Levosimendan: The Inotrope of Choice in Cardiogenic Shock Secondary to Takotsubo Cardiomyopathy?

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Takotsubo cardiomyopathy (TC) has become an increasingly recognised entity in Western literature since its initial reporting in Japan. The pathogenesis underlying the myocardial stunning and systolic dysfunction is thought to be induced by elevated systemic levels of catecholamines and neuropeptides. Whilst the majority of patients are haemodynamically stable, a small proportion can develop cardiogenic shock. This creates a therapeutic dilemma because inotropic support using exogenous catecholamines (adrenaline, dobutamine, dopamine) may be counterproductive. Two cases where the calcium sensitizer levosimendan (a non-catecholamine inotrope) was used successfully in TC-related cardiogenic shock are presented. The management of circulatory compromise in TC is then discussed.

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Introduction

Takotsubo cardiomyopathy (TC) is a form of reversible cardiac stunning with angiographically "innocent" coronary arteries first described in the early 1990s. The myocardial dysfunction seemingly involves more than one vascular perfusion territory causing apical and mid-ventricular akinesis (or dyskinesis) and basal hyperkinesis. Initially thought to be a Japanese phenomenon, reports began emerging a decade later in Western literature under various entities such as LV apical ballooning syndrome, stress cardiomyopathy, reversible LV dysfunction and "broken heart" syndrome. The common theme of clinical presentation following severe emotional or physiological stress was also found in Western studies. An important initiating factor for the systolic dysfunction is thought to be the supra-physiologic levels of plasma catecholamines and stress-related neuropeptides. It is unclear, however, whether this is truly causal or an epiphenomenon as only 75% of TC patients have increased catecholamines measured. The clinical presentation is similar to an acute myocardial infarct or acute coronary syndrome with most cases described in post-menopausal women. A recent review showed that TC accounts for ~2% of ST-segment elevation coronary syndromes. This has important implications in centres where coronary angioplasty is unavailable and the patient becomes exposed to the risks of unnecessary thrombolysis. Approximately 70% of patients present with chest pain and ~18% with dyspnoea. Serious complications such as cardiogenic shock (4.2%) or ventricular fibrillation (1.5%) can also occur.

Marked ECG changes in the acute and subacute phase include ST-segment elevation (89.6%) and/or T-wave inversion (64.3%). QTc prolongation has also been reported. In contrast, although cardiac enzymes such as CKMB and troponins are elevated, the increase is minimal compared with the ECG abnormalities. Echocardiography reveals left ventricular dysfunction at the apex and the mid-ventricle. Contraction in the basilar portion is normal or hyperkinetic. Other variants with only mid-ventricular ballooning have also recently been described. The ejection fraction may decrease to 20–49% in the acute phase. Possible complications of TC such as dynamic left ventricular outflow tract obstruction, mitral regurgitation due to systolic anterior motion (SAM) of the anterior leaflet and LV thrombus formation have also been documented. Although rare, free wall rupture can also occur.

Coronary angiography and ventriculography confirm the diagnosis. It reveals (a) no obstruction or significant stenosis in the coronary epicardial arteries and (b) hyperkinetic basal region and an akinetic apex and mid-ventricle. This gives the end-systolic appearance of...
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Figure 1. Japanese fisherman’s octopus bottle (Takotsubo).

Figure 2. Case 1: pre-intubation ECG demonstrating non-specific changes.

Case Reports

Case 1

An 80-year-old lady was admitted to hospital with difficulty swallowing and neck muscle weakness secondary to an exacerbation of myasthenia gravis. Despite pyridostigmine, neostigmine and methylprednisolone she developed a myasthenic crisis. She was admitted to the intensive care unit (ICU) with worsening Bulbar palsy, hypercapnoea and increasing obtundation. Muscle relaxants were avoided and the patient intubated using propofol intravenously and lignocaine sprayed in the oropharynx. Following airway intubation, acute anterolateral T-wave inversion was noted on a 12 lead ECG (Figs. 2 and 3). An urgent transthoracic echocardiogram (TTE) revealed normal LV size with severe apical and mid-LV segmental systolic dysfunction and reduced left ventricular ejection fraction at 30–35%. The basal posterior and lateral walls were relatively preserved. Given worsening hypotension, peripheral shutdown and increasing lactate, the patient was diagnosed clinically to be in cardiogenic shock and commenced on dobutamine and noradrenaline infusions. Surprisingly, an urgent coronary angiogram revealed normal epicardial coronary vessels. The ventriculogram, however, demonstrated apical and mid-ventricle akinesis with basal hyperkinesis consistent with Takotsubo cardiomyopathy (Fig. 4). A pulmonary artery catheter was inserted and a satisfactory cardiac index (CI) of 2.69 L/min/m² was obtained on dobutamine (5 mcg/kg/min) and noradrenaline (11 mcg/min). At this point it was decided to try and limit catecholamine dose and levosimendan (0.2 mcg/kg/min) was introduced (without a loading dose). Dobutamine was weaned and ceased. CI increased to 3.5–4 L/min/m². Levosimendan

