

# Pulsed Levosimendan in advanced heart failure due to congenital heart disease: a case series

James Cranley \*, Antonia Hardiman <sup>2</sup>, and Leisa J. Freeman <sup>2</sup>,

Cardiology Department, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, UK

Received 8 October 2019; first decision 23 October 2019; accepted 17 March 2020; online publish-ahead-of-print 1 May 2020

## Background

Levosimendan is a non-adrenergic calcium-sensitizing agent with positive inotropic and vasodilatory effects. Its use in acute decompensation of heart failure is established. Good evidence now exists for repetitive infusions of Levosimendan to improve symptoms and reduce hospitalization in advanced heart failure (AdHF) populations. Its use in heart failure resulting from congenital heart disease is not yet commonplace.

## Case summary

We present three cases in which pulsed Levosimendan was used in the management of AdHF secondary to underlying congenital heart disease. There was symptomatic and biomarker evidence of improvement.

## Discussion

Intermittent Levosimendan may represent a valuable therapy to reduce hospitalization and improve quality of life in adults with congenital heart conditions.

## Keywords

Advanced heart failure • Levosimendan • Adult congenital heart disease • Case series

## Learning points

- Patients with advanced heart failure secondary to congenital heart disease are growing in number owing to increasing survival to adulthood in surgically palliated conditions.
- Levosimendan is a calcium-sensitizing inotropic agent which has shown benefit in other heart failure settings.
- The long half-life of Levosimendan lends itself to intermittent therapy in the outpatient setting, and in our case series, it improved symptoms and avoided hospital admission.

## Introduction

Levosimendan is an inodilator, improving contractile force without affecting calcium transient magnitude by binding to the cardiac troponin C subunit. It causes vasodilation by increasing the opening probability of ATP-sensitive potassium channels on vascular smooth muscle cells, leading to reduced systemic and pulmonary vascular

resistance.<sup>1</sup> The combined effect reduces afterload and increases inotropy with consequent improvement in cardiac output and reduction in systemic and pulmonary congestion. It is administered intravenously (IV) through central or peripheral veins but is excreted via the small intestine and has an acetylated active metabolite (OR-1896) with an excretion half-life of approximately 3 days.<sup>2</sup>

Its clinical use has been primarily studied in the setting of acute decompensated heart failure and following cardiac surgery typically in a critical care environment, where it has been found to be beneficial as sole or adjunctive therapy.<sup>3,4</sup> Levosimendan has a slow elimination such that it may be administered intravenously at 2- to 4-week intervals. This is a unique property amongst inotropes, permitting repetitive infusion in the outpatient setting. Levo-Rep, LION-Heart, and LAICA trials have offered evidence of clinical advantage<sup>5</sup> and provide support for repetitive Levosimendan treatment in the European Society of Cardiology position statement on advanced heart failure (AdHF).<sup>6</sup>

Advanced heart failure secondary to adult congenital heart disease (ACHD) represents a small subgroup posing unique challenges in terms of the specifics of its management. At present, Levosimendan

\*Corresponding author. Tel: +44 (0)1603 286 286, Email: [james.cranley@nhs.net](mailto:james.cranley@nhs.net)

Handling Editor: Domenico D'Amario

Peer-reviewers: Christoph Sinning, Esther Cambrero-Cortinas, and Dejan Milasinovic

Compliance Editor: Amir Aziz

Supplementary Material Editor: Vassilios Parisis Memtsas

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

remains under-studied in ACHD. It has the potential to reduce hospitalization and improve quality of life, making it an enticing prospect in these patients, a growing population who have been identified as causes of 'high resource use' admissions. A recent review found that median charges for an ACHD-related heart failure admission was \$59 055; however, the median cost in the most expensive decile of the admissions was \$1 018 656.<sup>7</sup>

We present three cases of congenital heart disease complicated by heart failure treated with pulsed Levosimendan.

