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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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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

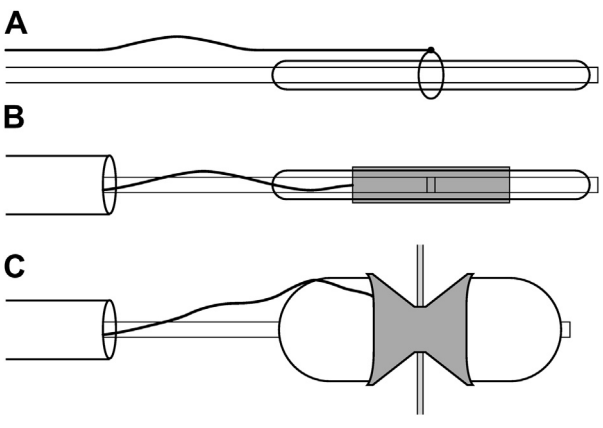

Figure 1 **The Diabolo Fenestrated Stent Technique for Mounting a Stent**

(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).

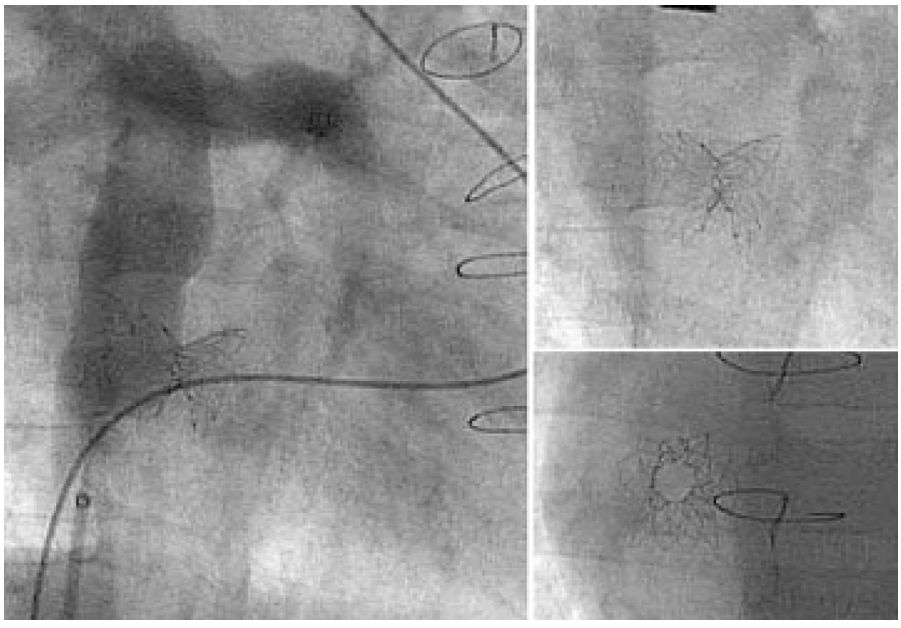

Figure 2 Final Position of the Stent Across the Atrial Septum

The stent can then be further dilated or constricted depending on the patient's hemodynamics. Reprinted with permission from Stümper et al. (27).

in the course of their disease may offer a survival advantage rather than using AS in the latter stages of disease. The timing of AS should occur before the development of RAP ≥20 mm Hg, left ventricular end-diastolic pressure >18 mm Hg, pulmonary vascular resistance index >55 U/m^2, or baseline O_2 saturations <90% in room air, as these factors have been shown to be predictive of a 25% procedural mortality rate (2,17).

