Super-response to cardiac resynchronization therapy in orthotopic heart transplant with atypical right bundle branch block and cardiac allograft vasculopathy

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Introduction

There is very limited data regarding the use of cardiac resynchronization therapy (CRT) in patients following cardiac transplant. We describe the use of CRT in a patient who developed cardiomyopathy, biventricular heart failure, and atypical right bundle branch block (RBBB) after orthotopic heart transplant (OHT) in the setting of cardiac allograft vasculopathy (CAV). Right ventricular (RV) function normalized, and left ventricular (LV) dimension and ejection fraction (EF) significantly improved by 5 months post CRT implant.

Case report

A 45-year-old male patient underwent a combined heart and kidney transplant in May 2015 for end-stage heart failure secondary to nonischemic cardiomyopathy from viral myocarditis and advanced polycystic kidney disease. A posttransplant electrocardiogram (ECG) showed sinus rhythm and incomplete RBBB with a QRS duration of 100 ms (Figure 1A). The early postoperative course was complicated by an acute cerebrovascular accident. The patient otherwise did well for several years after transplant with surveillance right heart catheterization and endomyocardial biopsy showing normal filling pressures, cardiac output, and absence of cellular- or antibody-mediated rejection. Annual coronary angiograms were also normal for the first 5 years after transplant. A complete atypical RBBB developed on ECG by January 2019 (Figure 1B) with no change in clinical status. However, on annual right heart catheterization in May 2020, severely elevated biventricular filling pressures with a right atrial pressure of 15 mm Hg, a pulmonary-capillary wedge pressure of 29 mm Hg, cardiac output of 5.1 L/min, and a cardiac index of 2 L/min/m^2 using the thermodilution method were noted. Coronary angiography showed evidence of mild CAV involving both the left and right coronary systems.

KEY TEACHING POINTS

- Cardiac synchronization therapy in orthotopic heart transplant has been rarely reported.
- Left ventricular conduction delay may occur simultaneously with atypical forms of right bundle branch block.
- Cardiac resynchronization therapy may benefit selected patients with appropriate indications post heart transplant; however, the long-term outcomes of cardiac resynchronization therapy in heart transplant complicated by allograft vasculopathy are unknown.

Investigation and early management

Endomyocardial biopsy was performed, and blood was drawn for donor-specific antibody testing; however, there remained no evidence of cellular- or antibody-mediated rejection. The patient reported shortness-of-breath symptoms with moderate exertion and compliance with antirejection medications. This was confirmed by a therapeutic serum tacrolimus level. Transthoracic echocardiography (TTE) showed an LV end-diastolic diameter of 5.6 cm, EF of 25%–30%, severe global hypokinesis of the left ventricle, and severely decreased function of the right ventricle. LV end-systolic index was 54.8 mL/m^2. In the absence of any evidence of rejection, with new heart failure and decrease in LV function, the CAV was categorized as "CAV3" per International Society for Heart and Lung Transplant classification.[1] Creatinine level was slightly elevated at 1.4 mg/dL, but was unchanged

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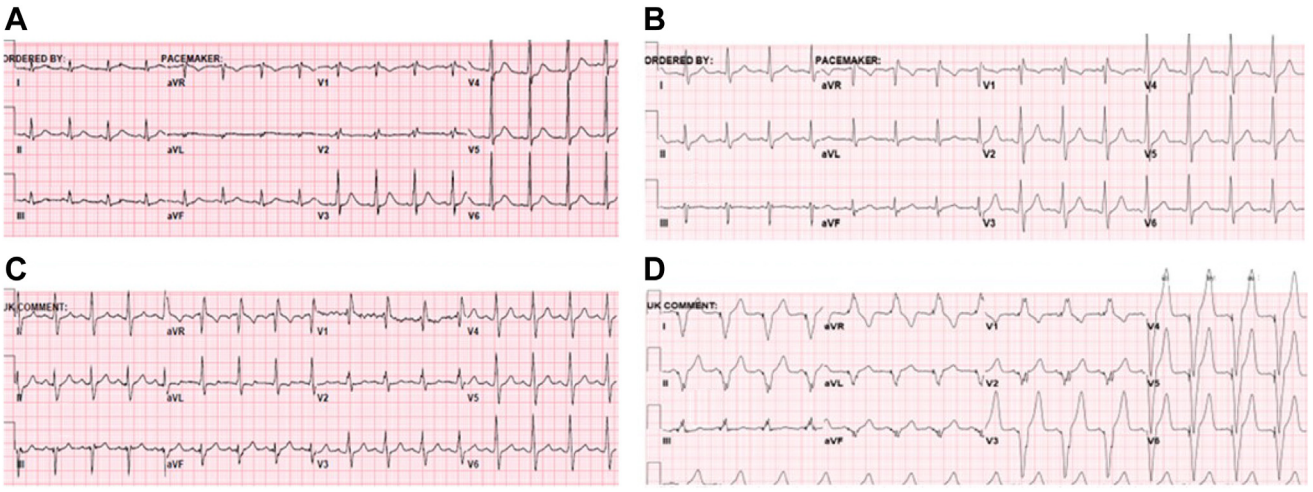