## Timeline

## Case presentation

### Patient 1

This patient had a history of pulmonary atresia and a large ventricular septal defect (VSD). Pulmonary blood supply was from a single major aorto-pulmonary collateral artery dividing into two right-sided branches and single, tortuous left branch. There was no central pulmonary artery (PA). Initial left Blalock–Taussig (BT) shunt aged 1 with attempt at unifocalization failed within 1 year. Age 2, a right BT shunt provided some pulmonary blood flow into adolescence. Attempt at balloon dilatation age 21 failed. Further interventional/surgical

#### Patient 1

Neonatal life

Pulmonary atresia with a large ventricular septal defect (VSD), with only a single major aorto-pulmonary collateral artery (MAPCA) and no main pulmonary arteries. Patient underwent neonatal left and right Blalock–Taussig (BT) shunts.

Age 1

Left BT shunt blocked

Age 2

Right BT shunt blocked

Age 21

Right BT shunt angioplasty, subsequent re-occlusion.

Age 30—initial evaluation

Care transferred to our adult congenital heart disease centre. Advanced heart failure requiring repeated hospital admission for decompensations.

13 months after evaluation

First infusion of Levosimendan (25 mg every 28 days). Marked improvement in symptoms and 6-min walking test for 21 days, followed by return of symptoms.

16 months after evaluation

Levosimendan dose reduced (12.5 mg every 28 days). Improvement for initial 14 days post-infusion, followed by return of symptoms. Required (planned) IV diuretics in second half of 28-day cycle.

24 months after evaluation

Sudden cardiac death, presumed arrhythmic.

#### Patient 2

Neonatal life

Congenital atrial septal defect (ASD) and VSD.

Age 3

Pulmonary artery (PA) banding.

Age 9

ASD and VSD repair surgery.

Age 37

Pause-dependent ventricular tachycardia (VT), pacemaker implanted.

Age 43

Right ventricular aneurysm resection.

Age 51

Scar-related atrial flutter ablation.

Age 52

Cardiac resynchronization therapy-defibrillator implanted. Repeated admissions with decompensated heart failure.

Age 53

Levosimendan commenced (12.5 mg every 28 days). Improved symptoms for 14 days post-infusion then recurrence of symptoms.

12 months after Levosimendan commenced

Infusion frequency increased to 12.5 mg every 18 days.

22 months after Levosimendan commenced

Sudden cardiac death, presumed arrhythmic.

#### Patient 3

Neonatal life

Tetralogy of Fallot with subsequent right BT shunt

Age 5

VSD closed, right ventricular outflow tract resected, MAPCA ligated.

Age 17

Right ventricle–PA homograft for severe pulmonary regurgitation.

Age 26

Xenograft pulmonary valve replacement.

Age 36

Atrial flutter ablation. Implantable cardioverter-defibrillator implant.

Age 40

VO<sub>2</sub>max 26 mL/kg/min.

Age 41

VT ablation. Left ventricular ejection fraction (LVEF) 43%.

Age 43

VO<sub>2</sub>max 14 mL/kg/min. Recurrent admissions for decompensated heart failure. LVEF 24%.

Age 44—initial Levosimendan therapy

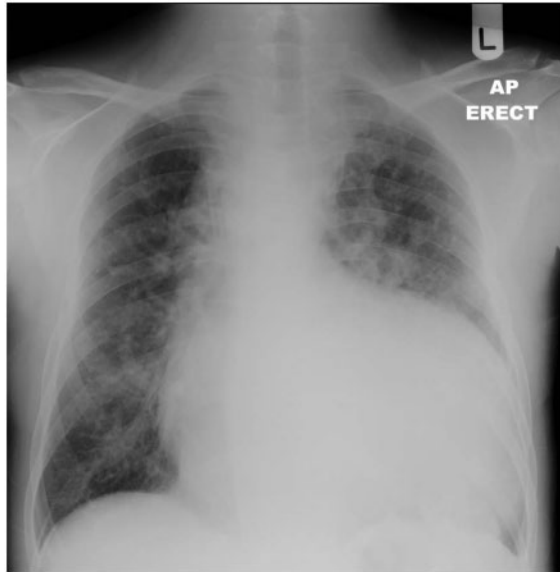
Therapy commenced at 12.5 mg every 28 days.

Age 47–32 months after Levosimendan commenced

First admission with decompensated heart failure since Levosimendan started. Treated with IV diuretics.

Age 48–56 months after Levosimendan commenced

Remains symptomatically improved.



