretic resistance is both a marker and a ’player’. Whatever the pathophysiological mechanisms involved, it has been well established that the development of loop diuretic resistance is an ominous prognostic sign in patients with HF.

Increased efforts are underway to measure loop diuretic responsiveness and determine whether it predicts clinical outcome. Hasselblad et al. have reported a close correlation between the maximum in-hospital daily dose of loop diuretic and subsequent mortality in patients with HF\(^7\) (Figure 2). Two recent studies in patients hospitalized with HF have measured loop diuretic responsiveness and have related it to subsequent clinical outcomes. Testani et al. calculated what they termed ’loop diuretic efficiency’ as the fluid output in ml per 40 mg of furosemide equivalents administered. They found, in a post-hoc analysis, that patients whose loop diuretic
efficiency was below the median had a significantly higher mortality than those in whom it was above the median. Importantly, they then validated this approach in a second population.

Valente et al., in a post-hoc analysis of HF patients in the PROTECT trial, have now quantified the diuretic response defined as ‘Δ weight kg/40 mg furosemide’. Like Testani et al., they reported that a low diuretic response was an independent predictor of mortality and that it was an independent predictor of HF rehospitalization as well. A reduced diuretic response also correlated significantly with low systolic pressure, high blood urea nitrogen (BUN), diabetes, and arteriosclerosis, but surprisingly not with serum creatinine or estimated glomerular filtration rate. In addition, they found that age, BUN, and systolic pressure (all simpler to measure than diuretic responsiveness) were also independent predictors of mortality. Another recent analysis of the PROTECT trial, by some of the same authors, showed that the risk of mortality and hospital readmission could be predicted by renal function, as assessed by both creatinine and BUN 7 days after entry, as well as by the trajectory of plasma creatinine concentration during the first 7 days after hospital admission.

Figure 2 Relationship between maximum daily dose of loop diuretic, expressed in furosemide equivalents, and mortality at 180 days in 395 patients admitted to the hospital with decompensated heart failure.

The aforementioned efforts to quantify the diuretic response and to relate it to clinical outcome are highly commendable, since they may ultimately aid in the development of more individualized treatment plans for patients with HF, as more therapeutic options, such as device therapy, become available. However, there are significant limitations to both metrics, some of which have been recognized by the authors: (i) Both urine output and weight changes, while obviously simple markers of diuretic responsiveness, are notoriously difficult to measure precisely in hospitalized patients unless very special care is taken by a trained and motivated staff. (ii) Sodium intake is an important determinant of diuretic responsiveness, and is often difficult to control, even in hospitalized patients. (iii) The co-administration of other diuretics such as thiazides and/or mineralocorticoid receptor antagonists that are often administered to patients with loop diuretic resistance, as well as drugs which affect cardiac performance, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-adrenergic blockers, were not controlled. All of these could affect the diuretic response. (iv) The dose–response curve to loop diuretics is far from linear, and normally reaches an asymptote with increased dosing (Figure 1). This makes changes in weight or urine volume per 40 mg of furosemide equivalents difficult to interpret. (v) Finally, in the two studies mentioned above, the loop diuretics were administered both intravenously and orally. The conversion factor among these routes may differ between patients with HF whose intestinal absorption of orally administered drugs may differ. This conversion factor may also change in any given patient as the severity of HF waxes and wanes.

Given the aforementioned issues, the interpretation of these metrics is challenging and they may not yet be of value in the assessment of individual patients. It would be interesting to ascertain their reproducibility in the same subjects and under similar conditions. However, they may be quite useful in comparing groups of patients in assessing the effect of interventions on such groups. For example, the analysis by Valente et al., which was carried out in 1745 patients who were randomized to rololofylline, an adenosine A1 antagonist, or to placebo, showed a statistically significantly better diuretic response in the rololofylline group. Despite the current limitations, the efforts of these investigators represent the first serious attempts to put a number on an important variable in patients with HF—loop diuretic responsiveness, a variable that clinicians have previously described only qualitatively. This work is the forerunner of future approaches which will provide precise measurement of loop diuretic responsiveness and will thereby permit optimal dosing of these important drugs.
References

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