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CASE REPORT

Mechanical ventricular assist device as a bridge to recovery post-ABO-incompatible heart transplantation for failed Fontan circulation

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Summary

A girl received an ABO-incompatible heart transplantation (ABOiHTx) at the age of 3.5 years for failed univentricular palliation with protein-losing enteropathy (PLE). She was born with a hypoplastic left heart syndrome and underwent multistage palliation to a Fontan circulation at 2½ years of age. After the Fontan surgery, she developed PLE, necessitating a Fontan revision, followed by a Fontan takedown and eventually HTx, which was performed with a blood group B heart into an O recipient. Right ventricular (RV) failure secondary to increased pulmonary vascular resistance (PVR) evolved immediately after HTx. A temporary right ventricular assist device (RVAD) was implanted and later switched to a pneumatic pulsatile RVAD. With the adaption of PVR on the RVAD, the PLE resolved and the RVAD was explanted. In the following 12 months, she developed multiple relapses of PLE which eventually resolved after exchange of the calcineurin inhibitor.

Introduction

Since the establishment of a staged surgical strategy for the palliation of functional single ventricles in 1968 by Fontan and Baudet [1], the Fontan procedure has undergone many revisions to improve survival and decrease long-term morbidity [2].

Despite improved survival, these patients are at high risk of late morbidity and death [3]. Late complications of Fontan palliation include ventricular dysfunction, atrioventricular valve regurgitation, arrhythmias, and PLE. If these pathologic features are not amenable to medical, surgical, or catheter-based interventions, HTx provides the only alternative for these patients [4,5].

However, after HTx failing, Fontan patients face many challenges, including increased risk of bleeding, increased PVR [6], subsequent RV failure, and problems due to HLA sensitization leading to high early post-transplant mortality [7].

ABOiHTx was pioneered in the late 1990s [8] and has evolved into a routine approach for infants in many centers [9,10]. However, age limits and thresholds of immune maturation remain unclear. Less than 10 cases of individuals older than 2 years of age have presently received intentional ABOiHTx. Our patient being transplanted at an age of 3.5 years across an anti-B titer of 1:32 reflects a successful extension beyond previously perceived limits [10].

Case report

The presented patient was born with a hypoplastic left heart syndrome, aortic, and mitral atresia. She underwent a Norwood-Sano procedure at the age of 2 weeks, followed by a bidirectional Glenn at 4 months of age. She did well for the following 2 years. Cardiac catheterization demonstrated normal pulmonary artery (12 mmHg) and central venous (8 mmHg) pressures, moderate tricuspid regurgitation, and preserved RV function, and she was considered suitable for a Fontan procedure. At the age of 2½ years, a lateral tunnel total cavopulmonary anastomosis with a 4–mm-wide fenestration was performed. After the surgery, she developed peripheral edema and pleural effusions. Cardiac catheterization showed a narrowing of the Fontan circuit below the pulmonary artery connection. A Fontan revision was performed to a nonfenestrated, extracardiac Fontan with a 16-mm Gore-Tex conduit. She remained symptomatic with persistent pleural effusions, generalized edema and decreased albumin levels (18 g/l). She did not respond to treatment with budesonide and diuretics. Cardiac catheterization revealed increased Fontan pressures (18 mmHg) and narrowing of the Fontan connection. She required an urgent Fontan takedown (reconnection of the inferior vena cava to the common atrium) for clinical deterioration and was subsequently listed for HTx. Consideration was given to the implantation of a systemic VAD as a bridge to transplant; however, given the normal systolic function, minor AV regurgitation and the associated adverse events, it was not considered as a favorable strategy. Due to the high likelihood of her not surviving for the expected wait time for an ABO-matched organ, an ABOiHTx was performed after 1 year on the wait list with an anti-B titer of 1:32 at the age of 3.5 years. She received induction therapy with rituximab for B-cell depletion in addition to antithymocyte globulin, steroids, and antibody removal in the operating room prior to implantation of the donor heart. Endomyocardial biopsies remained free of cellular and antibody-mediated rejection in the following weeks. Anti-B titers remained at 1:1 or below. Despite increasing inotropic support, her RV became increasingly dysfunctional within 72 h post-transplant, requiring the implantation of a Centrimag® RVAD. Cardiac catheterization revealed a significant gradient in the ascending and transverse aorta originating from the graft anastomosis. After surgical reconstruction of the aorta, several attempts to reduce the RVAD support failed despite normalized left atrial pressures.

The patient was switched to a Berlin Heart Excor® RVAD and was considered for retransplantation due to persistent RV dysfunction. During 8 months, her RV function significantly improved, her albumin levels normalized, and she remained free of pleural effusions. Consequently, the RVAD was weaned over 20 weeks (Fig. 1) and explanted 15 months post-transplant.

During 5 months, she remained clinically stable. On echocardiography, there was evidence of good RV function and estimated systolic PA pressures in the high-normal range (30 mmHg). Anti-B titers have remained negative; biopsies and coronary angiograms have demonstrated

