

# Catheter-Based Therapies for Patients With Medication-Refractory Pulmonary Arterial Hypertension

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**P**ulmonary arterial hypertension (PAH) is a disease of progressive distal pulmonary artery remodeling that leads to increased pulmonary vascular resistance, right ventricular failure, and premature death. The diagnosis of PAH is made by right heart catheterization when the mean pulmonary artery pressure is  $\geq 25$  mmHg at rest with a pulmonary vascular resistance of  $>3$  Wood units and a pulmonary capillary wedge pressure of  $<15$  mmHg.<sup>1</sup> Once diagnosed with PAH, the 1- and 5-year survival rates are 86.3% and 61.2%, respectively, with a median survival of only 7 years.<sup>2,3</sup> Although there have been advances in pharmacotherapies for PAH, there are subsets of patients that are medication nonresponders or that continue to have a clinical decline despite maximal medical therapy. The latter is particularly evident when the right atrial pressure is  $>20$  mmHg or the cardiac index is  $<2.0$  L/min per  $m^2$ , both indicators of a poor prognosis.<sup>4</sup> For these patients, there are several invasive strategies, such as atrial septostomy, a Potts shunt, and pulmonary artery denervation that have a therapeutic or palliative role in the management of PAH and are transitioning from surgical to catheter-based interventional procedures.

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**See Article by Chen et al**  
**See Article by Rothman et al**

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### Atrial Septostomy

Atrial septostomy, a procedure that creates an interatrial right-to-left shunt, is typically reserved for drug-refractory patients with right ventricular (RV) failure and syncope. Atrial septostomy unloads the RV, augments left ventricular preload and, thereby, increases cardiac output.<sup>5</sup> The rationale for atrial septostomy is based on the observation that PAH patients with a patent foramen ovale live longer than those without right-to-left shunting and that patients with Eisenmenger syndrome with similar mean pulmonary artery pressures and pulmonary vascular resistance have lower right atrial pressures, less severe RV dysfunction, higher cardiac outputs, and lower mortality rates compared with PAH patients.<sup>6</sup> Review of the

current worldwide experience shows that  $\approx 86\%$  of patients undergoing atrial septostomy survive the procedure and  $\approx 90\%$  have improved functional capacity.<sup>5</sup>

Catheter-based balloon dilation atrial septostomy is performed via a controlled puncture of the interatrial septum with a Brokenbrough needle followed by serial dilation of the septal perforation using noncompliant peripheral balloons. The patient's oxygen saturation and left ventricular end-diastolic pressure are measured with each stepwise increase in balloon diameter to avoid decreasing the oxygen saturation by  $>10\%$  or increasing the left ventricular end-diastolic pressure to  $>18$  mmHg and precipitating pulmonary edema.<sup>4</sup> Patient selection for this procedure is critical owing to the high rates of periprocedural mortality; right atrial pressure  $>20$  mmHg and a resting oxygen saturation of  $<90\%$  on room air have been shown to predict adverse events.<sup>7</sup> After the procedure, patients have an immediately detectable decrease in right atrial pressure, increase in left atrial pressure, increase in cardiac output, and a drop in arterial oxygen saturation because of shunting of deoxygenated blood. These hemodynamic improvements have been documented at rest and it is likely that there are further gains with exercise. This may underlie that observation that atrial septostomy has been shown to improve 6-minute walk distance and New York Heart Association functional class with a decrease in B-type natriuretic peptide levels.<sup>8,9</sup>

Small contemporary studies have provided some insight into longer-term outcomes of adult patients with PAH that undergo atrial septostomy. In a single-center report of 16 adults with PAH treated with prostanoids, 30-day and 1-year survival rates were 75% and 64%, respectively. In these patients, mortality was associated with a failure to increase the cardiac output after the septostomy procedure.<sup>10</sup> It is also recognized that outcomes after atrial septostomy as a stand-alone intervention are not as good as when the procedure is performed in patients receiving PAH-specific medications. The median survival for patients treated with atrial septostomy alone patients was 53 months compared with 83 months ( $P<0.01$ ) for patients who underwent atrial septostomy while receiving PAH medications.<sup>8</sup>

