Levosimendan in Congenitally Corrected Transposition of the Great Arteries: A Case Report

Lilian Mantziari[*,1] Vasileios Kamperidis[1], Georgios Giannakoulas[1], Constantinos Davos[2], Haralambos Karvounis[1], Vassilios P. Vassilikos[1] and Ioannis H. Styliadis[1]

[1]*First Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece*

[2]*Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece*

Abstract: We present a case of acute decompensated heart failure in a patient with congenitally corrected transposition of great arteries treated with levosimendan, an agent with positive inotropic and vasodilatory effects. Levosimendan infusion resulted in symptomatic and functional improvement, improvement of the subpulmonary left ventricular systolic function and amelioration of the diastolic but not the systolic function of the systemic right ventricle. A number of factors may account for the poor response of the systemic right ventricle to levosimendan, such as altered myofibrillar structure and coronary flow together with the particular loading conditions of the systemic right ventricle.

Keywords: Congenital heart disease, inotropic agents, systemic right ventricle, systolic function.

INTRODUCTION

Congenitally corrected transposition of great arteries (ccTGA) is a rare abnormality characterized by both atrioventricular and ventriculoarterial discordance [1]. Anatomically the right atrium connects *via* the mitral valve to the morphological left ventricle (LV) which supplies the pulmonary artery, while the left atrium connects *via* the tricuspid valve to the morphological right ventricle (RV) which supplies the aorta. The clinical presentation and prognosis of the disease are closely associated to the competence of the systemic atrioventricular (tricuspid) valve and the function of the systemic RV [2].

Data regarding the pharmacological management of the dysfunction of a systemic RV are limited and current practice tends to incorporate standard therapies that are known to improve systemic LV dysfunction [3]. Reports on the effect of inotropic agents on the systemic RV are lacking because of the rarity of this condition [4]. We present a case of a patient with ccTGA and decompensated heart failure treated with levosimendan (Simdax, Orion, Espoo, Finland), a newer cardio-stimulant agent with both positive inotropic and vasodilatory effects, known to improve left ventricular (LV) function in acquired heart failure [5]. Levosimendan has unique pharmacologic properties acting *via* two mechanisms. The first is calcium sensitization of the contractile proteins in the cardiomyocytes, which leads to increased contractility of the heart and the second is opening of the adenosine triphosphate-sensitive potassium channels on vascular smooth muscle leading to coronary and peripheral vasodilatation [6]. Thus, levosimendan has hemodynamic advantages compared to other inotropic agents and it has been shown to improve heart function in various clinical settings [6].

*Address correspondence to this author at the First Cardiology Department, AHEPA University Hospital, St. Kiriakidi 1 Street, 54636, Thessaloniki, Greece; Tel: +30 2310994830; Fax: +30 2310994673;
E-mail: lmantziari@yahoo.com

CASE PRESENTATION

A 60-year-old Caucasian male patient with ccTGA was admitted with decompensated chronic heart failure. The patient's history included a permanent pacemaker implantation 20 years ago due to high grade atrioventricular block, later upgraded to an implantable cardioverter defibrillator (ICD) because of an episode of ventricular tachycardia. Medication on admission (daily dosages) was carvedilol 25 mg, ramipril 5 mg, eplerenone 25 mg, furosemide 40 mg, alopourinol 100 mg and clopidogrel 75 mg. Blood pressure was 100/70 mmHg, heart rate 95 bpm and oxygen saturation was 95% in room air. He had mild peripheral edema and orthopnoea with bilateral basal rales. Following intravenous furosemide administration (80 mg daily for 6 days), orthopnea was improved, peripheral edema and rales resolved, but the patient's dyspnoea on mild exertion persisted. His functional capacity was deteriorated and he walked 231 meters in a 6-minute walking test.