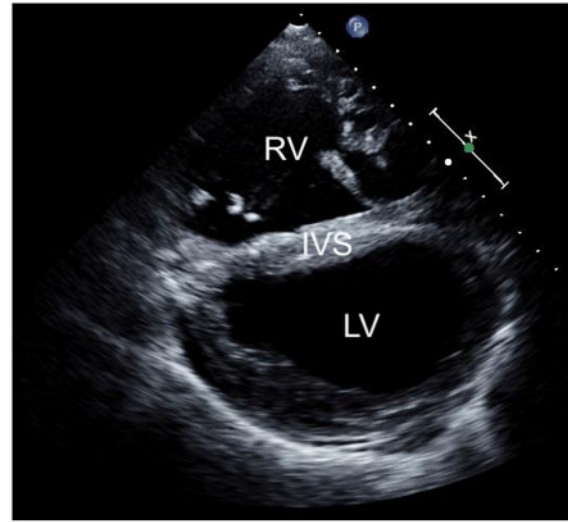
**Figure 1** Patient 1: chest radiograph showing cardiomegaly.

options were deemed futile. He was unsuitable for heart–lung transplantation due to high antibody burden. Aged 30, he was transferred to our centre for palliative care from a tertiary ACHD centre.

At the time of initial evaluation, he had cardiomegaly (*Figure 1*) secondary to severe tricuspid regurgitation and aortic regurgitation, itself due to marked aortic dilatation. He had also suffered with previous atrial flutter and ventricular tachycardia (VT), both successfully treated with amiodarone. He had pulmonary hypertension, intolerant of targeted therapy. He was rejected for heart and lung transplant.

His left ventricular (LV) ejection fraction was 20% and his right ventricle was severely dilated and impaired (*Figure 2*, [Supplementary material online, File S1](#)). He was not a candidate for cardiac resynchronization therapy due to his normal QRS complex duration. Defibrillator implantation had been considered but was deemed inappropriate in view of the palliative nature of his treatment. Management of his heart failure required frequent admissions for intravenous (IV) diuretics, inotrope infusions, and fluid restriction for 2–3 weeks at a time. He would manage approximately 1 week and then he would require readmission (despite a trial of domiciliary nurse-administered IV diuretics). He had two young children and was desperately keen to avoid long spells in hospital and was frustrated not to be able to play with them at all due to poor exercise tolerance, his 6-min walking test (6MWT) being <100 m. Furthermore, he had AdHF-related cardiorenal syndrome.

Approval for repetitive infusions of Levosimendan was obtained. Initially, funding was obtained for two 12.5 mg vials of Levosimendan each month, each being infused over 24 h. For the first 21 days following each treatment, he had excellent control of his heart failure; for the latter 6 days, he gradually deteriorated. As a result of funding issues, Levosimendan was reduced to one vial every month. He continued to have symptomatic improvement for approximately 14 days following infusion but thereafter required readmission, initially at 24 days, then 18 days post-infusion due to heart failure



**Figure 2** Patient 1: echocardiogram showing dilated right ventricle, with ‘D-ing’ of the interventricular septum towards the left ventricle in keeping with elevated right-sided pressures. IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

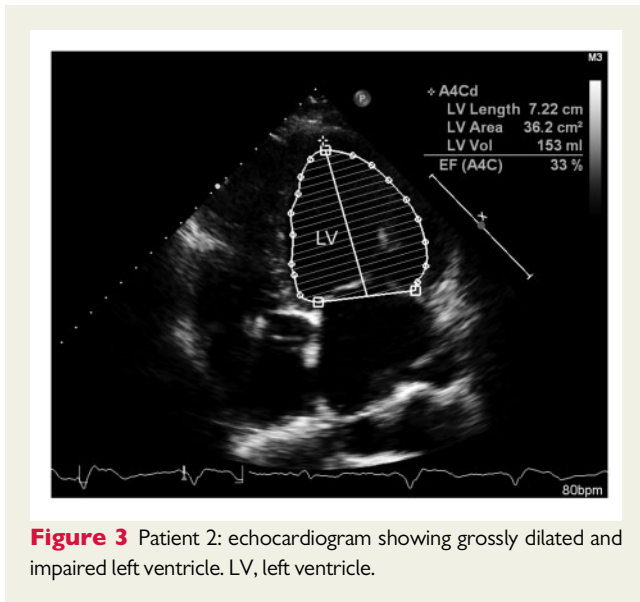
symptoms. His 6MWT immediately post-Levosimendan infusion doubled (360 m).