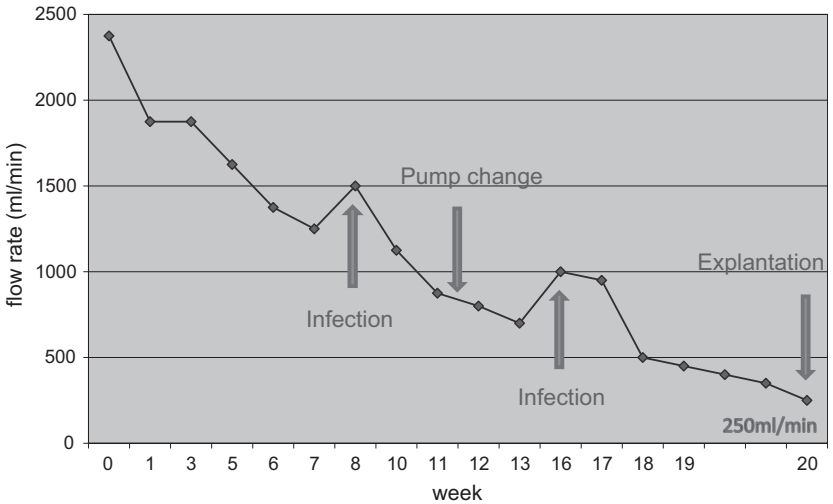

Figure 1 RVAD weaning process over 20 weeks. Reduction of pump rate by a maximum of 10 beats per min per week, using echocardiographic guidance, ensuring improvement of RV function and hemodynamic stability. Pump change after 11 weeks from a 25-ml to a 10-ml pump to avoid thrombus formation. Continuation of the weaning procedure until a minimal safe flow rate of 250 ml/min. After 20 weeks, the RVAD support was completely turned off. Controlled by echocardiography, the device was manually operated by a hand pump once every minute for a period of 15 min to prevent clotting, followed by RVAD explantation 2 days later.

absence of allograft rejection. Six months after discharge, she developed diarrhea, peripheral edema, and ascites. Laboratory findings revealed low albumin (15 g/l) and increased fecal alpha-1-antitrypsin levels (4.6 mg/g wet wt.), which made the diagnosis of relapsing PLE probable. Cardiac catheterization revealed minimally increased MPAP (25 mmHg) and PVR (1.9 Wood units). The medical therapy consisted of daily albumin infusions, budesonide, spironolactone, and sildenafil. Stabilization of PLE could temporarily be achieved with total parenteral nutrition. Discontinuation of mycophenolate mofetil (MMF) did not improve the abdominal situation. Eventually, the calcineuring inhibitor was switched from tacrolimus (TAC) to cyclosporine (CyA). Two months later, the patient's symptoms of PLE subsided, and she did no longer require albumin supplementations. She has since remained free of PLE for 9 months, MMF was successfully reintroduced, and she is managed as an outpatient, showing an excellent quality of life.

Discussion

Despite the increasing number of survivors of Fontan patients, long-term challenges in the early and late postoperative period remain prevalent [2,3]. One particularly elusive problem is the clinical syndrome of protein loss into the lumen of the gastrointestinal tract, generalized edema, and ascites referred to as PLE [11]. The multifactorial etiology of PLE includes decreased cardiac output, increased systemic venous pressure, increased mesenteric vascular resistance, and inflammation.

Since the initial description of PLE multiple treatment strategies have been proposed, therapeutic options include diuretics, afterload-reducing agents, heparin, steroids, somatostatin analogs, and cardiovascular maneuvers such as balloon dilatation of obstructed vessels or the fenestration to the atrium [11]. Resolution of PLE after fenestration of the atrial septum or relief of pathway obstructions of the Fontan circulation has been reported [12]. Refractory PLE following a Fontan surgery represents one of the indications for HTx [4,13].

There have been previous case reports suggesting that PLE resolves after HTx. [14,15]. Bernstein *et al.* [13] reported the outcome of listing for cardiac transplantation in 97 patients with failing Fontan. In their dataset, PLE resolved in a 100% of the patients who survived for 30 days after HTx.

PLE in our patient remained refractory to medical management and Fontan revision. HTx was considered a rescue modality. RV failure after HTx necessitated the implantation of a Centrimag® RVAD, followed by a Berlin Heart Excor® RVAD, allowing the pulmonary vasculature to remodel and the RV to recover. Our case is the first to describe the successful bridge to recovery of RV dysfunction through the application of a RVAD, thereby providing an option for transplantation of high-risk patients with failing Fontan circulation.

We confirm recent reports that successful ABOiHTx can be performed at an older age, with higher isohemagglutinin titers than initially assumed, and similar antigen-specific tolerance can be achieved. Our patients Anti-B titers have remained negative despite the recovery of B-lymphocytes 2½ years after induction therapy with rituximab, suggesting elements of induced immune tolerance [10].

The clinical course with absence of signs of acute cellular or antibody-mediated rejection in multiple biopsies, echocardiography, ECG, and persisting quasi absence of antibodies against donor blood group B make a relevant contribution of rejection to the RV failure highly unlikely.

Possible explanations for the recurrence of PLE might be that patients with previous PLE display altered lymphatic and mesenteric circulations. These changes could be more permanent within the intestines and less amenable to hemodynamic improvement after HTx. Chronic inflammatory bowel diseases in liver transplant recipients were found to have a significantly lower risk of relapse under CyA compared with TAC, and a similar contribution may impact the inflammatory component of PLE.

In conclusion, HTx for failing Fontan patients with PLE remains a high-risk procedure; however, it may be the only viable option for children failing conservative management. ABOi HTx can be successfully performed across previously perceived safety limits with regards to age and isohemagglutinin titers. RVAD support is an option to facilitate a bridge to recovery of RV dysfunction, remodeling of the pulmonary vasculature, and improvement of increased PVR. The choice of immune suppression may be relevant for the recovery from PLE.

Authorship

SS: conducted study, collected the data, analyzed the data and wrote the paper. HB: contributed important information and data on mechanical circulatory assist devices. IR: contributed important information and data on heart transplantation and cardiac surgery. DR: contributed important information and data on heart transplantation and cardiac surgery. LW: contributed important information and data on ABO incompatible heart transplantation and immunology. SU: supervised the study, supervised the evaluation and interpretation of data and clinical information.

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