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'Door-to-furosemide' timing: early treatment of heart failure

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Almost 10 years ago Maisel and his group,[1] analysing the ADHERE Registry (Acute Decompensated Heart Failure National Registry) for the management of heart failure in the Emergency Room, first introduced the 'door-to-diuretic' time. The authors demonstrated that patients with chronic obstructive pulmonary disease, and previous episodes of heart failure or evident pulmonary congestion (dyspnoea, rales, or positive chest roentgenogram) were more likely to receive early treatment; for each 4 h delay in initiation of diuretic treatment, mortality increased significantly. Previously, an analysis of the same Registry[2] outlined that the decision to shift the initiation of treatment from the Emergency Room to the hospital wards entailed an unacceptable delay (2.7 h vs. 18.3 h), while, on the contrary, the early treatment reduced the hospital stay. In the same Registry,[3] slightly less than two-thirds of the patients received treatment within the first 6 h, and one-third 48 h after hospital admission. In the latter group of patients, mortality was correlated with the timing of treatment, and increased by 6.8% for every 6 h of delay. Hospital stay, need for intensive care unit, and symptoms at discharge were more prevalent in patients receiving late treatment.

These studies were criticized for their retrospective nature, the lack of a uniform estimation of the delay in treatment, and of the therapy delivered, prompting the first prospective study,[4] published in 2017, assessing mortality according to the timing (within or after the first hour) of treatment with furosemide in almost 1300 patients with heart failure. Patients receiving early treatment were slightly more than one-third and were affected with acute onset of symptoms, higher blood pressure and heart rate, and more evident signs of congestion. In-hospital mortality was higher for patients receiving late treatment (6% vs. 2.3%, $P = 0.002$), and remained as such after adjustment for heart failure severity indices (5.9% vs. 2.5%, $P = 0.038$), whether 30 days mortality was not significantly higher. The study also defined an optimal cut-off of 100 min for the first dose of furosemide, in fact, the curve correlating the timing of furosemide to mortality steeply increased the mortality risk to, approximately, the first 100 min, but this effect levelled off thereafter. As outlined by the authors and the accompanying editorial comment,[5] the therapy delay could explain the increased mortality because the persistence of heart failure may cause more significant organ dysfunction and the need for vasoactive drugs at higher doses, and a higher likelihood of untoward effects. On the other hand, the correlation between speed of intervention and decreased mortality could represent a response of a less compromised patient, or better yet, a 'virtuous' organizational system able to guarantee not only rapid interventions but also enduring optimal care.

In any event, the studies so far available had the merit to focus attention over the often overlooked issue of therapy delay in heart failure and stimulate the search of its cause.

At variance from the studies addressing the treatment of acute myocardial infarction, the timing of treatment in acute heart failure has been, to this point, underestimated. There is a strong suggestion, based on retrospective studies and the recent first prospective study, which appropriate time of treatment could reduce hospitalization and improve prognosis.

Interpreting these data is more debatable that in myocardial infarction, where early intervention save 'muscle', but in heart failure is not equally convincing that timely treatment could preserve the heart and other organ function.

Timely intervention in heart failure could reflect a better overall organization in the delivery of care, which, by itself, improves the prognosis of these patients.

It is clear that studies considering timing of intervention as a variable to assess the efficacy of treatment will be

necessary and is predictable that data will be derived from Registries rather than randomized studies for the ethical limitation in randomizing patient to early vs. delayed treatment.

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