Editorial

Where are the Benefits of Treating Acute HF in Light of Evidence-Based Medicine?

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Over the last 35 years, cardiology, especially the field of heart failure (HF), has witnessed a true therapeutic revolution based on scientific evidence. First, with vasodilators, moving on to the neurohumoral pathophysiological hypothesis with ACE inhibitors (ACEI), beta-blockers, mineralocorticoid antagonists, and, more recently, neprilysin inhibitors and SGLT2 inhibitors, caused a reduction in morbimortality rarely seen in the history of medicine. However, virtually all evidence associated with this impressive reduction in events comes at the expense of benefits in patients with chronic HF. The treatment of acute HF, despite its unequivocal biological plausibility, did not demonstrate the same success when tested in light of the best scientific evidence.[1] Nevertheless, where has evidence-based medicine failed?

The first point to be discussed is the heterogeneity of patients with acute HF. In this spectrum, we can range from individuals with sudden changes in blood pressure or patients with acute myocardial infarction, leading to ventricular dysfunction, to patients with chronic ventricular dysfunction, with recent decompensation of the compensatory mechanisms of their disease.[2] Still on this topic, we need to understand that the same syndrome can involve everything from extremely congested cases to people with hypovolemia, hypertensive emergencies, or extreme states of poor perfusion, leading each phenotype to different treatments and prognoses.[3]

Perhaps the point where few people disagree is the usefulness of diuretics in acute HF, especially loop diuretics. The main study testing loop diuretics in this scenario was DOSE-HF;[4] however, this trial tested intravenous furosemide against itself due to the extreme biological plausibility of its use, evaluating dose intensification schemes or frequency of administration. DOSE-HF only showed improvement in signs of congestion with "high doses", defined as 2.5 times the oral dose. More recently, the CLOROTIC[5] and ADVOR[6] studies demonstrated better results in decongesting patients when, respectively, hydrochlorothiazide and acetazolamide were added to loop diuretics in patients with acute HF, but both without results in mortality or other harsh outcomes.

Due to the benefit of SGT-2 inhibitors in the chronic treatment of HF and their action on the proximal convoluted tubule, studies have been dedicated to evaluating their role in association with loop diuretics for decongestion. To date, the results are still conflicting, but a good safety profile is admitted with the potential to increase urinary output, although with lower natriuresis compared to thiazides. There are still no studies with the association of SGLT-2 inhibitors and acetazolamide or thiazides, which should be carried out in the coming years since with the introduction of this class in the treatment of chronic HF, a large proportion of patients will be hospitalized using these medications.[7,8]

In patients with low output and poor perfusion, the use of inotropes is widely accepted as a rescue therapy. However, when we look at the trials that test them, the results are discouraging. Among the most used drugs in this class, dobutamine does not even have a large trial. The phosphodiesterase 3 inhibitor, milrinone, was evaluated in the OPTIME-CHF study, which demonstrated no difference in hospital stays with its use, suggesting harm in patients with ischemic cardiomyopathy.[9,10] The calcium channel sensitizer levosimendan even demonstrated a benefit within 30 days in the LIDO[11] study in relation to the improvement of hemodynamic parameters and mortality. However, when evaluated in a larger population sample and over a longer period in the SURVIVE study, it did not show any effectiveness.[12]

All of this can be explained by the fact that poor perfusion in patients with acute HF does not necessarily result from low cardiac output but rather from sympathetic hyperactivation, leading to intense peripheral vasoconstriction, which may lead us to believe that vasodilators would be the preferred solution. Neseritide (ASCEND-HF), Ularitide (TRUE-AHF), Serelaxin (RELAX-AHF-2), and a multiple strategy with hydralazine, nitrates, ACE inhibitors or angiotensin receptor blockers (GALACTIC) were tested without any positive hard outcome.[13-16] However, the vasodilators most used in clinical practice (especially sodium nitroprusside) were tested in smaller trials and with more promising results, mainly in patients with low cardiac output, justifying the premise that poor perfusion has a less intuitive pathophysiology in

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this case scenario. Mullens et al. demonstrated that the use of nitroprusside in patients with low output led to greater hemodynamic improvement, with less need for inotropes and less renal dysfunction, and even lower mortality from all causes.[17]

After hemodynamic compensation and correction of the causal factor for the exacerbation, a phase called transition of care begins, in which the patient is prepared for hospital discharge. At this stage, at least 3 measures must be implemented as they translate into prognostic improvement: a) guarantee euvolemia, avoiding as much as possible dehospitalization of the patient with residual or subclinical congestion; b) introduce disease-modifying drugs, pillars of pharmacological treatment responsible for the effective reduction of morbidity and mortality in the disease; c) schedule an early post-discharge return, ideally between 7-14 days. Recently, the STRONG-HF study demonstrated that after hospitalization for HF, the institution of an intensive strategy of titrating disease-modifying medications associated with close monitoring is capable of reducing death from any cause or hospitalization for HF, highlighting once again the importance of following the patient's care, especially in the vulnerable period.[18]

Perhaps it is at this point where the benefits of treating acute HF are most present. Not necessarily in a drug or an isolated therapeutic intervention, but rather in seeking a standardized, agile, aggressive therapeutic optimization strategy that allows patients in the post-hospital discharge phase to benefit from treatments already established for chronic HF (the 4 pillars). After all, when does acute HF become chronic HF?

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