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EDITORIAL COMMENT

Redefining the role of inotropes in advanced heart failure

Redefinindo o papel dos inotrópicos na insuficiência cardíaca avançada

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Continuous improvements in pharmacologic and nonpharmacologic therapies have markedly improved the prognosis of chronic heart failure (HF). Even so, up to 10% of patients progress to an advanced stage of the disease, defined by severe symptoms, low cardiac output (CO), persistent congestion and end-organ damage. At this point patients experience very low quality of life (QoL), frequent hospitalizations and high mortality. Conventional treatments are no longer sufficient to control symptoms and improve prognosis, and these patients require advanced therapeutic strategies, including heart transplantation and durable mechanical circulatory support.[1] For those deemed candidates, maintaining end-organ function is critical for ultimate success. In this context, periodic infusion of inotropes can be helpful as a bridge therapy to transplantation, left ventricular assist device (LVAD), or even palliative therapy, in the event of the first two solutions being unfeasible due to patient's characteristics.

Inotropes aim at increasing CO by enhancing cardiac contractility. They are the drugs of choice in patients with acute HF with hypoperfusion, but the history of their use in chronic HF is filled with disappointment. Despite hemodynamic and symptomatic improvement, there is no compelling evidence of a survival benefit. In fact, some inotropes can increase short- and long-term mortality,[2] a negative outcome attributed to a series of detrimental effects, including increased myocardial oxygen consumption, hypotension, tachycardia, and arrhythmogenesis.[3] However, most of the studies that reported detrimental outcomes predated the use of modern HF medications, implantable electronic devices (implantable cardioverter-defibrillators and cardiac resynchronization therapy devices), and even beta-blockers. More recent evidence has shown that treatment with intermittent low-dose inotrope infusions, in an outpatient clinic or at home, improves QoL without impairing survival.[4]

Levosimendan has some theoretical advantages in the setting of advanced HF due to its prolonged-action active metabolites, which have long-lasting effects (up to 14 days). Unlike other inotropes, levosimendan does not increase intracellular calcium or myocardial oxygen consumption, and thus enhances cardiac contractility with a lower risk of the ventricular arrhythmias that plague older inotropes. Levosimendan also has anti-inflammatory and antiapoptotic properties that may benefit patients with advanced HF.

In advanced HF, levosimendan has been studied in the setting of intermittent outpatient administration. In the

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LevoRep trial, four six-hour cycles (0.2 μg/kg/min) were administered at two-week intervals. There was no improvement in functional capacity or quality of life compared with placebo after 24 weeks.[5] However, the authors found a non-statistically significant 50% reduction in the composite outcome of risk of death, heart transplant, or acute HF. In the more recent LION-HEART trial, levosimendan significantly reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. This translated into clinical improvement, with reductions in composite endpoints, including hospitalization (all-cause, cardiovascular or HF) and terminal events with similar safety and tolerability to placebo.[6] These results suggest that cyclic administration of levosimendan in an outpatient setting is a safe treatment with clinically beneficial effects. The ongoing LeoDOR trial tests the hypothesis that repetitive levosimendan infusions improve outcomes when applied during the vulnerable post-discharge period.

A special population within advanced HF patients consists of those awaiting heart transplantation. Irreversible pulmonary hypertension puts potential heart transplant candidates at high risk of post-transplant right ventricular (RV) failure. Appropriate and frequent pre-transplant assessment of cardiopulmonary hemodynamics is therefore crucial to risk stratification in patients with increased pulmonary vascular resistance. This may be improved by using vasodilators or inotropes to provide a dynamic assessment of pulmonary circulation. Recent evidence from our center suggests that when used for vasodilatory challenge, levosimendan had a more significant impact on cardiac index, and increased both left and right ventricular stroke work, compared to nitric oxide and iloprost. Levosimendan was the only drug that reduced filling pressures.[7] With its favorable effects on end-organ function, particularly in the kidney, levosimendan could serve as the ideal bridge for patients awaiting heart transplantation. Recently, Ponz de Antonio and colleagues have shown that in a population of 11 patients waiting for heart transplantation, a fixed-time scheduled infusion of levosimendan reduced the rehospitalization rate and the need for urgent transplantation compared to historical data.[8]

The beneficial hemodynamic and non-hemodynamic effects of levosimendan have similar importance for patients awaiting LVAD implantation. As pulmonary hypertension and RV failure are also significant hazards post-implantation, levosimendan can play a unique beneficial role.[9] Small case series also suggest that the adjunctive use of levosimendan in patients with severe mitral regurgitation and left ventricular (LV) dysfunction undergoing edge-to-edge mitral repair may increase technical success, by reducing LV volumes and mitral valve annular dimensions, and be associated with a lower risk of hemodynamic deterioration. Although these results are promising, they derive from small, uncontrolled local experiences, and their external validity and applicability must be viewed with caution.

In this issue of the *Journal*, Reis et al. present the first Portuguese experience of intermittent levosimendan administration in outpatient advanced HF patients.[10] They deserve to be congratulated for their excellent work. Despite the limitations of a pragmatic design, they performed clinical, biochemical, and, most importantly, advanced echocardiographic and functional assessments using cardiopulmonary exercise testing (CPET). The population was highly symptomatic, with more than 50% of patients in New York Heart Association (NYHA) functional class IV referred as a bridge to heart transplantation or LVAD. The care of these patients is highly challenging and, we dare to state, is among the most specialized and high-value forms of healthcare a cardiology department can offer, even in the era of devices and complex structural interventions. The excellent results achieved, including five patients eventually receiving a heart transplant, cannot be attributed solely to levosimendan or any current or future drug. Such success is only possible by including these patients in a structured multidisciplinary program led by specialist heart failure professionals, in which levosimendan administration, coupled with a multitude of other interventions, ultimately leads to better outcomes. Significant reductions in NYHA class, hospitalizations and NT-proBNP were observed, without any significant adverse effects. The authors also performed advanced echocardiographic assessments, reporting significant improvements in LV systolic function, as measured by LV ejection fraction and global longitudinal strain. One of this work's most innovative aspects is its use of CPET to measure functional capacity. The improvements in both peak oxygen uptake (+2.5 ml/kg/min) and ventilatory efficiency (−3.1 in VE/VCO_2 slope) could have both symptomatic and prognostic significance.

Although evidence in its favor is mounting, the story of intermittent inotrope infusions in advanced HF has only just begun, and many questions are still unanswered:

- What is the optimal dose and duration of treatment for outpatient advanced HF?
- Is the effect maintained over time, or does tachyphylaxis develop?
- Can patients with HF with preserved ejection fraction derive similar benefits?

Those of us who care for these patients are eager for answers.

Conflicts of interest

The authors have no conflicts of interest to declare.

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