cucium sensitiser levosimendan. To our knowledge, its use has not been described before in TC. Two such cases where levosimendan was successfully used are presented.
was ceased after three days. Given ongoing vasodilation, noradrenaline continued and ceased after 3.5 days. The longer-than-standard (three vs. one day) duration of therapy with levosimendan was because of its removal from plasma with plasma exchange which the patient required as part of myasthenic crisis treatment. The patient was sedated with propofol and dexmedetomidine to facilitate ongoing mechanical ventilation.

TTE, two days post-levosimendan, showed improved LV function with only mild segmental LV dysfunction and mild distal and mid-septum hypokinesis. TTE, one week post-levosimendan, showed normal LV systolic function.

Her myasthenia improved such that she could be extubated. Hypertension and tachycardia subsequently developed requiring anti-hypertensives and beta blockers.

Case 2
A previously healthy 80-year-old male underwent functional endoscopic sinus surgery (FESS) under local anaesthetic (bupivicaine with adrenaline) and sedation (midazolam). A small dose of opiate (fentanyl 75 μg in increments) was also used. Although the procedure proceeded uneventfully, postoperatively he developed a sinus tachycardia (140 beats per minute) and hypertension (236/144 mmHg) in the recovery room. Despite intravenous glyceryl trinitrate and esmolol, he also developed acute pulmonary oedema requiring intubation and mechanical ventilation.

A 12 lead ECG demonstrated acute ST elevation across the anteroseptal leads. Only subcostal views were possible on a TTE which showed normal LV size but severe hypokinesis involving the entire apex, inferoapical and anteroapical segments. RV was normal in size with mildly reduced systolic function. An urgent coronary angiogram was performed with intra-aortic balloon pump insertion but demonstrated no significant coronary stenoses. The ventriculogram, however, demonstrated classic Takotsubo cardiomyopathy with anteroapical akinesis and basal hyperkinesis. The LVEDP was 25 mmHg with no gradient across the left ventricular outflow tract.

Despite adequate blood pressure augmentation with the IABP, a progressive lactic acidosis developed and a pulmonary artery catheter was inserted revealing a CI of 1.46 L/min/m². Levosimendan was commenced at 0.05 and then increased to 0.1 mcg/kg/min and the cardiac index improved to 3.1–4.7 L/min/m² for the remainder of the ICU stay. The metabolic acidosis resolved after 1 h of levosimendan use and the pulmonary oedema cleared such
that the patient was extubated at 16 h. The balloon pump was able to be weaned and removed after 24 h. The levosimendan was ceased after 37 h (day 2). ACE inhibitors were commenced on day 3 and beta blockers on day 4. He was discharged home on day 8. A follow-up outpatient TTE was performed on day 10. LV and RV systolic function had returned to normal with no residual wall motion abnormalities.

Discussion

When shock intervenes in TC, treatment options include intra-aortic balloon pump insertion and, in cases of refractory hypotension, inotropes such as adrenaline, dopamine and dobutamine. However, these drugs increase cAMP within the cell, increase myocardial oxygen consumption and may worsen myocardial stunning.22 Phosphodiesterase inhibitors such as milrinone also increase cAMP within the cell.22 Whilst they do not significantly increase myocardial oxygen consumption, they may also be problematic as they can cause vasodilation, hypotension and atrial arrhythmias.21

Levosimendan, by contrast, is a non-catecholamine inotrope and does not increase myocyte cAMP or oxygen consumption. It binds to the N terminal lobe of cardiac TnC and stabilises the Ca2+-bound conformation of this regulatory protein.23 This produces a prolongation of interaction between actin and myosin filaments in systole and hence increases myocardial systolic performance during the higher systolic levels of cytosolic Ca2+. By contrast, this interaction ceases during the lower cytosolic Ca2+ levels of diastole, thereby not compromising LV diastolic function.24 Unlike catecholamines (adrenaline, dobutamine, dopamine) or phosphodiesterase inhibitors (milrinone), which increase cAMP and hence Ca2+ fluxes within the cell, levosimendan increases contractility (and cardiac output) using normal cellular calcium fluxes. In addition, it opens adenosine triphosphate-dependant potassium (KATP) channels which causes vasodilation. This decreases preload, pulmonary vascular resistance and afterload, and improves coronary perfusion. The (KATP) channel opening also has an anti-stunning, anti-ischaemic effect.23 Positive long-term survival effects for up to six months have been demonstrated with levosimendan use.24,25

