Interventional and Surgical Modalities of Treatment for Pulmonary Arterial Hypertension

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Beyond medical therapy, different interventional and surgical approaches exist for treatment of pulmonary arterial hypertension (PAH). Atrial septostomy has been applied in patients with lack of response to medical therapy in the absence of other surgical treatment options. With growing experience, procedure-related death rates have been reduced to 5.4%, and the most suitable patient group has been identified among patients with a mean right atrial pressure between 10 and 20 mm Hg. Pulmonary endarterectomy is the accepted form of treatment for patients with chronic thromboembolic pulmonary hypertension. Establishing the diagnosis and the classification of the type of lesions by pulmonary angiography is crucial for optimal patient selection. Perioperative mortality rates have been reduced to <10% in experienced centers, and the hemodynamic improvement is dramatic and sustained. Lung and heart-lung transplantation remains the procedure of choice for patients unsuitable for other treatment modalities. Timing of the procedure is difficult because waiting times vary between centers and usually are in a high range. Early referral of patients unresponsive to other treatment forms is therefore of importance to avoid transplantation of patients with established significant comorbidity. The survival rate during the first five years after transplantation for PAH is intermediate among the lung diseases, lower than chronic obstructive pulmonary disease but higher than idiopathic pulmonary fibrosis. (J Am Coll Cardiol 2004;43:73S–80S) © 2004 by the American College of Cardiology Foundation

Different interventional and surgical approaches for treatment of pulmonary arterial hypertension (PAH) have been developed in the last two decades. We review here the three major components: atrial septostomy, pulmonary endarterectomy, and lung transplantation.

ATRIAL SEPTOSTOMY

The use of atrial septostomy (AS) in PAH is supported by the fact that deterioration in symptoms and death in PAH are associated with right ventricular failure (RVF). An AS in this setting creates a right-to-left shunt that increases cardiac output and, despite the fall in systemic arterial oxygen saturation, augments systemic oxygen transport (SOT). In addition, the shunt decompresses the heart andameliorates RVF.

Blade balloon atrial septostomy (BBAS) as a palliative therapy for refractory PAH was first reported in 1983 (1,2). Graded balloon-dilation AS (BDAS), a variant of BBAS, is the technique most used in recent series (3,4), and it has produced results similar to those of BBAS in terms of symptomatic and hemodynamic benefits but with an apparent reduction in the procedure-related risks. Procedures should be performed only in centers experienced in both interventional cardiology and PAH (5,6).

The precise role of AS in the treatment of PAH remains uncertain because most of the knowledge regarding its use comes from small series or case reports. The potential beneficial effects and risks of AS were addressed in a review derived from an analysis of 64 cases from the published reports (5). This knowledge has now expanded with the report of another 56 cases in the last few years (3,7,8). Severe idiopathic PAH has been the main indication for AS. Other indications have included PAH associated with surgically corrected congenital heart disease, peripheral chronic thromboembolic pulmonary hypertension (CTEPH) (5), and, more recently, PAH associated with systemic sclerosis (8). Most patients who have undergone AS had not responded to conventional treatment (5), had failed long-term prostacyclin therapy (3,9), or were treated with the intention of bridging to lung transplantation (3,9).

In most reports the patients have been considered terminally ill. Accordingly, there is an inherent risk of complications and death during the procedure. In the prior worldwide experience (5), there was an overall procedure-related mortality of 16%, and by univariate analysis, a baseline mean right atrial pressure (mRAP) >20 mm Hg was the variable.
most significantly associated with peri-procedural death. However, ever since recommendations to minimize this risk have been established (5), procedure-related mortality appears to be decreasing. In 74 recently reported BDAS procedures (3,4,9), there were only 4 immediate procedure-related deaths (5.4%). The improvement in hemodynamic parameters at rest (i.e., an increase in cardiac index and SOT) is not the same for all patients and appears to depend on the level of mRAP. Patients with a baseline mRAP between 10 to 20 mm Hg seem to have a better risk/benefit ratio (5,6). Little information exists with regard to the long-term hemodynamic effects of AS, and in only one study (5) did it demonstrate an improvement in right ventricular function over time (7 to 27 months).

In most reports, symptoms and signs of RVF are improved immediately after AS (i.e., syncope and/or signs of systemic venous congestion either disappear or decrease in intensity) (5). Likewise, exercise endurance, as assessed by the 6-min walk test, was also improved in most of the patients after AS (4). Although not completely elucidated, mechanisms such as a decompression effect on the heart (i.e., reduction of afterload) and an increase in SOT seem to be responsible for the hemodynamic and beneficial clinical effects (6).