Levosimendan infusion was chosen to be the next pharmaceutical option for this patient. Before the infusion he underwent an echocardiographic examination, which showed impaired biventricular function, biatrial dilatation and severe tricuspid regurgitation (Fig. **1**). Ejection fraction was calcutated by the Simpson's biplane method [7] and myocardial performance index (MPI) was derived from the tissue Doppler measurements of ejection time (ET), isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) according to the formula: MPI= (IVCT+IVRT)/ET [8]. The patient received levosimendan 0.1 μg/kg/min in continuous intravenous infusion for 24 hours (without loading dose and uptitration because of the low systolic blood pressure) which resulted in improvement of symptoms and increased 6-minute walking distance from 231 to 300 meters. The echocardiogram was repeated 24

1876-5335/12

hours after the end of the infusion by the same echocardiographer and showed an increase in LV ejection fraction from 44.5% to 48.5% a decrease of LV MPI from 1.22 to 0.84, but no change in the systolic function of the morphological RV (Tricuspid annular plane systolic excursion-TAPSE 1.00 cm to 1.04 cm) and RV MPI deterioration from 0.86 to 1.01. However, tricuspid regurgitant volume and left atrial volume were significantly reduced from 40.3 ml to 15.6 ml and 112 to 84 ml respectively (Figs. **2**, **3**), while E/E' of the systemic RV was reduced to 24 from 49.

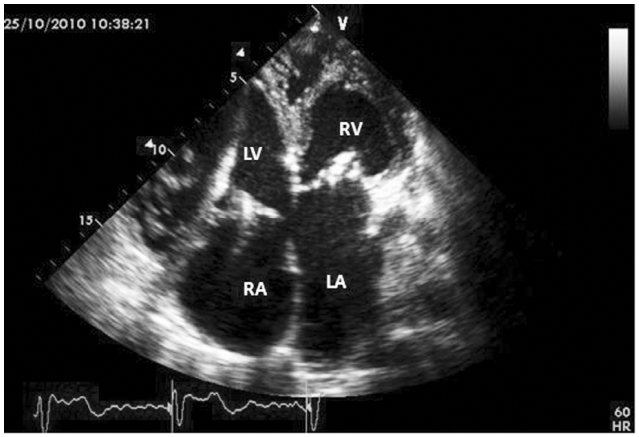

Fig. (1). Apical four-chamber view of echocardiogram shows the anatomy in ccTGA: RA, right atrium; LV, left ventricle (subpulmonic); RV, right ventricle (systemic); LA, left atrium. Note the defibrillator lead inside LV.

DISCUSSION

Levosimendan infusion in this patient with ccTGA and decompensated heart failure resulted in amelioration of subpulmonary LV global function, reduction of the systemic RV filling pressures and clinical improvement without affecting the systolic function of the systemic RV.

Levosimendan mediates its inotropic action through binding to troponin C and facilitating the actin-myosin interaction without affecting the intracellular calcium concentration [9]. Systolic function of the systemic RV is altered and resembles that of the LV, with increased circumferential fiber mass and predominantly circumferential rather than longitudinal shortening of the RV free wall. However, in the systemic RV, torsion is absent and this feature may contribute to RV dysfunction [10]. At the cellular level, in normal hearts, although there are no differences in expression levels of Ca^{2+}-ATPase between the two ventricles, a major fraction of available Ca^{2+}-pump units are inert [11]. Subsequently, maximal sarcomere shortening is less in RV myocytes and the peak calcium transient in LV myocytes is larger than in RV myocytes [12]. These differences at the cellular level, in the myofibrillar architecture along with the lack of torsion of the systemic RV, may have played a role in the poor response of the systemic RV to levosimendan.

Levosimendan induces peripheral and coronary vasodilatation *via* opening of ATP-sensitive potassium channels, resulting in a decrease of the peripheral vascular resistance and an increase in the coronary blood flow respectively [13]. Excessive right ventricular hypertrophy increases myocardial oxygen requirements that cannot be met by the right coronary system. Hence, the RV perfusion is impaired leading to myocardial fibrosis and reduced coronary flow reserve [2] which may additionally account for a limited benefit in our patient. However, in our case, levosimendan mediated peripheral vasodilatation may have resulted in the reduction of the tricuspid valve regurgitant volume and the resultant decrease in the left atrial volume. Moreover, levosimendan reduced RV filling pressures, leading to functional improvement [14].