He was found dead in bed at home having been well that morning—a presumed arrhythmic death. He had survived for 11 months longer than expected, maintaining a good quality of life.

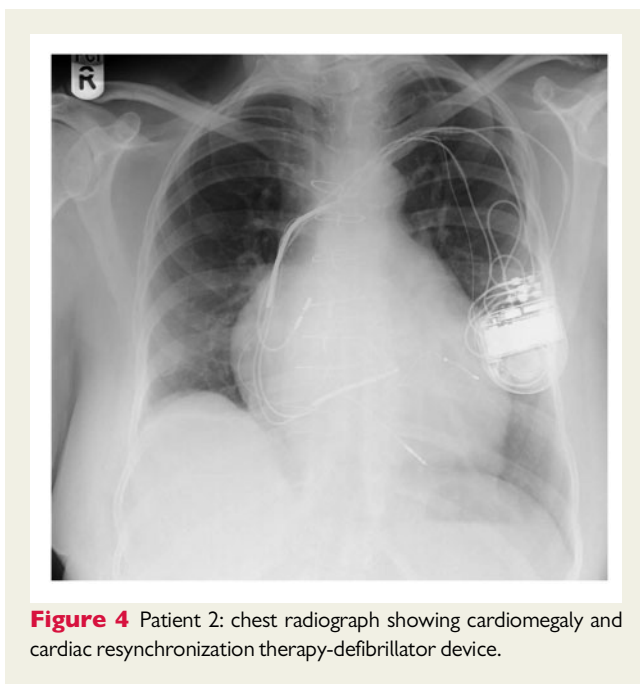
## Patient 2

This patient was born with atrial septal defect and VSD, undergoing PA banding aged 3 with subsequent septal defect closure aged 9. She had episodic bradycardias with pause-dependent VT, which responded to pacing. At age 43, she underwent resection of a right ventricular (RV) aneurysm (related to previous ventriculotomy for VSD repair). She had a successful atrial flutter ablation at age 52 (atriotomy scar). Long-standing impaired ventricular function was thought secondary to late repair and lack of myocardial preservation techniques during her childhood surgery. Both right and left ventricles were severely impaired (*Figure 3*). Coronary assessment was unremarkable. Despite cardiac resynchronization therapy with defibrillator function (CRT-D), her LV ejection fraction remained poor at 21% and she had little improvement in symptoms or frequency of hospital admissions (*Figure 4*, [Supplementary material online, File S2](#)). Each admission with biventricular heart failure (10–14 days) was managed with IV diuretics, fluid restriction, traditional inotropes, and conventional heart failure management. She would remain at home for 7–10 days and then require readmission. Due to 97% HLA antibodies, she was rejected for transplantation.

Approval for repetitive Levosimendan infusion was sought and approved. During the following 18 months, she was admitted for pulsed Levosimendan therapy every 28 days (1 vial over 24 h). During this period, she remained free of admissions for decompensated heart failure (she had one admission with pneumonia and a pre-renal