The impact of AS on long-term survival of patients with PAH has not been established in prospective and controlled studies. Most reported series, however, have suggested a beneficial effect. In one report (3), long-term clinical outcome was dependent on the immediate hemodynamic response to the procedure. In the worldwide experience (5), median survival was 19.5 months (range, 2 to 96 months), and late deaths primarily resulted from progression of the pulmonary vascular disease (5).

Presently, the use of AS in the management of PAH is justified because of the disparate availability of treatments throughout the world, especially the limited access to lung transplantation. Current indications for AS, therefore, include failure of medical therapy (including oral calcium channel blocker, prostacyclin, or bosentan) with persisting RVF and/or recurrent syncope, bridging to transplantation and the absence of other therapeutic options (10).

To address some of the unanswered questions prospectively (timing of procedure, combination with other therapies, and so forth) regarding the precise role of AS, an International Registry on the use of AS in PAH is underway.

**PULMONARY ENDARTERECTOMY**

Chronic thromboembolic pulmonary hypertension is an underdiagnosed consequence of unresolved acute pulmonary embolism with an incidence that is higher than generally appreciated (11). It is characterized by intraluminal thrombus organization and fibrous stenoses or complete obstructions of the pulmonary artery (PA) branches, causing a persistent elevation of PA pressure, pulmonary vascular resistance (PVR), and progressive right heart failure (11,12). The prognosis of patients with thromboembolic pulmonary hypertension is poor, and the survival rate is inversely proportional to the degree of PAH (13). As in patients with acute pulmonary embolism, the diagnosis is often missed or delayed because the main symptoms (e.g., dyspnea) are nonspecific. Additionally, there is a general lack of awareness of this disease and the chance of surgical cure.

**Diagnostic investigations.** When PAH is clinically suspected to be the cause of exertional dyspnea, right heart dysfunction can be detected by transthoracic echocardiography, whereas left heart conditions leading to PAH can be excluded. Pulmonary perfusion scanning allows differentiation between thromboembolic and primary pulmonary perfusion defects (12). High-resolution computed tomography using maximal intensity projections shows the distribution of typical obstructive PA lesions at the main, lobar, and segmental levels and a mosaic pattern of lung attenuation due to regional perfusion differences.

Pulmonary angiography remains the gold standard for the diagnosis and preoperative evaluation of patients with thromboembolic pulmonary hypertension. Biplane plate film or digital subtraction angiography shows the exact localization and the type of PA obstructions (11). Specific experience is required for the interpretation of angiograms of CTEPH patients: irregularities of the vascular wall, intraluminal filling defects, stenoses or occlusion of central, lobar, segmental, and peripheral arteries caused by thrombotic masses or fibrous webs and bands are characteristic angiographic features in CTEPH (Fig. 1).

Pulmonary fiberoptic angioscopy can be used to define operability in selected patients with unclear angiographic findings or disproportionately severe PAH with mild angiographic obstructions. With increasing experience, magnetic resonance imaging using high-field technology and

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**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AS</td>
<td>atrial septostomy</td>
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<tr>
<td>BBAS</td>
<td>blade balloon atrial septostomy</td>
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<td>BDAS</td>
<td>balloon dilation atrial septostomy</td>
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<td>CTEPH</td>
<td>chronic thromboembolic pulmonary hypertension</td>
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<td>mRAP</td>
<td>mean right atrial pressure</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>PA</td>
<td>pulmonary artery</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<td>PEA</td>
<td>pulmonary endarterectomy</td>
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<td>PH</td>
<td>primary pulmonary hypertension</td>
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<td>PTE</td>
<td>pulmonary thromboendarterectomy</td>
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<td>PVR</td>
<td>pulmonary vascular resistance</td>
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<tr>
<td>RVF</td>
<td>right ventricular failure</td>
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<td>SOT</td>
<td>systemic oxygen transport</td>
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fast imaging techniques is becoming a helpful noninvasive investigation in CTEPH patients because the lumen as well as the organized tissue in the wall of the PA branches can be precisely depicted in combination with an exact evaluation of right heart function.