Although previous studies have reported beneficial effects of levosimendan on the RV function of patients with acquired heart failure [15], the RV systolic improvement could be secondary to the LV systolic improvement and reduction of the pulmonary vascular resistance and thus it may not represent a direct effect of levosimendan on the myocardium of the RV. Furthermore, the different loading conditions of a systemic RV, in contrast to those of a normal subpulmonary RV, might also account for a poorer response to levosimendan.

In conclusion, levosimendan infusion in a patient with ccTGA resulted in clinical and functional improvement secondary to decreased tricuspid regurgitation and RV filling pressure, together with amelioration of the systolic function

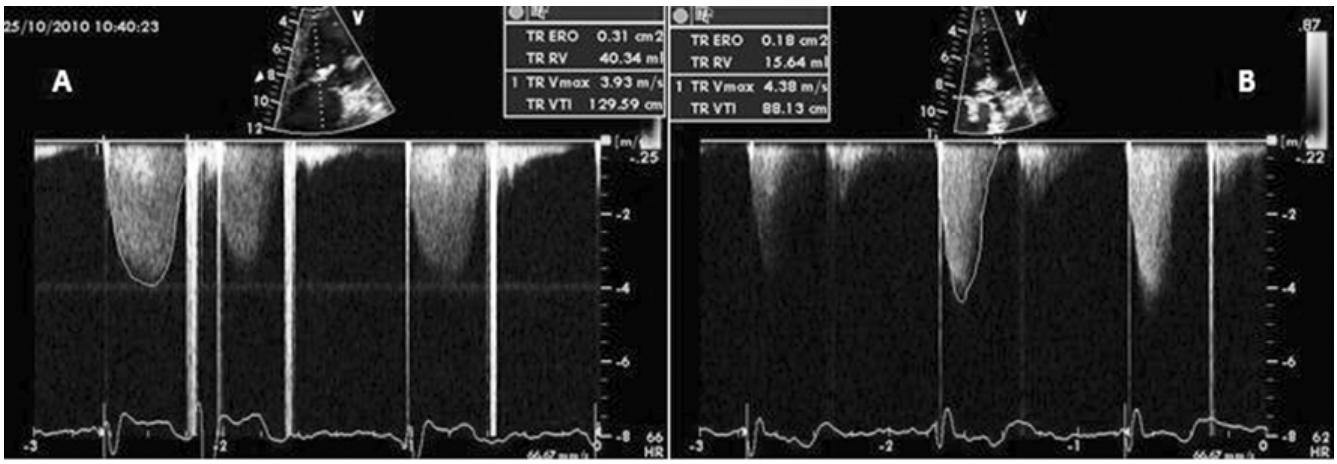

Fig. (2). Systemic atrioventricular valve (tricuspid) regurgitation before (A) and after (B) levosimendan infusion.

of the subpulmonary left ventricle. However, this treatment did not affect the systolic function of the systemic right ventricle.