Complications and survival. Procedural complications include balloon rupture and embolization of balloon fragments, cardiac perforation or damage including rupture of the atrial appendage, failure to deflate the balloon, stroke, and vascular complications (29). Patients with severe right heart failure and extremely high pulmonary pressures do not tolerate AS because massive right-to-left shunting may result in severe systemic arterial oxygen desaturation and

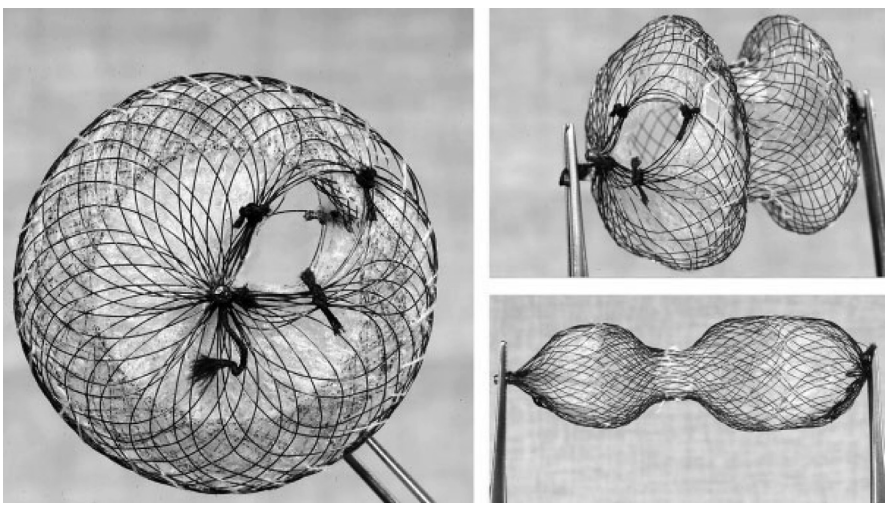

Figure 3 Modified Standard Amplatzer Atrial Septal Occluder With Self-Made Fenestration

Reprinted with permission from Lammers et al. (25).

hypoxia leading to ischemia and death. The risk of death is higher for patients with advanced disease, but these are the patients thought to benefit most from the procedure (2,30). Immediate mortality rates after AS vary from 0% to 20%, with 30-day mortality rates as high as 23% (15,30). The mean survival medium term after AS (excluding procedural deaths) has been shown to be 63.1 months (2). Most studies have compared the effect of AS on survival by comparing survival rates post-procedure with survival rates as predicted by the regression equation obtained from the IPAH registry of the U.S. National Institutes of Health (31). The limitations to this approach are that the characteristics of the population studied in the registry were very different from those in patients undergoing AS. For example, all National Institutes of Health–enrolled patients had IPAH, and no patients were included with secondary causes of PH. Less than 50% of these patients were taking long-term anticoagulation, and none received advanced disease-targeting therapies. Consequently, using the National Institutes of Health equation could potentially underestimate survival rates and overstate the potential benefits of AS on survival.

Pott's Shunt

An alternative method of decompressing the right ventricle is by forming a direct anastomosis between the descending aorta (dAo) and the left pulmonary artery (LPA), a Pott's shunt (32). This offers several theoretical advantages over the creation of an AS. Blood is shunted directly into the dAo, which avoids exposing the brain and myocardium to desaturated blood. A Pott's shunt may offer more reliable shunting than would an atrial septal defect by addressing suprasystemic pulmonary artery surges. Furthermore, uncontrolled hypoxemia can be potentially avoided by the use of a pressure-restrictive shunt. The largest experience described in the literature is a series of 8 children, all of whom were in NYHA/World Health Organization functional class IV with symptoms of repeated syncope or signs of right heart failure (32). Six of 8 patients survived and remained well at a mean follow-up of 63 months, with improvements in RV dimensions on echocardiography, improved functional status, as well as lower BNP levels.

Transcatheter creation of an aortopulmonary shunt has been successfully performed in animals (33) and more recently in humans (34). Ten piglets had a Pott's shunt created by radiofrequency perforation from the aorta to the pulmonary trunk, followed by stent implantation (bare-metal stents or polytetrafluoroethylene-covered coronary stents). Oxygen saturation improved from 63% (range 53% to 72%) in the right atrium to 84% (range 59% to 92%) in the pulmonary artery ($p < 0.005$). At follow-up, 4 of 6 stents were obstructed because of tissue ingrowth in the bare-metal stents and thrombus formation in the covered stents.