**Patient selection.** Once the diagnosis of CTEPH is established, the decision for surgical therapy is made based on the degree of functional impairment, the severity of PAH, and the surgical accessibility of the thromboembolic lesions (14). A preoperative period of at least three months of adequate anticoagulation is mandatory. Patients considered for surgery are usually severely incapacitated with dyspnea at minor levels of exertion or at rest (NYHA functional class III or class IV). Although the mean preoperative PVR in CTEPH patients is 800 to 1,000 dynes·s·cm⁻⁵, young patients with exertional dyspnea, almost normal PVR at rest, and a significant increase at exertion may also be accepted for surgery, as earlier operation could have the potential to prevent a secondary vasculopathy in the unobstructed pulmonary vascular bed.

The surgical accessibility of the thromboembolic lesions is heavily dependent on the experience of the surgical team. With growing experience, endarterectomy of subsegmental PA branches is possible. The operative risk is increased if a major discrepancy exists between the degree of PAH and the extent of angiographic PA obstructions based on significant microvascular disease.

**Principles of operation.** Although the operation historically has been described as pulmonary thromboendarterectomy (PTE), it is better termed PEA (11). Fewer than 3,000 PEA operations have been performed worldwide, although it is a potentially curative treatment option for very sick patients with CTEPH. The surgical techniques and evolving modifications have been well described by the San Diego group (14,15). With rare exceptions, thromboembolic pulmonary hypertension is a bilateral disease, and therefore PEA is a bilateral procedure. The operation is not an embolectomy but a true endarterectomy removing the organized and incorporated fibrous obstructive tissue from the PAs. Because visibility in the distal PA branches is essential and bronchial artery collateral flow is significant in CTEPH, extracorporeal circulation and periods of circulatory arrest under deep hypothermia are essential for successful endarterectomy.

Following a proximal intrapericardial PA incision, the correct endarterectomy plane is established and circumferentially followed down to the lobar segmental and sometimes subsegmental branches of each lobe using special suction dissectors. The endarterectomy procedure on one side is usually possible within one 20-min period of circulatory arrest followed by a period of reperfusion and another period of circulatory arrest for the endarterectomy on the contralateral side. After closure of the PA incision, additional cardiac procedures can be performed during the rewarming period, if necessary. As tricuspid valve competence usually returns after successful PEA, tricuspid valve repair is not necessary.

Jamieson et al. (16) have proposed an intraoperative classification of CTEPH: type I (central thrombus present) and type II (thickened intima, fibrous webs and bands) represent the typical condition of surgical patients. Type III occlusions in the segmental and subsegmental branches require adequate surgical experience with dissection within the peripheral pulmonary arteries. Type IV disease represents secondary in situ thrombosis in patients with primary pulmonary hypertension (PPH) and cannot be treated by PEA, whereas lung transplantation is an option for these patients.

**Postoperative management.** In contrast to the majority of cardiac surgical procedures, the postoperative course is determined primarily by the physiological changes of right heart function and pulmonary perfusion, pulmonary hemodynamics, and gas exchange (17). The postoperative management of patients undergoing PEA can be challenging; in addition, the usual complications associated with cardiac surgery are encountered. The most important complications are persistent PAH due to inadequate endarterectomy or significant secondary vasculopathy and reperfusion edema in the endarterectomized parts of the lung (18). Postoperative care centers around maintaining sufficient right ventricular function and organ perfusion, adequate oxygenation and renal function, and in
preventing early pulmonary artery reocclusion. Extensive circulatory monitoring, including continuous online measurement of cardiac output, mixed venous oxygen saturation, and arterial blood gases, has proved to be helpful.

Following nonaggressive pressure-controlled mechanical ventilation, early extubation on the first or second postoperative day is advocated even in cases with modest reperfusion edema and hypoxia. In rare cases with severe reperfusion edema, oxygenation can be improved by prone positioning, continuous nitric oxide inhalation, or extracorporeal membrane oxygenation. By means of cautious fluid and albumin infusion, the doses of vasoactive drugs administered via left atrial catheter can be limited to a low dose level. Reocclusion prophylaxis is started within 4 to 8 h following surgery using intravenous heparin infusion followed by continuous anticoagulation with warfarin between days 8 and 14.

**Outcome.** Recently, Fedullo et al. (18) have reviewed the world literature on thromboembolic pulmonary hypertension and endarterectomy and found mortality rates between

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**Figure 2.** Postoperative and long-term follow-up hemodynamic changes after pulmonary endarterectomy (data from Johannes Gutenberg University, Mainz, Germany, n = 50). CI = cardiac index; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.
5% and 24%. As there is a distinct learning curve for the preoperative evaluation, the operation, and the postoperative care, mortality rates are lower in centers with a large volume of procedures.

