

Levosimendan: New hope therapy for takotsubo syndrome

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Takotsubo syndrome (TS) is acute usually reversible heart failure (HF) which has gained increasing recognition since first described by Sato et al. in 1990 [1]. Although it has been diagnosed more often over the past decades, the clinical features of TS are complex including multifaceted clinical presentation, often mimicking acute coronary syndrome and symptoms not always preceded by a stressful physical or emotional trigger [2]. In the vast majority, TS affects post-menopausal women (~90%), however ~10% of males develop TS with a higher risk of more frequent life-threatening complications (i.e. cardiac arrest, ventricular fibrillation, sudden cardiac death etc.). Evidence from numerous case reports and international registries indicates that TS commonly features left ventricle (LV) dysfunction with apical ballooning and contrast retention in the apex and occurs in the absence of culprit atherosclerotic epicardial coronary artery occlusion [3]. However, it may also involve the right ventricle, LV with many anatomical variants and can present with co-existing coronary artery disease (CAD) [2, 4]. Generally, TS is regarded as a reasonably benign condition with a good long-term prognosis and diagnostic criteria nearly resolved > 4 weeks [5]. However, in the acute phase TS can result in HF, cardiogenic shock, arrhythmia, mitral regurgitation, ventricle thrombus, LV outflow tract obstruction and cardiac rupture with up to 4–5% in-hospital mortality, 3–17% 5-year mortality and with a recurrence rate ranging between 5% and 22% over a 5-year period, with the second episode occurring 3 months to 10 years after the first diagnosis [2, 3, 6]. While this clinical experience has advanced our knowledge, leading to a better understanding

of clinical features and anatomical variants which makes TS more complex and multifactorial than originally thought with the underlying pathophysiology still unclear. Therefore, therapeutic management for TS is still under debate and remains empirical with no evidence from randomized clinical trials available to date. Moreover, the use of catecholamine infusion is controversial and should be rather avoided in compromised TS, likely inducing or worsening ventricle dysfunction. In this context, levosimendan may become a new player in the field of TS therapy. Indeed, levosimendan currently indicated for the treatment of acute decompensated HF appears to be a promising therapeutic approach in TS patients [7]. Levosimendan exerts both inotropic and vasodilatory effects via increasing cardiac contractility mediated by calcium sensitization of troponin C and producing vasodilation through opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle cells. Aside from its clinical indication in treating acute decompensated HF, benefits of levosimendan have been demonstrated in other clinical conditions including cardiogenic or septic shock, cardiac surgery and advanced chronic HF [8–10]. First evidence for the use of levosimendan comes from 4 case reports who developed TS-related cardiogenic shock [11–13] or sepsis-associated TS [14]. Further support demonstrating the safety, feasibility and efficacy of levosimendan has been reported in a first prospective pilot study which included 13 consecutive patients with TS and severe ventricle dysfunction [15]. A continuous infusion of levosimendan at a dose of 0.1 µg/kg/min within the first 24-h of hospital admission improved

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LV ejection fraction ($28 \pm 5\%$ at admission vs. $51 \pm 8\%$ at discharge, $p < 0.001$). In general, levosimendan was well-tolerated however there was 1 case of sinus tachycardia and a case of torsade de point without inducing ventricular tachycardia. Average hospital stay was 10 ± 4 days and all patients were followed-up on average over 441 days.

In this issue of 'Cardiology Journal' Yaman et al. [16] provide first evidence for the effectiveness of a loading dose of levosimendan administered in the acute phase in TS patients with LV dysfunction. An infusion of levosimendan at a rate of $0.1 \mu\text{g}/\text{kg}/\text{min}$ with its loading dose of $10 \mu\text{g}/\text{kg}$ added to standard-drug therapy (i.e. ACE/ARB, beta-blockers) reduced recovery time with LV ejection fraction returning to $> 50\%$, the time for normalization of troponin values and hospitalization in TS patients ($n = 17$) when compared to those TS patients ($n = 25$) who did not receive levosimendan within the first 24 h following hospital admission. All patients at admission demonstrated the absence of CAD in angiogram and demonstrated acute LV dysfunction triggered by preceding physical or emotional stress. While there were no electrocardiographic changes at follow-up between both groups, notably the recovery period associated with levosimendan therapy was reduced.

Although this study is retrospective and non-randomized which could be viewed as a limitation, authors deserve credit for conducting this investigation further aimed at determining the role of a loading dose of levosimendan in the treatment of TS. The patient follow-up was inadequate to assess prognosis and recurrence rate over the longer term following levosimendan therapy which hopefully further multicentre randomized clinical trials will address. Given the uncertainties regarding the TS pathophysiology there is a need to continue with further research to unravel mechanisms underlying this condition which is integral to establish a treatment for TS.

Conflict of interest: None declared

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