Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 7, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.11.022

STATE-OF-THE-ART PAPER

Percutaneous Interventional Therapies for the Treatment of Patients With Severe Pulmonary Hypertension

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Despite improvements in medical therapy, the overall prognosis of patients with severe pulmonary arterial hypertension remains poor. Heart-lung transplantation or bilateral lung transplantation is the final pathway for a minority. This paper describes both established and novel percutaneous interventional techniques that may palliate or bridge pulmonary hypertension patients to transplantation. (J Am Coll Cardiol 2014;63:611–8) © 2014 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) is a progressive and irreversible disorder eventually resulting in right ventricular (RV) failure and death. Despite advances in the treatment of PH, the overall prognosis remains poor, with an approximate annual mortality rate of 11.8% in patients with idiopathic pulmonary arterial hypertension (IPAH), and 16.6% in those diagnosed with scleroderma-related PH (1).

Heart-lung transplantation (HLTx) and bilateral lung transplantation (BLTx) remain the final options for patients with PH remaining in New York Heart Association (NYHA) functional class III/IV despite combination therapy. Patients in NYHA functional class IV or who remain in functional class III despite combination therapy should be referred early to a PH center of excellence or other tertiary center for transplantation assessment. Predictors of survival after lung transplantation include the 6-min walk distance (6MWD) and peak myocardial oxygen consumption, right atrial pressure (RAP) >15 mm Hg, and a cardiac index <2.0 l/min/m^2 (2).

BLTx is the operation of choice for patients with IPAH and those with severe secondary PH, as single-lung transplant has an increased risk of perioperative allograft edema (3). In patients with congenital cardiac abnormalities, particularly Eisenmenger syndrome, and severe right and/or left heart dysfunction, HLTx provides survival advantages and may be considered the procedure of choice (4,5). In other etiologies of PAH, the choice of either HLTx or BLTx depends on individual center choice and policy and donor availability. Overall survival rates of BLTx and HLTx are similar; however, freedom from obliterative bronchiolitis–related death has been reported to be significantly greater in the latter (6). After transplantation, there is an immediate decrease in pulmonary artery pressure (PAP) and RV size and normalization of septal geometry (7). Unadjusted 3-month mortality is highest in patients with PH pre-transplantation (8). However, among those surviving at least 1 year, better conditional half-lives after transplantation occur in patients with PAH (10 years) compared with patients with other underlying diagnoses such as chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis (6.8 years for both) (8). Heart-lung transplant recipients with Eisenmenger syndrome and IPAH have significantly better overall survival than patients with other congenital abnormalities (8). After 1-year survival post-transplantation, long-term survival rates are relatively good, and ~50% of patients remain alive >9 years after transplantation (8).

Unfortunately, lung transplantation is only a viable option in approximately one-third of patients with PAH referred for lung transplantation (9). This paper describes both established and novel percutaneous interventional techniques that may palliate symptoms or serve as a bridge to transplantation in selected patients with PH.

Atrial Septostomy

Atrial septostomy (AS) is indicated in some patients with RV failure and associated PH in whom medical therapy has failed. It should only be attempted in centers with extensive experience in managing patients with PAH and lung transplantation. AS may be used as a bridge to lung transplantation

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Manuscript received August 2, 2013; revised manuscript received November 5, 2013, accepted November 11, 2013.

JACC Vol. 63, No. 7, 2014
February 25, 2014:611–8

Abbreviations and Acronyms

AS = atrial septostomy
BLTx = bilateral lung transplantation
BNP = B-type natriuretic peptide
BPA = balloon angioplasty of the pulmonary artery
CTEPH = chronic thromboembolic pulmonary hypertension
dAo = descending aorta
HLTx = heart-lung transplantation
IPAH = idiopathic pulmonary arterial hypertension
LPA = left pulmonary artery
MSNA = muscle sympathetic nerve activity
NYHA = New York Heart Association
PADN = pulmonary artery denervation
PAP = pulmonary artery pressure
PEA = pulmonary endarterectomy
PH = pulmonary hypertension
RAP = right atrial pressure
RV = right ventricular
6MWD = 6-min walk distance

or as a therapy where there is limited access to lung donors. Severe IPAH has been the main indication for AS in adults, but other common indications include PAH associated with congenitally corrected heart disease, connective tissue disease, and distal chronic thromboembolic PH (10).