Although there has not been a controlled study, and such an investigation probably will never be performed, the outcomes of PTE with regard to functional status, quality of life, hemodynamics, right ventricular function, and gas exchange are very favorable. Most patients are in NYHA functional class III or IV before the operation and return to class I or II with a good exercise capacity after surgery (19,20).

In several studies, significant and persistent decreases of PA pressures and PVR after PTE surgery are reported (19) (Fig. 2). Cardiac output is increased and oxygenation can be normalized. Right heart function assessed by echocardiography or MRI is significantly and persistently improved postoperatively (Fig. 3). Tricuspid valve regurgitation is also significantly improved within a few days after surgery; in most patients, tricuspid competence returns to normal. Long-term survival after endarterectomy with a five-year survival rate of 75% to 80% is very favorable compared to medical treatment or lung transplantation. Therefore, lung transplantation is inappropriate for most patients with this condition.

**LUNG AND HEART-LUNG TRANSPLANTATION**

With the advent of effective drug treatments in the last decade, lung transplantation has become the final option in the management of PAH; at the same time, selection of recipients and timing of the procedure have become more complex.

Whereas prostaglandins and endothelin receptor antagonists can alter the clinical features and course of PPH in many patients, their impact on the underlying pathobiology is uncertain, and they are not curative remedies. The majority of patients already have moderate to severe PAH when the diagnosis is made, and all patients do not respond to treatment. Less than 10% of patients with idiopathic PAH have a significant response to a calcium channel antagonist. Moreover, in two recent series approximately 25% of patients with PPH failed to improve with epoprostenol treatment, and those who remained in NYHA functional class III and IV with epoprostenol treatment had a poor prognosis, with three-year survival rates in the range of 30% to 60% (21,22).

Finally, even among responders, the escalating dose of epoprostenol that is often needed to sustain its beneficial effects may eventually cause intolerable side effects. Thus, ultimately transplantation will be the only alternative for many patients with idiopathic PAH and other forms of PAH.

**Pretransplantation assessment.** The purpose of the pretransplantation assessment is to identify patients whose prognosis will be improved by transplantation and whose cardiopulmonary status or other medical problems will not unduly jeopardize the success of transplantation—that is, to choose the right patient and the right time for transplantation. The major specific goals of the evaluation for transplantation are to confirm the diagnosis, to assess the severity of the disease, and to optimize medical management. The potential role of transplantation (prognosis of the disease vs. that of transplantation) has to be established, and suitable candidates for transplantation have to be selected together with the ideal transplant procedure. The clinical status must be reexamined periodically, and medical management and transplantation strategy adjusted accordingly.

Pathways, which are based on vasoreactivity and on functional impairment, have been standardized to optimize the management paradigm, and transplantation should be reserved until it will confer a survival advantage. However, a long waiting period for transplantation should be expected, and this delay has to be incorporated into the plan. Thus, the pretransplantation evaluation and waiting list registration must anticipate the need for transplantation later, or the opportunity for transplantation may be missed.

Consensus guidelines for selecting patients for transplantation have been promulgated by the major societies (23), and most transplant centers use similar criteria. In addition to a comprehensive assessment of the patient’s cardiopulmonary status, any other medical problems should be fully
characterized to ascertain their potential influence on the outcome of transplantation, and all health maintenance testing that is recommended for the patient’s age and gender should be completed.

**Choice of transplant operation.** Choosing the transplant operation is another facet of the preoperative evaluation. Both heart-lung and lung transplantations have been performed for pulmonary vascular disease, but heart-lung transplantation should be reserved for patients who are not candidates for lung transplantation alone. In general, most forms of PAH except complex congenital heart disease do not require heart-lung transplantation unless there is a significant cardiac problem other than cor pulmonale.

The threshold of unrecoverable right ventricular dysfunction is unknown, if such a boundary even exists. Severe right ventricular dysfunction has been reversible after isolated lung transplantation. However, although afterload is immediately reduced by lung transplantation, right ventricular function does not revert to normal right away, and hemodynamic instability is a common problem in the early postoperative period.