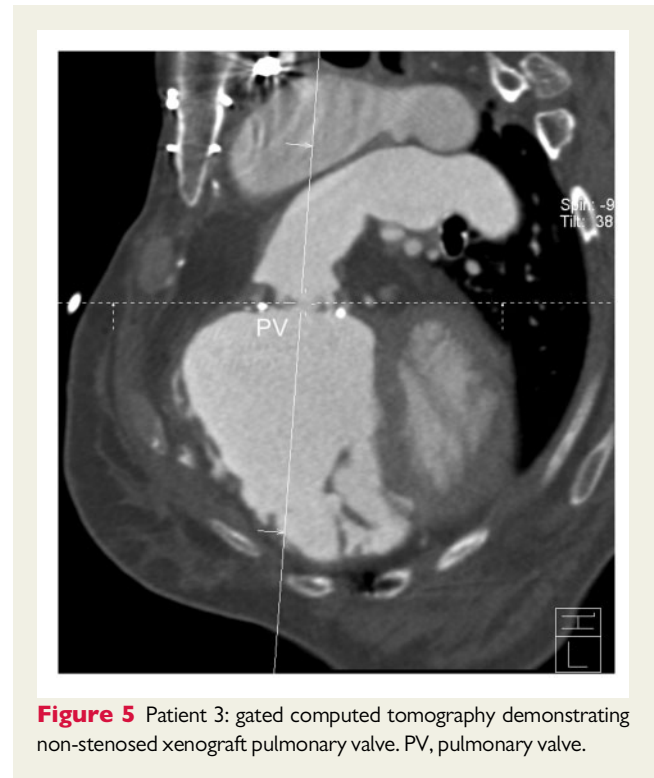


**Figure 3** Patient 2: echocardiogram showing grossly dilated and impaired left ventricle. LV, left ventricle.



**Figure 4** Patient 2: chest radiograph showing cardiomegaly and cardiac resynchronization therapy-defibrillator device.

acute kidney injury from which she recovered). Following the infusion, she was aware of a significant improvement in activities of daily living for 14 days but then a deterioration with fluid retention and increasing breathlessness in the days prior to the next planned infusion. Infusion frequency was increased to every 18 days with good effect. She suffered from a presumed vasodilatation headache for 2–3 days after infusion which responded to 5 days of Triptan with good effect. 21 months into Levosimendan therapy she suffered 18 defibrillator shocks due to VT. Ablation therapy was considered however the patient requested deactivation of her device. She died suddenly the next month aged 55, almost 2 years after commencing Levosimendan.



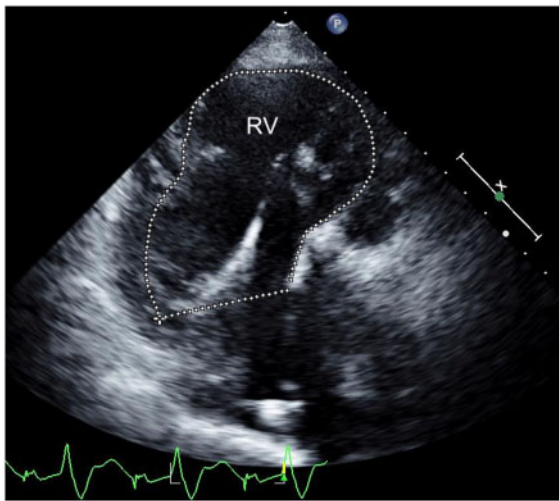
**Figure 5** Patient 3: gated computed tomography demonstrating non-stenosed xenograft pulmonary valve. PV, pulmonary valve.

### Patient 3

Patient 3 was born with Tetralogy of Fallot, undergoing a right BT shunt in the first year of life. In childhood, she had repair surgery with VSD patch closure, RV outflow tract resection, and an aorto-pulmonary collateral from the descending aorta was ligated. At age 17, a right ventricle–PA homograft was required for severe pulmonary regurgitation, later this became stenosed and required xenograft pulmonary valve replacement aged 26. The xenograft pulmonary valve remains without significant stenosis or regurgitation, and no coronary disease on computed tomography (Figure 5). She underwent ablations for atrial flutter and VT and had a dual-chamber implantable cardioverter-defibrillator (ICD) implanted. Severe RV dysfunction is a late consequence of palliative surgery for Fallot's tetralogy. The RV dysfunction never remodelled following redo homograft implantation aged 17 nor improved following PVR aged 26. In consequence, she has severe functional tricuspid regurgitation due to annular ring dilatation secondary to her markedly dilated right ventricle (Figure 6, Supplementary material online, File S3). Cardiopulmonary exercise testing at age 40 showed a  $\text{VO}_2\text{max}$  of 26 mL/kg/min (normal >24.5 mL/kg/min) however by age 43 this had fallen to 14 mL/kg/min and she began to have recurrent admissions for decompensated heart failure. She was not accepted for transplantation due to her body mass index of 15.9, 95% HLA antibodies, Group A blood type and significant restrictive lung function. Mechanical ventricular assist devices were not considered since they are reserved as a bridge to transplant in our health care system.

Approval for Levosimendan infusion was granted when her 6MWT was 40 m and her B-type natriuretic peptide (BNP) was 1599 ng/L (normal range 0–114 ng/L). She had an excellent response, her monthly Levosimendan infusions have permitted her to remain at home.