To date, there are unanswered questions about the use of balloon dilation atrial septostomy in adult patients with PAH. These include determining the optimal timing of the procedure, the size of the shunt, and the long-term durability of the procedure when not used as a bridge to transplant as it is not uncommon for the shunt to close spontaneously after several months.<sup>5</sup> Although other technical approaches to the procedure have also been tested, such as the use of cutting balloons, modified butterfly stents, fenestrated Amplatzer devices, and cryoablation, none of these techniques has proven superior to balloon dilatation.<sup>11</sup>

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### Potts Shunt

The Potts shunt is an infratricuspid shunt that creates an anastomosis of the left pulmonary artery to the descending aorta to unload to the RV. The main advantage of this procedure over atrial septostomy is that the shunt does not lead to arterial oxygen desaturation in the upper part of the body, thus sparing the brain and coronary circulations. Although the majority of the experience with the Potts shunt in PAH has come from surgical procedures in children, recently the shunt has been created using a percutaneous approach in adults.

The surgical Potts shunt was first reported in 2004 when 2 boys with suprasystemic pulmonary hypertension, RV failure, and syncope underwent the surgery. It was successful and both boys had improved RV function and New York Heart Association functional class but developed lower extremity cyanosis and polycythemia as a result of the right-to-left shunting.<sup>12</sup> Similar findings were reported in a cohort of 19 children (mean age, 7.7 years) with drug-refractory PAH who received a surgical Potts shunt. In this group, there were 3 deaths and 3 other perioperative complications. The decrease in lower extremity oxygenation ( $93.5 \pm 4.1\%$  versus  $70.0 \pm 9.3\%$ ;  $P < 0.001$ ) was detectable during hospitalization. After a median follow-up of 2.1 years, all survivors had significant improvement in their 6-minute walk distance, decrease in the number of PAH-specific therapies and were able to catch up to normal growth curves.<sup>13</sup>

In a small subgroup of children, a transcatheter Potts shunt was performed if they were found to have a small or probe-patent ductus arteriosus. The ductus arteriosus was crossed with a wire from the pulmonary artery and stented using a bare metal stent to maintain patency. The stent was sized to be large enough to equalize the pulmonary artery systolic pressure with the systemic pressure. After the shunt was created, echocardiography confirmed a widely patent stent with unrestricted flow and improved RV function.<sup>13,14</sup>

In 2013, Esch et al<sup>15</sup> described the first experience with a transcatheter Potts shunt in adults with symptomatic drug-refractory PAH that had a significant risk of sudden death. Because these adults did not have a patent ductus arteriosus, the shunt was created by retrograde perforation of the descending aorta at the point where it is in close apposition to the left pulmonary artery. The newly formed tract between the pulmonary artery and the aorta was bridged with a covered stent (iCAST 7×22 mm) that served as the functional shunt. There was procedural success in 3 of the 4 patients who underwent the procedure with 1 death because of uncontrolled hemothorax. Another patient died 5 days after the procedure, although this death was attributed to the patient's comorbidities. The remaining 2 patients were alive at 4 and 10 months and both reported symptomatic and functional improvement.

With this limited experience, it is evident that the transcatheter Potts shunt in adults should still be considered an experimental therapy, albeit one with promise. Future efforts should be directed toward determining the optimal stent size for shunt creation, the long-term durability of the stent in this position, and identifying potential late complications. It is notable that there have been modifications to the surgical Potts shunt, such as the insertion of a polytetrafluoroethylene

patch that allows for intermittent unidirectional blood flow.<sup>13,16</sup> Thus, it is plausible that a partially valved covered stent may also work well in this setting.