Percutaneous aortopulmonary shunt formation was also reported in a series of 4 adults (34) in whom a modified Brockenbrough needle and the "stiff" end of a 0.014-inch wire were used to puncture the dAo and LPA. After balloon dilation, an iCAST 7 × 22-mm covered stents (Atrium Medical Corporation, Hudson, New Hampshire) spanning the LPA and dAo walls was implanted. Follow-up was limited to 4 to 10 months. This technique is very high risk, as any misjudgment in stent length to span the distance between the LPA and dAo can result in hemorrhage. One patient died 8 days post-procedure of pneumonia and multiorgan failure, and 1 died of catastrophic intrathoracic bleeding.

Another group described 3 patients with IPAH and severe PH who had a small patent ductus arteriosus or probe-patent patent ductus arteriosus (35). This allowed insertion of a stent to provide a communication between the dAo and LPA. The stent size used varied from 6 to 9 mm in diameter and was gradually dilated to equalize PAP and aortic pressure. After a mean follow-up of 14 ± 9 months, all 3 patients showed improved functional capacity and improved RV function. Importantly, there were no major complications or deaths.

Both of the series described were small but indicate a possible role for intervention as an additional therapy in an already difficult to-treat group of patients. After a stent anastomosis is created, there is the possibility that it could be further dilated to increase the degree of shunting. At present, these techniques are experimental and will require larger numbers of patients with longer follow-up periods to determine their full effects on survival. The optimal timing of the percutaneous Pott's shunt is yet to be determined. It currently appears to be high risk and should be reserved for patients in whom AS or lung transplantation is contraindicated.

Segmental Balloon Pulmonary Angioplasty for Treatment of CTEPH

Pulmonary endarterectomy (PEA) is the definitive treatment for chronic thromboembolic pulmonary hypertension (CTEPH), with operative mortality rates reported as 4% to 7% and 5-year survival rates of 90% at centers of excellence (36). However, it is contraindicated in the presence of severe underlying lung disease (37). Lesions located in distal arterioles are often inaccessible and are associated with higher operative mortality rates (36). Furthermore, as many as 30% of patients continue to have residual PH post-PEA. Although this appears not to have a significant effect on mortality, it is associated with reduced exercise capacity and lower objective measures of quality of life such as physical function, general health, and emotional well-being (38,39).

Medical therapy may play a role in the subset of patients who are not suitable for PEA. The BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) study randomized inoperable or persistent CTEPH patients to bosentan or placebo (40). After 16 weeks of treatment with bosentan, there was a

24% reduction in peripheral vascular resistance (−146 dyn·s·cm^{-5}; $p < 0.0001$) compared with placebo, but with no significant difference in 6MWD or improvement in NYHA functional class status between the 2 groups.

Balloon angioplasty of the pulmonary artery (BPA) has also been used with encouraging results in adult patients with CTEPH in whom distal disease is inaccessible and too high risk (41–44). Physiologically, it improves pulmonary blood flow distribution and increases pulmonary vascular capacitance, decreasing RV afterload. Feinstein et al. (43) performed BPA in 18 patients with CTEPH who were poor surgical candidates because of either medical comorbidities or surgically inaccessible disease. Pulmonary artery stenoses were gradually dilated using balloons that were sized to be 75% to 100% of the vessel diameter. This is in contrast to previous BPA experience in congenital patients in whom a larger ratio of balloon to minimal luminal diameter was preferred (45). This resulted in clear improvements in NYHA functional class, 6MWD, and mean PAP. Repeat angiography demonstrated that all previously treated vessels remained patent at 1 to 40 months after initial BPA.