It was 32 months following commencement of Levosimendan that she had her first admission with decompensated heart failure. This appeared to be pre-terminal with a high BNP (1220 ng/L) and reduced 6MWT (224 m). She was referred for palliative care and her ICD was deactivated. However, following IV diuretics and continued monthly Levosimendan infusions, she has returned home and resumed most of her usual activities. 6MWT improved back to 426 m and BNP to 770 ng/L (Figure 7). At present, she remains symptomatically stable, over 5 years since her first Levosimendan infusion.



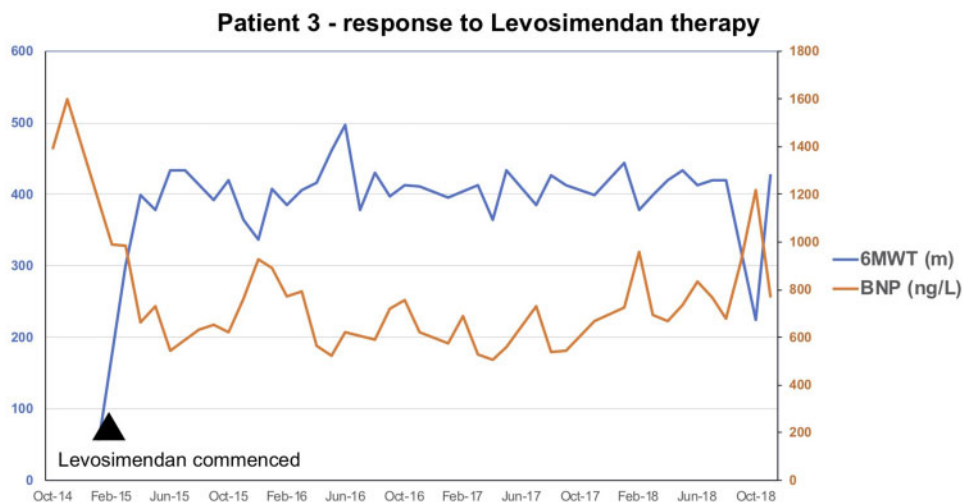
**Figure 6** Patient 3: echocardiogram showing severely dilated right ventricle. RV, right ventricle.

## Discussion

Adult survival with complex congenital heart disease is now expected in more than 90% of cases due to improved palliative intervention or surgery, optimal medical therapy and careful clinical surveillance in dedicated adult congenital heart clinics. Nearly half of subsequent deaths are due to heart failure at a median age of death of only 48.8 years.<sup>8</sup> As in the cases described here, the recurrent admissions for conventional intravenous heart failure therapy have limited short-term benefit but poor subsequent outcomes.<sup>9</sup> Heart failure medications, validated in acquired heart failure, are not seen to confer the same benefit—particularly in patients with failing systemic right ventricles or severely impaired sub-pulmonary ventricles. Heart transplantation may be possible for some but high HLA antibody burden (often related to prior transfusions) and other comorbidities often prevent listing. A single UK congenital heart transplant centre reported that 56% of referred ACHD cases were not listed. If listed, they spend a long time on the heart transplant list due to more restrictive donor selection, and ventricular assist devices have not shown the benefit seen in those with acquired heart conditions awaiting transplantation.<sup>10</sup>

An excellent review of the literature and evidence base<sup>5</sup> lends support to the approach adopted for the specific cases described. In each of our patients, there was a symptomatic improvement associated with marked reduction in hospitalization (observed in RELEVANT-HF) and better quality of life for their remaining life span. Levosimendan was well tolerated, without symptomatic hypotension—as found in LIONHEART.<sup>11</sup> Levosimendan infusions were started every 4 weeks with a 24 h infusion (no bolus). Cases 1 and 2 required a reduction in time between infusions (14–21) days, whereas Case 3 continues at almost five years from initiation on 28-day infusions.