### Pulmonary Artery Denervation

There has been recent interest in pulmonary artery denervation as a therapeutic intervention in PAH based on the finding that increases in pulmonary artery pressure occur with pulmonary nerve stimulation.<sup>17</sup> Early preclinical studies of pulmonary artery denervation demonstrated that when catheter ablation was performed <2 mm proximal to the main pulmonary artery bifurcation, there was a significant decrease in RV and pulmonary artery pressures. These studies, however, provided only short-term follow-up and no histological assessment demonstrating adequate nerve damage to explain the hemodynamic improvements.<sup>18,19</sup>

The pilot first-in-man PADN-1 (Pulmonary Artery DeNervation for treatment of PAH) study that enrolled 21 patients with PAH (13 treatment and 8 controls) deemed nonresponsive to medical therapies suggested that the procedure may have clinical benefits. Thirteen patients underwent pulmonary artery denervation at the bifurcation of the main pulmonary artery and the ostium of the right and left pulmonary arteries using a radiofrequency ablation catheter with a temperature sensor (temperature >50°C, energy=10 W, time=60 s). Procedural success, defined as a decrease in the pulmonary artery pressure of  $\geq 10$  mmHg without procedural complications, occurred in 12 of 13 patients. Compared with individuals that refused the procedure and served as controls, at the 3-month follow-up, pulmonary artery denervation-treated patients had a reduction in mean pulmonary artery pressures as well as improved RV function and 6-minute walk distance.<sup>20</sup> This initial report was met with skepticism owing to the nonrandomized nature of the study, the low-risk patient population studied, and the short-term follow-up.

In this issue of *Circulation: Cardiovascular Interventions*, 2 new studies of pulmonary artery denervation move the field forward. Chen et al<sup>21</sup> now expand their previous clinical study and report the hemodynamic and outcome data from 66 patients with pulmonary hypertension of different pathogeneses that were treated with pulmonary artery denervation. These patients underwent the same denervation protocol used in the pilot study. This study enrolled 39 patients with World Health Organization Group 1 PAH with the remaining 27 patients having pulmonary hypertension attributable to left heart disease or chronic thromboembolic disease. The absolute reduction in the mean pulmonary artery pressure from a baseline of  $53.1 \pm 19.1$  mmHg was 5 mmHg immediately after the denervation procedure and 6.6 mmHg at 24 hours. At 6-month follow-up, the mean pulmonary artery pressure was decreased further to  $44.8 \pm 16.4$  mmHg ( $P < 0.001$ ) and this effect persisted at 1-year. These hemodynamic improvements were associated with a decrease in pulmonary vascular resistance and an increase in cardiac output. During the course of the 1-year follow-up, there was an increase in PH-related events, indicating progression of disease in treated patients. Although findings from this study broaden the experience with pulmonary artery denervation in pulmonary hypertension,

firm conclusions are limited by the small and heterogeneous nature of the study population, the open-label nonrandomized study design, and the limited number of operators performing the procedure. The study does, however, provide the basis for a multicenter randomized placebo-controlled clinical trial that is necessary to determine if this therapy has efficacy in the treatment of PAH.

In the second study, Rothman et al<sup>22</sup> provide mechanistic insight into the pulmonary artery denervation procedure by demonstrating the anatomic distribution of nerves surrounding the pulmonary artery and the pattern of nerve injury in a porcine model of acute pulmonary hypertension. Here, they document the circumferential distribution of nerves with differences in their vascular location with respect to the vessel lumen. Histology performed acutely after pulmonary artery denervation showed that the ablation lesions were visible in the pulmonary artery with intimal disruption and decreased medial thickness. Vascular staining for nerve associated S100 protein was decreased indicating effective nerve injury. Thus, it is clear that when performed in a relevant large animal model, pulmonary artery denervation does result in nerve ablation and this corresponds to the acute decrease in pulmonary artery tone and pressures. Further long-term studies are warranted to examine the durability of the procedure and determine whether nerve regrowth occurs.<sup>17</sup>

### Conclusions

Although the aforementioned catheter-based procedures are performed infrequently or are still considered experimental, it is becoming evident that interventional cardiologists will play an increasingly prominent role in the procedural management of adults with PAH. As with any other complex disease, periprocedural decision making should be done by a multidisciplinary cardiopulmonary team and procedures performed at centers with expertise in the area. Catheter-based interventions in PAH also present an opportunity for adult and pediatric interventional cardiologists to collaborate as some procedures have been performed more frequently in children. Finally, the use of catheter-based interventions as therapeutic or palliative modalities in PAH is an area of high innovation and it is likely that future management of the disease will include some combination of pharmacological and interventional strategies to improve clinical outcomes.

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### Disclosures

None.

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