Kataoka et al. (44) investigated the effects of BPA in 29 patients with CTEPH. An older cohort was used in this study: 37% of patients were >70 years of age compared with 11% in the study by Feinstein et al. (43). Rather than all patients being inoperable, an undisclosed number of patients had thromboembolic disease that was amenable to PEA, and 3 patients had residual PH after previous PEA. The majority of patients were receiving advanced medical therapies. Interestingly, BPA did not result in any immediate hemodynamic effect, confirming that a certain amount of time is required for positive remodeling of the pulmonary vasculature, as seen in PEA (2). Right heart catheterization at 6 months demonstrated significant improvements in hemodynamic parameters as well as significant improvements in functional exercise capacity and BNP levels. Unfortunately, follow-up was for only 6 months, and so no conclusions can be made about the impact of BPA on long-term survival. Mizoguchi et al. (42) performed BPA in 68 subjects, all of whom had surgically inoperable CTEPH. All patients showed significant improvements in PAP, BNP levels, and functional exercise capacity. One patient died of right heart failure 28 days after BPA, another died of pneumonia, and the remaining 66 patients are alive at 2.2 ± 1.4 years. Follow-up at 1 year confirmed normalized PAP and improved angiographic appearance of the pulmonary arteries.

Reperfusion pulmonary injury can be a fatal complication that occurs with a reported incidence as high as 68% after BPA compared with 10% to 15% after PEA (41–44,46). Increased local pulmonary blood flow and pressure in a previously underperfused vascular bed cause an acute increase in capillary perfusion pressure. Strategies to reduce reperfusion edema include limiting dilation to no more than 2 vessels per sitting (42), the use of pharmacological agents before BPA (42,43), and intrapulmonary imaging to reduce the risk of reperfusion pulmonary injury and rupture of the pulmonary artery. Intravascular ultrasound and optical coherence tomography have been used to determine optimal balloon size for dilation of pulmonary vessels (41,42). Although a small balloon was used for the initial dilation to avoid rupture and dissection of the pulmonary artery, further dilation was based on intravascular ultrasound sizing using the vessel diameter, ensuring that the maximal size is not >90% of the original size of the vessel diameter. These techniques do result in detailed anatomic images; however, in the absence of a control group, it is difficult to determine whether these techniques are helpful.

Once CTEPH has been diagnosed, patients should be referred for surgical evaluation by an experienced multidisciplinary team (2). In candidates found to be unsuitable for PEA, BPA can be considered an alternative, providing that the unit has the appropriate expertise. The timing of this procedure is similar to that of patients awaiting PEA (i.e., patients should be referred for assessment with a resting pulmonary vascular resistance of at least 300 dyn·s·cm^{-5}, or ~4 Wood units) (47).

Pulmonary Artery Vasoconstriction and Denervation

Pulmonary artery denervation (PADN) is a novel technique under investigation as a treatment for PH. It is thought to work by reducing sympathetic stimulation of the pulmonary vasculature. The mechanisms for increased sympathetic activation are not clear, but comparisons have been made with chronic heart failure and associated activation of the renin-angiotensin-aldosterone system (48,49). In addition, hypoxia within the pulmonary arteries is thought to lead to enhanced transcription of β_1-adrenoreceptor messenger ribonucleic acid, with resultant increases in β_1-adrenoreceptor expression on pulmonary blood vessels (50). Chronic levels of adrenergic excitation have been shown to adversely affect RV modeling. In an animal model of RV heart failure caused by pulmonary artery banding, adrenergic β-receptor density was reduced compared with control animals in the stressed right ventricle (51). In human subjects affected by primary PH, it has been shown that the β-receptor number is reduced only in the failing right ventricles, confirming that β-receptor down-regulation is chamber specific (52). The up-regulation of α_1-adrenoreceptors and reduction of adrenergic β-receptors is likely to lead to vasoconstriction rather than vasodilation of the pulmonary vasculature.

Sympathetic nervous system activity has been assessed indirectly by using peroneal nerve microneurography. This has confirmed that PH patients have increased levels of sympathetic activity as demonstrated by higher MSNA (23). Furthermore, in PH patients post-AS, MSNA levels have been shown to decrease compared with control patients, implying that AS decreases sympathetic hyperactivity. The decrease in MSNA was directly related to the

decrease in RAP, suggesting that sympathetic overactivity in patients with severe PAH is related to right atrial distension (22).