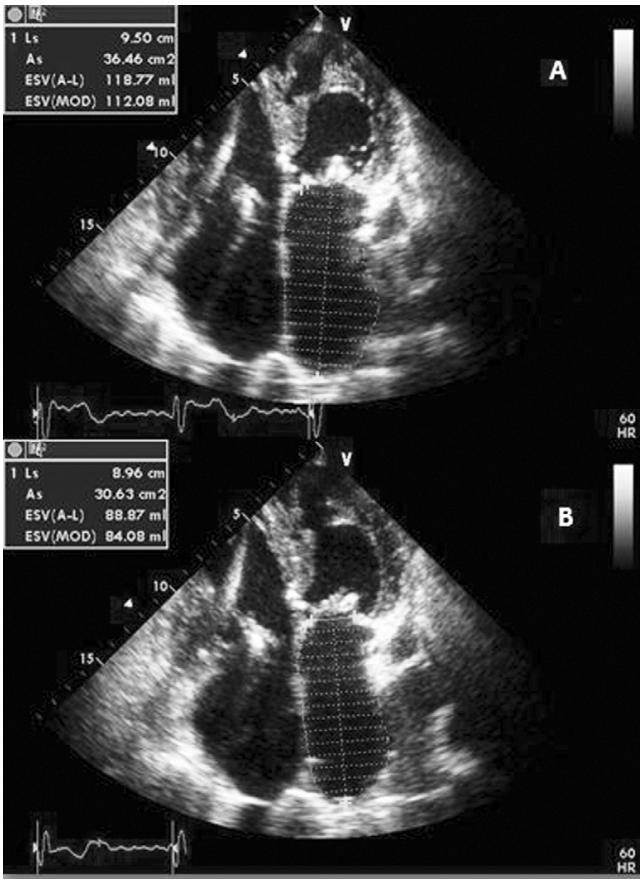

Fig. (3). Left atrial volume before (**A**) and after (**B**) levosimendan infusion.

ACKNOWLEDGEMENT

Declared none.

CONFLICT OF INTEREST

Declared none.

REFERENCES

[1] Sloth AD, Jensen JK, Steffensen FH, Norgaard BL. Congenital transposition of the great arteries newly diagnosed in a 76-year-old woman. Ugeskr Laeger 2009; 171: 319-21.

[2] Hornung TS, Calder L. Congenitally corrected transposition of the great arteries. Heart 2010; 96: 1154-61.

[3] Tutarel O, Meyer GP, Bertram H, Wessel A, Schieffer B, Westhoff-Bleck M. Safety and efficiency of chronic ACE inhibition in symptomatic heart failure patients with a systemic right ventricle. Int J Cardiol 2012; 154: 14-6.

[4] Graham TP Jr, Bernard YD, Mellen BG, *et al*. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. J Am Coll Cardiol 2000; 36: 255-61.

[5] Parissis JT, Rafouli-Stergiou P, Paraskevaidis I, Mebazaa A. Levosimendan: from basic science to clinical practice. Heart Fail Rev 2009; 14: 265-75.

[6] De Luca L, Colucci WS, Nieminen MS, Massie BM, Gheorghiade M. Evidence-based use of levosimendan in different clinical settings. Eur Heart J 2006; 27: 1908-20.

[7] Hergan K, Schuster A, Fruhwald J, Mair M, Burger R, Topker M. Comparison of left and right ventricular volume measurement using the Simpson's method and the area length method. Eur J Radiol 2008; 65: 270-8.

[8] Abd El Rahman MY, Hui W, Dsebissowa F, *et al*. Comparison of the tissue Doppler-derived left ventricular Tei index to that obtained by pulse Doppler in patients with congenital and acquired heart disease. Pediatr Cardiol 2005; 26: 391-5.

[9] Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol 1995; 26(Suppl 1): S10-S9.

[10] Sathish V, Xu A, Karmazyn M, Sims SM, Narayanan N. Mechanistic basis of differences in Ca2+-handling properties of sarcoplasmic reticulum in right and left ventricles of normal rat myocardium. Am J Physiol Heart Circ Physiol 2006; 291: H88-H96.

[11] Pettersen E, Helle-Valle T, Edvardsen T, *et al*. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol 2007; 49: 2450-6.

[12] Walker LA, Buttrick PM. The right ventricle: biologic insights and response to disease. Curr Cardiol Rev 2009; 5: 22-8.

[13] Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007; 46: 535-52.

[14] Tay EL, Frogoudaki A, Inuzuka R, *et al*. Exercise intolerance in patients with congenitally corrected transposition of the great arteries relates to right ventricular filling pressures. Int J Cardiol 2011; 147: 219-23.

[15] Yilmaz MB, Yontar C, Erdem A, *et al*. Comparative effects of levosimendan and dobutamine on right ventricular function in patients with biventricular heart failure. Heart Vessels 2009; 24: 16-21.

Received: January 5, 2012 Revised: April 13, 2012 Accepted: April 18, 2012