



## Diuretic resistance in decompensated chronic heart failure: trying to get out of the “loop”

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Although the advances due to the development of new therapies in the last 2 decades, chronic heart failure (CHF) represents so far a major healthcare issue, taking into account its high prevalence, the frequent presence of associated comorbidities and the still poor outcomes [1]. Frequent rehospitalizations for fluid overload and congestion often occur in patients in CHF, also being associated with an impaired quality of life and their related costs for healthcare systems [2]. Loop-diuretics are the cornerstone of the management of congestion in acute decompensated CHF [3], albeit their effects are often limited by the occurrence of diuretic resistance (DR), a condition defined as the presence of symptoms and signs of congestion despite appropriate diuretic dose.

The data reported by Trullás et al. [4] on this issue of *Internal and Emergency Medicine*, provide several insights on this relevant topic. The authors of this work performed an analysis on patients enrolled within a national-wide registry of patients with CHF (RICA-Registro Nacional de Insuficiencia Cardiaca) presenting to the emergency room with an acute decompensated CHF. Of note, patients without a prior known diagnosis of CHF were excluded from this analysis. The study aimed to compare patients with DR (defined as the presence of congestion despite a daily dose of  $\geq 80$  mg of furosemide or equivalents) with a second group of patients treated with a lower dose of loop-diuretics and a third group of patients not assuming any diuretics [4]. Trullás et al. [4] reported that 435 (21% of the total cohort of 2067 patients) presented symptoms at admission despite a diuretic dose of  $\geq 80$  mg of furosemide or equivalent dose of any other loop-diuretics (Torsemide or Bumetanide). This cluster of

patients was burdened by higher rate of comorbidities (such as diabetes, chronic kidney disease, hypercholesterolemia and cancer), and more advanced functional class. Diuretic resistance was also able to independently predict 1-year all-cause mortality (HR = 1.37, 95% CI 1.06–1.79;  $p = 0.018$ ) [4].

Several aspects of this works are worth to be stressed. First, according to these real-world nation-wide data, almost one patient each five presenting to the emergency room with congestion and fluid overload and a previous CHF diagnosis has already a background therapy with a consistent dose of loop-diuretic. Second, a possible role of comorbidity is suggested by the finding that patients with DR displayed higher rate of concomitant clinical conditions. Third, patients with DR represent a cluster of patients burdened by lower 1-year post-discharge survival. As suggested by the authors of this study, this subgroup of patients warrants more attention to implement more aggressive treatment strategies.

Further comments are also needed. According to baseline characteristics of this study, patients with DR are commonly undertreated, with a lower proportion of patients in the DR group assuming ACE-inhibitors (41% vs 48%, in DR patients and not DR patients, respectively). Moreover, patients with DR are also presenting with higher values of pulmonary pressures. We could speculate that the impairment of the right heart-pulmonary circulation unit is likely to lead to increased venous congestion that finally might result in more gastrointestinal edema and reduced absorption of drug [5]. Unfortunately, data regarding both right heart dimension and function, as well as measures of gastrointestinal congestion were not provided by the authors. Moreover, the presence of fluid overload was based on investigators' discretion and not based on objective data, as also acknowledged by the authors. Another limitation is that the definition used for DR is not standardized, since different definitions were used in other available studies [6, 7].

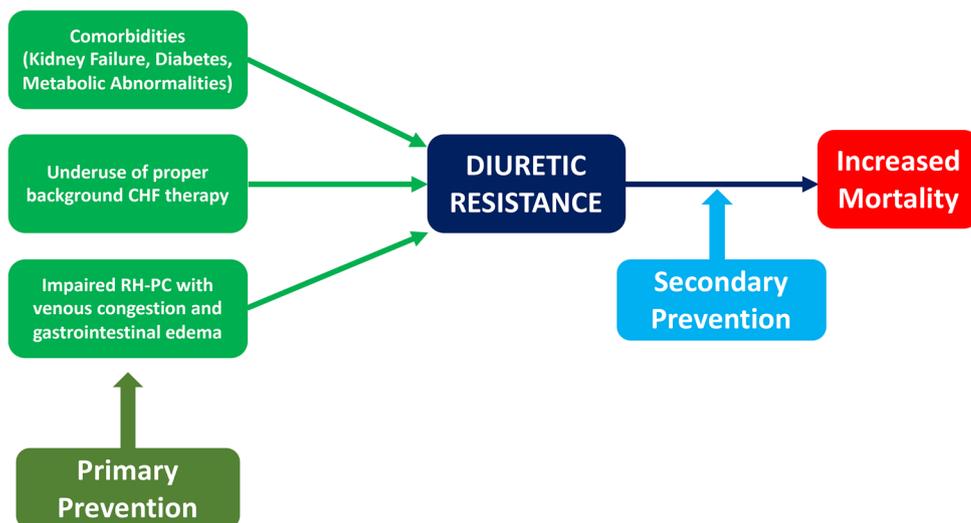
Summarizing, the aforementioned study of Trullás et al. [4] shed new light on a common condition of the all-day

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**Fig. 1** Possible underlying mechanisms of diuretic resistance and future prevention strategies. *CHF* chronic heart failure, *RH-PC* right heart-pulmonary circulation



CHF management. Several mechanisms might be associated with diuretic resistance in CHF (Fig. 1). Preventive strategies may help physicians in preventing such phenomenon. Moreover, given the strict association between diuretic resistance and poor outcomes, those patients with signs and symptoms of congestion should undergo more aggressive treatment to avoid either further rehospitalization and risk of all-cause mortality. Future studies are needed to focus on both these issues, to better enlighten the causes of diuretic resistance, promote strategies to prevent its occurrence and establish new treatment paradigms to treat more properly those patients with fluid overload despite appropriate dosage of diuretics.

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### Compliance with ethical standards

**Conflict of interest** The author(s) declare that they have no conflict of interest.

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### References

- Braunwald E (2013) Heart failure. *JACC Heart Fail* 1:1–20. <https://doi.org/10.1016/j.jchf.2012.10.002>
- Bello NA, Claggett B, Desai AS, McMurray JJV, Granger CB, Yusuf S et al (2014) Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail* 7:590–595. <https://doi.org/10.1161/CIRCHEARTFAILURE.113.001281>
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 37:2129–2200. <https://doi.org/10.1093/eurheartj/ehw128>
- Trullàs J-C, Casado J, Morales-Rull J-L, Formiga F, Conde-Martel A, Quirós R et al (2019) Prevalence and outcome of diuretic resistance in heart failure. *Intern Emerg Med*. <https://doi.org/10.1007/s11739-018-02019-7>
- Ferrara F, Gargani L, Ostfeld E, D’Alto M, Kasprzak J, Voilliot D et al (2017) Imaging the right heart pulmonary circulation unit: insights from advanced ultrasound techniques. *Echocardiography* 34:1216–1231. <https://doi.org/10.1111/echo.13594>
- Knauf H, Mutschler E (1997) Sequential nephron blockade breaks resistance to diuretics in edematous states. *J Cardiovasc Pharmacol* 29:367–372
- Neuberg GW, Miller AB, O’Connor CM, Belkin RN, Carson PE, Cropp AB et al (2002) Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 144:31–38

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