Previous investigations have shown that distention and occlusion of 1 branch of the pulmonary artery results in an increase in pulmonary vascular pressure and resistance (53,54). This increase occurs in the absence of any significant change in RV or left ventricular end-diastolic pressure, aortic pressure, and cardiac output. It is postulated that baroreceptors are situated close to the bifurcation of the main pulmonary artery and are involved in facilitating a neural reflex as a result of activation by stretch receptors (54). In animal studies, dissection of the areas of the pulmonary artery under the bifurcation prevented the increase in vascular resistance response to balloon inflation. Furthermore, there was no effect of breathing 100% oxygen on PAP during pulmonary artery distention, suggesting that hypoxia was not the principal cause of observed pulmonary vasoconstriction (53). It is unlikely that the parasympathetic nervous system is involved in this reflex because vagotomy does not have any effect on pulmonary vascular resistance after balloon inflation (53).

Based on these experiments and the development of renal denervation as a treatment for drug-resistant hypertension (55), percutaneous PADN was performed in a dog model (56). Preliminary experiments (not published by the group) suggested that catheter ablation <2 mm proximal to the bifurcation of the main pulmonary artery was the most effective area for PADN. Occlusion of the left pulmonary interlobar artery by balloon inflation induced significant increases in PAP and RV pressure, which persisted for 10 min. Hemodynamic parameters induced by interlobar artery occlusion returned to baseline after PADN. The authors acknowledge that the gradual increase in inflation pressure itself could induce vasoconstriction and increase PAP, and they were unable to provide histological evidence of the effects of catheter ablation. PADN was demonstrated to abolish acute PH, but its effect on long-term causes of PH are not known. Furthermore, it is not known whether the effect of PADN is permanent because it has been shown in rats that sympathetic nerve reinnervation can occur (57).

A small first-in-humans study consisting of 21 patients with IPAH reported significant improvements in mean PAP after PADN (58). In addition, significant improvements in functional capacity and NYHA functional class were noted in subjects who underwent PADN. Limitations include the lack of randomization between control subjects and those undergoing PADN. Subjects were only followed for 3 months, and therefore, the long-term results of this treatment cannot be determined. PADN has only been performed in a small number of patients with IPAH who, despite being refractory to medical therapy, had normal RAPs, thus casting doubt on the severity of PH in the treatment group (58). It is, therefore, difficult to make any recommendations about the optimal timing of this very new technique because the efficacy remains to be proved in larger randomized, controlled trials.

Conclusions

Advances in medicine have improved the prognosis of patients with severe PH. However, there continues to be a subset of patients who may benefit from procedures that decompress the right ventricle. These techniques are highly specialized, and patients should be referred to specialist centers with expertise in PH and lung transplantation. The optimal timing of AS has yet to be determined, but observational data suggest that the combination of PAH-specific therapies in conjunction with AS in patients earlier in the course of their disease may offer a survival benefit rather than performing AS in the latter stages of their disease. Modification of AS techniques, such as those using modified fenestrated stents, may offer the possibility of increasing or decreasing the shunt at a later date and tailoring individualization of therapy in these very ill patients. Transcatheter Pott's shunt creation is highly challenging and so far has only been performed in a handful of subjects. Further refinements in the technique are required before it is considered a safe procedure. Nevertheless, it may obviate the need for thoracotomy and sternotomy in these high-risk patients. BPA, although technically challenging, has been shown to be an efficacious treatment for patients with CTPEH who have surgically inaccessible disease, albeit with a high incidence of reperfusion edema. Limiting the intervention to no more than 2 arteries per setting seems to be the most successful method of reducing the incidence of this complication. However, long-term and randomized, controlled trial data for both BPA and AS are not yet available. Results from PADN are still very preliminary, and the mechanisms of action are still not fully understood. However, it does provide an interesting alternative future approach to redressing the balance between vasoconstriction and vasodilation of the pulmonary vasculature.

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