Both single and bilateral lung transplantations have been performed for PPH and some other types of PAH (24–28), and these operations have been combined with repair of cardiovascular anomalies for Eisenmenger syndrome (25,29). Single-lung transplantation creates a tenuous ventilation-perfusion imbalance, and any complication in the allograft is associated with severe hypoxemia. Nevertheless, recipient survival rates have been similar after single and bilateral transplantation for PAH, and if technically feasible, either of these operations is an acceptable choice for most cases of PAH. However, in patients with Eisenmenger syndrome, the option of heart-lung transplantation should be carefully considered. For some defects, especially ventricular septal defect, the survival advantage of heart-lung transplantation was most prominent (29), and the option of heart-lung transplantation should be strongly considered for this subgroup.

**Timing.** The pretransplantation assessment does not end after the initial evaluation and waiting list registration. The waiting time for transplantation depends on the organ allocation system, and allocation systems vary significantly in countries around the world. Regardless of the allocation system, however, there is usually a long duration before transplantation, and during the waiting period both medical management and transplantation strategy must be modified in response to changes in clinical circumstances. Patients with PPH who are treated with epoprostenol should have a follow-up right heart catheterization. Those who have not responded to epoprostenol at their initial reassessment have a guarded prognosis (21,22) and they should proceed toward transplantation unless a contraindication intervenes.

Prognostic indexes that can be derived from repeatable, noninvasive tests are needed to supplement clinical judgment about the timing of transplantation after the patient is on the waiting list. As medical therapy has improved, it has been extended to its limit in many patients before transplantation. However, if refractory right heart failure develops on maximal drug treatment, little can be done to restore cardiopulmonary status, and secondary effects on other organs, especially the liver and kidney, become problematic. In this scenario potential recipients can be transformed into high-risk or unacceptable candidates for transplantation, and the opportunity for transplantation can be lost.

Serial noninvasive tests may be helpful in the decision about timing. The results of the 6-min walk testing and cardiopulmonary exercise testing have had prognostic implications in a few studies (30,31) and the predictive value of these tests deserves further study. Six-minute-walk distance correlated well with peak oxygen uptake in one study of PPH patients, and a 6-min walk distance <332 m portended a poor prognosis with a one-year mortality rate of approximately 40% (30). In a study of cardiopulmonary exercise testing in patients with PPH, both peak oxygen uptake and peak systolic blood pressure were prognostically important. A peak oxygen uptake ≤10.4 ml/kg/min and a peak systolic blood pressure ≤120 mm Hg were associated with one-year mortality rates of approximately 50% and 70%, respectively, and among patients with both of these risk factors, only 23% survived for one year (31). Thus, transplantation would offer a survival benefit to patients with any of these risk factors, and this threshold might be useful in foreseeing the favorable time for transplantation.

**Survival.** The outcome of lung transplantation can be gauged by several end points: survival, physiologic function, quality of life, and cost-effectiveness. Actuarial survival is...
well known from the U.S. Scientific Registry (32), the International Society for Heart and Lung Transplantation (ISHLT) registry (33), and reports from individual centers (26,27,34,35). Survival rates from the ISHLT registry are presented for PPH, Eisenmenger syndrome, and other forms of congenital heart disease in Table 1.

Recipients with PPH and Eisenmenger syndrome have had the highest perioperative mortality and the lowest three-month survival rates among the major diagnostic categories of lung transplant recipients in both the U.S. Scientific and the ISHLT registries (32,33). This difference is explained by the complexity of the surgery in severe pulmonary hypertension. Cardiopulmonary bypass is required routinely for the operation in cases of PPH or Eisenmenger syndrome, whereas it is rarely needed for other diagnoses. This increases the risk of hemorrhagic complications and contributes to early graft dysfunction. Furthermore, right ventricular function does not recover immediately, and hemodynamic instability is common in the first few days following transplantation.

In the ISHLT registry, both PPH and Eisenmenger syndrome/congenital heart disease have been associated with a significantly higher risk of death in the first year after lung transplantation than with other diagnoses (33). This increased mortality has been concentrated in the perioperative period; thereafter, the attrition rate for recipients with PPH and Eisenmenger syndrome has paralleled the rates for recipients with other diagnoses because the subsequent complications are not strongly influenced by the pretransplantation diagnosis.

The best transplantation operation of PPH has been debated. No clearly significant difference in survival has been apparent among the procedures (single lung transplantation, bilateral lung transplantation, and heart–lung transplantation) in the ISHLT registry and in some case series (27,33), but some centers have reported a different experience (35–37). In general, lung transplantation for PPH should be performed in specialized centers only, those familiar with the unique problems of this particular procedure and the complexity of the patients.

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