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Successful Cardiac Transplantation in a Patient with Elevated Pulmonary Vascular Resistance: A Relative Contraindication to Transplantation

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ABSTRACT

Elevated pulmonary vascular resistance in a transplantation candidate should be viewed as potentially reversible, and there are several options for therapy. We describe a young patient with congenital restrictive cardiomyopathy and a markedly elevated pulmonary artery pressure. The patient underwent successful orthotopic heart transplantation after pharmacologic lowering of the pulmonary artery pressure with a new drug combination of milrinone and nesiritide. The length of therapy can be extended to 3 days to allow for determining the pulmonary vascular responsiveness.

INTRODUCTION

Orthotopic heart transplantation can be hazardous in recipients with pulmonary hypertension, because with an increase in pulmonary vascular resistance (PVR) comes a progressive increase in the operative risk of right-sided heart failure [Bourge 1991]. The right ventricle of patients with chronic heart failure becomes conditioned to the high resistance induced by progressive left-sided heart failure. The determination of pulmonary vascular reactivity as a result of chronic left-sided heart failure becomes critical when cardiac transplantation is considered [Kirklin 2002]. An established level of reactivity in the pulmonary circulation may be more important than an actual value of stated pressure or resistance, expressed either as Wood units or in millimeters of mercury [Kirklin 2002]. In potential heart transplant recipients with a PVR >4 Wood units (or a transpulmonary gradient [TPG] >12 mm Hg), provocative testing in the cardiac catheterization laboratory is indicated.

We describe a young patient with congenital restrictive cardiomyopathy and a markedly elevated pulmonary artery pressure (PAP). The patient underwent successful orthotopic heart transplantation after pharmacologic lowering of the PAP with milrinone and nesiritide. This therapy demonstrated the responsiveness of the pulmonary vascular bed.

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CASE REPORT

A 16-year-old boy with Noonan syndrome and New York Heart Association functional class IV heart failure symptoms secondary to congenital cardiomyopathy was denied heart transplantation at the referring facility because of an elevated PVR. Medical therapy at that facility included furosemide, spironolactone, carvedilol, and telmisartan, but the patient's symptoms remained severe. He was referred to our institution for consideration for heart-lung transplantation. At age 10 years, the patient had undergone percutaneous treatment of aortic coarctation at another institution. A physical examination revealed sinus rhythm, good blood pressure, and severe scoliosis. The pulmonary examination revealed basilar crackles, and a cardiac radiograph showed pulmonary edema. The cardiac examination revealed jugular venous distention to 14 cm, a right ventricular heave, an S_3 and S_4 gallop, no ascites, and minimal pedal edema. An echocardiogram showed normal cardiac dimensions with severe concentric hypertrophy and an ejection fraction of 55%—findings consistent with restrictive cardiomyopathy. Laboratory values were within normal ranges, except for an elevated total bilirubin concentration of 4.5 mg/dL.

A cardiac catheterization evaluation revealed a PAP of 77/39 mm Hg (mean, 55 mm Hg) and a PVR of 7.4 Wood units. The pulmonary artery wedge pressure (PAWP) was 33 mm Hg, and the cardiac index (CI) was 2.0 L/min per m^2.

After 3 days of milrinone (0.375 µg/kg per min) and nesiritide (0.005 µg/kg per min) infusions, the PAP had decreased to 48/24 mm Hg (mean, 34 mm Hg), and the PAWP was 24 mm Hg. The patient's CI had normalized to 3.2 L/min per m^2, and the PVR had decreased to 3.0 Wood units. Initial discussions about the patient undergoing heart-lung transplantation were curtailed because of the response to pulmonary vasodilators and inotropes. In addition, the patient's severe scoliosis precluded heart-lung transplantation for anatomic reasons.

In September 2003, when an acceptable donor heart became available, the patient underwent orthotopic heart

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transplantation with a bicaval anastomotic technique. The donor was 1.6 meters tall and weighed 50 kg; the recipient was 1.5 meters tall and weighed 52 kg. On postoperative day 1, the PAP and the CI were 48/32 mm Hg and 3.5 L/min per m^2, respectively, while the patient was receiving isoproterenol, milrinone, nesiritide, and prostacyclin infusions. One week later, the patient was weaned from the infusions and was administered sildenafil and diuretics. The patient was discharged from the intensive care unit on postoperative day 10. The postoperative course was complicated by a loculated right pleural effusion that required decortication.

The patient was discharged home 3 weeks after transplantation on a medical regimen that included oral sildenafil (50 mg, 3 times/day), an angiotensin-converting enzyme inhibitor, and a diuretic. Two months after transplantation, the patient's pulmonary artery systolic pressure was 45 mm Hg, and the right atrial pressure was 10 mm Hg. Patient follow-up continued at the referring overseas facility, and repeated conversations with the family and referring physicians confirmed that the patient was following the course of a normal heart transplant patient. However, more than 2 years after transplantation, the patient was admitted to the hospital with severe rejection of the cardiac allograft, which eventually resulted in his death.

COMMENT

In the patient we have described, the response to therapy with standard measures performed in the catheterization laboratory at another institution did not change the PVR. However, after initial testing at our institution and 3 days of therapy with milrinone and nesiritide, we discovered that the patient had a reactive component to the elevated PVR; it decreased from 7.4 to 3.0 Wood units, making orthotopic heart transplantation possible.

Elevated PVR, which is defined as a TPG (TPG = mean PAP – PAWP) >12 mm Hg or a PVR >4 Wood units (TPG/cardiac output), has been shown to be a risk factor for early death secondary to acute right ventricular failure after cardiac transplantation [Griepp 1971; Bourge 1991]. Nevertheless, some reports have demonstrated successful heart transplantation in patients with elevated PVR [Addonizio 1987; Delgado 2001]. The majority of adult patients with advanced heart failure are known to have a reactive component to their elevated PVR. This component varies among patients and is related to the type of heart disease, the duration of heart failure, and other factors [Kirklin 2002]. After diuresis and inotropic therapy, the PVR usually decreases. In other patients, a reactive component may remain undiscovered despite diuresis, only to be exposed by further pulmonary vasodilator therapy administered in the cardiac catheterization laboratory.

Various protocols and drug treatments, such as milrinone, nitric oxide, prostaglandin E1, or dobutamine, have been developed to determine the responsiveness of the pulmonary vascular bed, an important factor for assessing patients' suitability for undergoing cardiac transplantation [Pamboukian 1999; Radovancevic 2005]. Typically, results are achieved within minutes of starting treatment, and patients can be classified as high, intermediate, or low risk for transplantation on the basis of their PAP and their response to vasodilator and inotropic therapy.

Longer periods of assessment and therapy before testing for pulmonary vascular responsiveness have been described [Perez-Villa 2006], but not with the present drug combination. The phosphodiesterase inhibitor milrinone is an effective pulmonary vasodilator and inotrope that worked well in this patient and, perhaps, synergistically with the nesiritide over a 72-hour period. Nesiritide is synthesized with recombinant DNA technology and is identical to the endogenous cardiac neurohormone brain natriuretic peptide. It has proved useful and safe in the treatment of decompensated heart failure, and it decreases PAP and PAWP [Colucci 2000].

The present case involved administration of a new drug combination for determining a patient's potential for undergoing successful cardiac transplantation. Elevated PVR in a transplantation candidate should be viewed as potentially reversible, and there are several options for therapy. Intravenous infusions of milrinone and nesiritide can be used with confidence in initially unresponsive pulmonary vascular beds. The length of therapy can be extended to 3 days to allow for determining pulmonary vascular responsiveness.

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