Figure 1 Patient electrocardiograms. **A:** Posttransplant electrocardiogram (ECG) in May 2015 showing sinus rhythm and incomplete right bundle branch block (RBBB) with a QRS of 100 ms. **B:** ECG from January 2019 showing atypical RBBB and a QRS of 122 ms with small S waves in leads I and aVL. **C:** ECG from August 2020 showing sinus rhythm with atypical RBBB, a QRS duration of 150 ms, and new left axis deviation. Note the following: (1) S waves in leads I and aVL are less than the R wave and remain <40 ms; (2) new upstroke slurring of the R wave in leads I and aVL; and (3) new QRS fractionation in leads II, III, and aVF. **D:** Post–cardiac resynchronization therapy implant 12-lead ECG.

from measures over the prior 2 years. N-terminal pro-brain natriuretic peptide was slightly elevated at 466 pg/mL. Total bilirubin, alanine and aspartate transaminase levels were all normal: 0.7 mg/dL, 18 U/L, and 18 U/L, respectively. The patient was admitted to the hospital after cardiac catheterization and treated with pulse dose corticosteroids and intravenous diuresis, and transitioned to oral diuretics. In addition, guideline-directed medical therapy (GDMT) with sacubitril-valsartan, carvedilol, and spironolactone was started. A new left-axis deviation with atypical RBBB and QRS duration of 150 ms was noted on 12-lead ECG (Figure 1C). The immunosuppressive regimen was changed from tacrolimus and mycophenolate mofetil to sirolimus and mycophenolate given the CAV.

Follow-up and subsequent management

TTE 3 months later in August 2020 showed a persistently depressed LV EF at 20%–30% with severe anterior, inferior, and inferolateral wall hypokinesis/akinesis despite titration to target GDMT (Supplemental Video 1). In the interim, the patient also developed significant proteinuria and was switched back to tacrolimus from sirolimus. Creatinine level, however, remained within the range of 1.2–1.4 mg/dL during titration of medical therapy. Given persistent systolic dysfunction despite optimized GDMT, New York Heart Association (NYHA) II functional class, and atypical RBBB $\geq$150 ms on ECG, a CRT implantable cardioverter-defibrillator (ICD) was successfully inserted with the LV lead placed in a lateral mid-basal position, and simultaneous biventricular timed pre-excitation programmed (Figure 1D, Figure 2). The Q-to-LV time was 119 ms. ICD settings also included a DDD mode, lower rate 40 beats per minute (bpm), upper rate 150 bpm; sensed/paced atrioventricular delays 80 ms and 130 ms, respectively; a single ventricular fibrillation zone $\geq$222 bpm; and atrial tachycardia/atrial fibrillation monitor detection >171 bpm. No changes in GDMT followed. Repeat TTE 5 months post implant showed a normalized LV end-diastolic diameter of 4.8 cm, LV EF increase to 42%, improvement of the previous wall motion abnormalities, save apical akinesis, and normalization of RV function. Interventricular timing was changed to left ventricle pacing early by 50 ms. based on surface 12-lead ECG QRS duration minimization at that visit as well. Echocardiography nearly 2 years post implant showed LV EF 45%–50% and LV end-systolic index 20.8 mL/m^2 with a clinical status of NYHA class I heart failure (Supplemental Video 2). Repeat cardiac catheterization was additionally notable for minimal luminal irregularities in the left and right coronary systems. There were no ventricular or atrial arrhythmias noted on remote or in-person interrogation since implant. An ECG with temporary cessation of pacing at last follow-up was notable for an atypical RBBB, QRS duration of 126 ms, and absence of left axis deviation.