The use of levosimendan has not been previously described in TC. However, its pharmacodynamics and the probable contribution of catecholamines to the pathogenesis of TC make it theoretically the inotrope of choice in TC-related shock. The underlying myocardial stunning is thought to be initiated by increased levels of plasma catecholamines and stress-related neuropeptides.2 This increase may occur during periods of emotional or physiological stress.26,27,28 However, the mechanism linking the catecholamine surge to the apical and mid-ventricular dysfunction has not been convincingly elucidated. The possible mechanisms canvassed in the literature include multivessel epicardial spasm, neurogenically mediated stunning, microvascular spasm and direct catecholamine-induced myocardial injury.2

All of these mechanisms, however, would indicate catecholamines should be avoided if possible.29 This is because they may not only prolong but also worsen TC regardless of the mechanism that is finally determined to be causal. Another mechanism that has recently been proposed is ‘spontaneous aborted myocardial infarction’.30 Although it is widely viewed that the area of akinosis in TC extends well beyond the perfusion territory of a single coronary artery,31 Ibanez et al. challenge this.30 They propose that TC patients may have a long ‘wrap around LAD artery’ that supplies not only the anterior wall but also the inferior LV apex.32 This is best displayed in the left lateral view (90° left anterior oblique). This view is not normally performed in most catheter laboratories. They argue that unless this view is obtained, one cannot conclude that the ‘wrap around LAD’ is absent. Whilst this theory does not explain the mid-ventricular dysfunction that is commonly seen in TTC, levosimendan has in fact been demonstrated to be effective for post-ischaemic myocardial stunning.25

Case Commentary

The increased sympathetic outflow precipitating TC in Case 1 may have been caused by hypercapnoea and laryngoscopy. Profound hypercapnoea obtundation, together with a small dose of propofol and lignocaine spray, was insufficient to ablate laryngeal reflexes and prevent a sympathetic surge. Including fentanyl or esmolol to facilitate intubation, however, may have averted this. Despite the adequate cardiac output (CO) with dobutamine, it was felt that catecholamines should be avoided. Levosimendan in this case was well tolerated. Desemdetomine was also used as a sedational agent to facilitate mechanical ventilation. Given that it is an α-2 agonist which has a sympatholytic effect, it also is an ideal choice for sedation in intubated TC patients. In higher doses, levosimendan can cause systemic vasodilation and decrease the MAP despite increasing the cardiac output. In this case noradrenaline was continued to support the blood pressure; however, its β1, α1adrenergic effect could have exacerbated or prolonged resolution of the TC.

Vasopressin is theoretically an attractive alternative to noradrenaline as it has been used in other causes of vasodilatory shock and hypotension. However, one would have to balance between systemic vasoconstriction to augment blood pressure and possible coronary vasoconstriction that may worsen TC.

In Case 2, the sympathetic stimulus may have been pain following a sedational anaesthetic. In this case the circulatory state was deteriorating despite IABP use. However, there was a rapid improvement following levosimendan commencement. Beta blockers and ACE inhibitors were able to commence relatively early.

It could be argued that given the low mortality of 1.1%2 and excellent prognosis, does it matter that catecholamines are used to support the acute phase? They are cheaper (in Australia) and there is wide familiarity with their use. However, it is equally possible that levosimendan may significantly accelerate the rate of recovery in TC-related cardiogenic shock. There is also widespread famil-
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Figure 5. Algorithm for the management of haemodynamic instability in Takotsubo cardiomyopathy. LVOT, left ventricular outflow tract; IABP, intra-aortic balloon pump; PiCCO, pulse-integrated continuous cardiac output; PAC, pulmonary artery catheter; ACE, angiotensin-converting enzyme.

...arity with its use especially in Europe. It also does allow the earlier introduction of beta blockers which are known to facilitate recovery in TC. There is a strong physiologic rationale for the use of levosimendan in TC. An algorithm (Fig. 5) for the management of haemodynamic instability in TC is suggested. However, despite our positive experience, further studies are required to determine whether levosimendan may be the inotrope of choice in TC.

Conclusion

The safe use of levosimendan when shock from TC is refractory to preload optimisation and IABP use has been demonstrated. Whilst there is a strong physiological rationale for its use, a randomised prospective trial is needed to answer whether levosimendan is conclusively the inotrope of choice in TC-related cardiogenic shock.

References