The principle of AS is based on the observation that patients with Eisenmenger syndrome have a better prognosis than those with IPAH (11). The physiological basis for improvements after AS include an improved cardiac output, RV decompression, and reduced sympathetic over-reactivity. An iatrogenic atrial septal defect improves left ventricular pre-load, thereby improving cardiac output. The decrease in systemic arterial oxygen saturation induced by right–left shunting is compensated for by an increase in cardiac output (2,12–19). Improvements in RV function after AS have been shown using echocardiography (20) and inferred using serial B-type natriuretic peptide (BNP) levels (21). AS has been shown to have a beneficial effect on reducing sympathetic nervous activation as measured by muscle sympathetic nerve activity (MSNA) (22,23). After AS, hemodynamic benefits have been shown to translate into functional benefits including improvements in 6MWD and NYHA functional class (2,19).

Technique. The creation of the interatrial opening was originally achieved by balloon AS, whereby an inflated balloon was forcefully jerked/pulled across the foramen ovale to tear the atrial septum and promote interatrial mixing of blood. As an alternative to balloon AS, balloon-dilated AS has been developed in which the atrial septum is punctured using a Brockenbrough needle (multiple manufacturers), and the interatrial opening is progressively dilated with increasing balloon size (24). This allows the size of the defect to be gradually increased, taking care to ensure arterial oxygen saturation does not decrease >10% and that left ventricular end-diastolic pressure does not increase to >18 mm Hg.

After balloon-dilated AS, the interatrial opening commonly closes, but repeated procedures can be performed with varying degrees of success. Fenestrated devices (or modified techniques of stent fenestration) have also been used to control the degree of shunt created and to maintain the patency of the interatrial opening (25–27). The diabolo-shaped stent improved symptoms and was free of thrombotic complications in selected small studies (26,27). The stents used were mounted on a standard valvuloplasty balloon catheter that was constricted by a loop using a temporary pacing wire (Fig. 1). Full balloon inflation resulted in a diabolo-shaped stent configuration (Fig. 2). The stent can be further dilated or constricted to increase or reduce the degree of shunting. Another approach using fenestrated devices has been the use of modified Amplatzer septal occluder devices (Fig. 3). However, these devices have a higher rate of thrombotic occlusion (25).

The timing of AS to achieve optimal benefit is uncertain. In the majority of cases, AS has been performed after failure of optimal medical therapy as a last resort before lung transplantation. However, one study suggested that patients receiving concomitant medical therapy after AS had a higher survival rate than patients who received AS alone (19). Limitations of that study include its retrospective nature and the fact that it did not include a subgroup of patients who received only IPAH-specific pharmacological therapy. It is possible that IPAH-specific pharmacological therapy would have resulted in an outcome similar to that achieved in the AS/medical therapy group. The 1-month mortality rate was only 2%, which may be due to the fact that approximately one-third of the patient group underwent AS early in the course of their disease (RV end-diastolic pressure <10 mm Hg). The same favorable outcome was found in a series of young children who underwent AS at a relatively early stage of their disease (mean RAP of 9 ± 5 mm Hg and syncope rather than overt right heart failure) (28). Nevertheless, it does seem intuitive that the combination of PAH-specific therapies in conjunction with AS in patients earlier

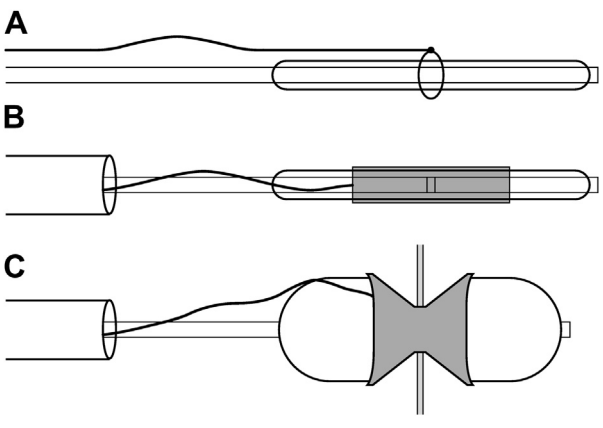

Figure 1 **The Diabolo Fenestrated Stent Technique for Mounting a Stent**

(A) A loop of defined diameter is created using a temporary pacing wire. This is placed over a standard balloon valvuloplasty catheter. **(B)** The stent, mounted and crimped with the loop centered. **(C)** The stent is placed across the fenestration, and the balloon catheter is fully inflated. Reprinted with permission from Stümper et al. (27).