Discussion

There have only been a few case reports in the literature of CRT following cardiac transplantation. Apor and colleagues[2] first described a patient with CAV, heart failure, depressed EF, and left bundle branch block (LBBB) 5 years after transplant treated with CRT placement.[2] In 2010, Mariani and colleagues[3] reported a patient with heart failure secondary to severe CAV with depressed EF, persistent atrial tachyarrhythmia requiring atrioventricular junction ablation, and subsequent dual-chamber ICD. Further worsening of LV function and heart failure prompted an upgrade to CRT 1 week later.[3] Finally, in 2013 Vural and colleagues[4] described a patient 5 years removed from transplant with new CAV that developed systolic heart failure, a depressed EF, and Mobitz II atrioventricular block who was implanted with CRT. In all 3 cases, CRT resulted in moderate improvement in ventricular function and heart failure symptoms, as one might now

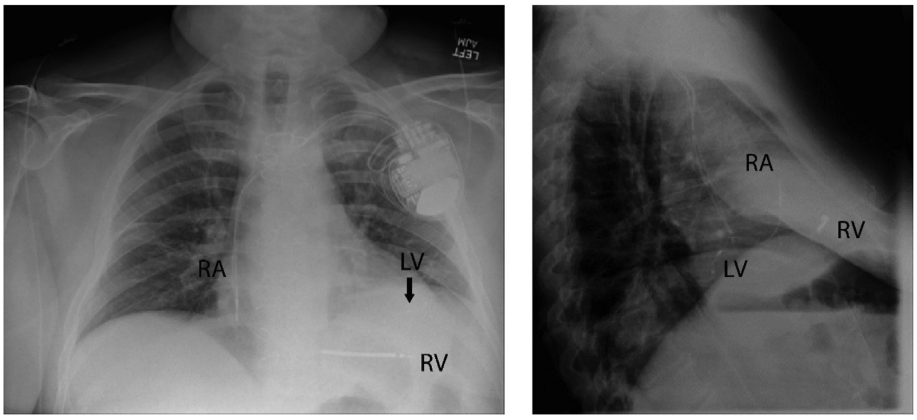

Figure 2 Postimplant chest radiograph. There is mild vascular congestion present. LV = left ventricular lead; RA = right atrial lead; RV = right ventricular lead.

reasonably expect, given the different indications in the contemporary guidelines that would respectively apply to each of these patients: EF <35%/class II-III NYHA CHF/LBBB >150 ms on GDMT (class I ACC/AHA/ESC), atrioventricular block with EF <35% and expectation of RV-based pacing >40% (class IIa ACC/AHA/ESC), and following atrioventricular junction ablation EF <35% on GDMT (class IIa ACC/AHA, class I ESC).[5,6] CRT also resulted in significant improvement in LV and RV dysfunction in this case. In contrast to the prior reports, the indication was for QRS ≥150 ms, class II NYHA CHF, EF <35% on GDMT that correlated with worsening of cardiac function (class IIb ACC/AHA, class IIa ESC).[5,6] Specifically, the indication and response in our case likely related to observations of CRT in atypical RBBB in which a delayed LV activation was additionally present, which may partly manifest as a slurred R wave in leads I and aVL,[7] absent or small S waves <40 ms in lateral leads I and aVL, a prolonged Q-to-local-LV time,[8] and a QRS duration–dependent response in non-LBBB patients.[9] Regardless of the indications, each of the 4 cases demonstrated similar initial benefit.

Interestingly, in a 2009 national survey of 59 cardiac transplant programs, 48% of respondents did not support the use of CRT in patients after OHT and in whom CAV with depressed EF had developed.[10] A clearer idea presently as to the likelihood of response to CRT vs that known in 2009 may partly explain this finding. However, this may also relate to experience with nonresponse to CRT in OHT. Admittedly the long-term data on CRT use in CAV with OHT is unknown. Reports of nonresponse to CRT in OHT are lacking in the literature.

Are we delaying the inevitable in CAV? By most definition there was a super-response to CRT therapy nearly 2 years from implant, and with no apparent progression of CAV in our case.[11] CRT use for approved indications may lead to enough improvement in LV function to delay the need for retransplant, or improve symptoms and outcomes until another donor heart is available. CAV is an accelerated and progressive fibroproliferative disorder with underlying immune and nonimmune risk factors that involves both epicardial and intramural vessels.[1] Thus, it is unlikely that CRT affects the natural course of CAV progression itself, but rather is still able to effect reverse remodeling from improved dyssynchrony despite CAV. As regards implantation of CRT with additional defibrillation capability, the evidence for ICD use in general for OHT patients affected with cardiomyopathy and CAV is neither strongly supportive for or against.[12] Ventricular fibrillation accounts for approximately 10% of sudden cardiac death cases in OHT with allograft dysfunction. Asystole and pulseless electrical activity are rather the predominant rhythms in allograft dysfunction and sudden cardiac death.[13–15] However, it is not known what, if any, impact CRT may have on mortality in OHT.

Conclusion

In heart transplant patients with allograft dysfunction and clinical symptoms of heart failure, and otherwise fulfilling class I and IIa/b contemporary indications, CRT may result in improvement in cardiac function and symptoms, and should be considered. The long-term effect on outcomes for CRT in this population remains unknown.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2022.11.008.

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