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

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Abstract: We present a case of acute decompensated heart failure in a patient with congenitally corrected transposition of great arteries treated with levsimendan, 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 levsimendan, 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 levsimendan (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, levsimendan has hemodynamic advantages compared to other inotropic agents and it has been shown to improve heart function in various clinical settings [6].

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, allopurinol 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, bialtral dilatation and severe tricuspid regurgitation (Fig. 1). Ejection fraction was calculated 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 levsimendan 0.1 μg/kg/min in continuous intravenous infusion for 24 hours (without loading dose and up titration 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...
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.

**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...
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.

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CONFLICT OF INTEREST
Declared none.

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