Individualized funding for Levosimendan infusion is required in the UK. Approval has been granted in the cases described, having demonstrated that the infusion cost (£920/month) is offset by bed-days saved. The meta-analyses of 345 patients, provides evidence of significant



**Figure 7** Patient 3: Graph depicting changes in 6-min walking test and N-terminal pro-B-type natriuretic peptide after commencement of Levosimendan. BNP, B-type natriuretic peptide; 6MWT, 6-min walking test.

benefit for repetitive or pulsed Levosimendan with a significant reduction in mortality in the AdHF population (with average follow-up period of  $8 \pm 8.3$  months) of 10.2% vs. 26.8% in the control group.<sup>4</sup>

With this series, we hope to encourage the formal study of this therapeutic option in this patient population. A limitation in our series is the lack of longitudinal objective data for cases 1 and 2, e.g. N-terminal pro-BNP levels. Furthermore, although not undertaken in this series, right heart catheterization data may be useful in determining those patients likely to benefit most from Levosimendan. Although its evidence lies primarily in left heart failure, there is growing data supporting the benefit of Levosimendan in pulmonary arterial hypertension and right heart failure.<sup>12</sup> This may explain the favourable results seen in our ACHD patients where both ventricles, as well as pulmonary vasculature play a role in heart failure.

## Conclusion

This case series demonstrates that repetitive Levosimendan infusions for end-stage heart failure in selected adult survivors of congenital heart disease is cost-effective with bed-days saved, is well-tolerated, improves quality of life and reduces admissions. The numbers of ACHD patients with end-stage heart failure is increasing and this treatment modality has an important role in the standard of care in that management.

## Lead author biography



Dr James Cranley graduated from Oxford medical school with distinction before working at Royal Brompton, Addenbrooke s, and Royal Papworth hospitals as an academic clinical fellow. He is currently a cardiology registrar in the East of England with a subspecialty interest in cardiac electrophysiology.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

## References

- De Hert SG, Wikström BG, Meyer S, Filippatos G, Yilmaz MB, Grossini E, Jörgensen K, Édes I, Guarracino F, González MJG, Parkhomenko A, Leppikangas H, Mebazaa A, Pollesello P, Landoni G, Parissis JT, Caimmi P, Fruhwald S, Schwinger RHG, Papp Z, Kivikko M, Algotsson L, Follath F, Salmenperä M, Morelli A. Levosimendan: Molecular mechanisms and clinical implications. *Int J Cardiol* 2012;**159**:82–87.
- Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. *Clin Pharmacokinet* 2007;**46**:535–552.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129–2200.
- Pollesello P, Parissis J, Kivikko M, Harjola VP. Levosimendan meta-analyses: Is there a pattern in the effect on mortality? *Int J Cardiol* 2016;**209**:77–83.
- Oliva F, Comin-Colet J, Fedele F, Fruhwald F, Gustafsson F, Kivikko M, Borbély A, Pözl G, Tschöpe C. Repetitive levosimendan treatment in the management of advanced heart failure. *Eur Heart J Suppl* 2018;**20**:i11–i20.
- Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505–1535.
- Chan J, Collins RT, Hall M, John A. Resource utilization among adult congenital heart failure admissions in pediatric hospitals. *Am J Cardiol* 2019;**123**:839–846.
- Verheugt CL, Uiterwaal C, Van Der Velde ET, Meijboom FJ, Pieper PG, Van Dijk APJ, Vliegen HW, Grobbee DE, Mulder B. Mortality in adult congenital heart disease. *Eur Heart J* 2010;**31**:1220–1229.
- Cao J, Cordina R, Jackson D, Kotchetkova I, Lal S, Celermajer DS. Heart failure admissions and poor subsequent outcomes in adults with congenital heart disease. *Eur J Heart Fail* 2018;**20**:812–815.
- Irving C, Parry G, O'Sullivan J, Dark JH, Kirk R, Crossland DS, Chaudhari M, Griselli M, Hamilton JRL, Hasan A. Cardiac transplantation in adults with congenital heart disease. *Heart* 2010;**96**:1217–1222.
- Comin-Colet J, Manito N, Segovia-Cubero J, Delgado J, García Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, Gonzalez-Vilchez F, Lambert-Rodriguez JL, Grau M, Bruguera J; on behalf of the LION-HEART Study Investigators. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. *Eur J Heart Fail* 2018;**20**:1128–1136.
- Hansen MS, Andersen A, Nielsen-Kudsk JE. Levosimendan in pulmonary hypertension and right heart failure. *Pulm Circ* 2018;**8**:2045894018790905.