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Interventional and Surgical Modalities of Treatment in Pulmonary Hypertension

Anne M. Keogh, MBBS, PHD,* Eckhard Mayer, MD,† Raymond L. Benza, MD,‡ Paul Corris, MD,§ Philippe G. Dartevelle, MD,‖ Adaani E. Frost, MD,¶ Nick H. Kim, MD,# Irene M. Lang, MD,** Joanna Pepke-Zaba, PHD,†† Julio Sandoval, MD‡‡

Sydney, Australia; Mainz, Germany; Pittsburgh, Pennsylvania; Newcastle upon Tyne and Cambridge, United Kingdom; Le Plessis Robinson, France; Houston, Texas; La Jolla, California; Vienna, Austria; and Mexico City, Mexico

Most patients with chronic thromboembolic pulmonary hypertension are operable, and pulmonary endarterectomy is the treatment of choice. Pulmonary endarterectomy should not be delayed for medical therapy, and risk stratification helps to define patients likely to achieve the best outcome. Inoperable patients should be referred for trials of medical agents. Atrial septostomy is promising but underutilized, although better ways of ensuring an adequate, lasting septostomy still need to be determined. Indications for the procedure are unchanged, and it should be considered more frequently. Bilateral sequential lung or heart–lung transplantation is an important option for selected patients, and potential candidates who are class IV or III but not improving should be referred early to a transplantation center. Currently, there is a need for right ventricular assist devices with flow characteristics suited to the circulation of patients with pulmonary arterial hypertension. Right ventricular synchronization therapy has not yet been tested. Novel shunts (e.g., Potts anastomosis) also hold promise. All surgery for pulmonary hypertension should be performed in centers with experience in these techniques. (J Am Coll Cardiol 2009;54:S67–77) © 2009 by the American College of Cardiology Foundation

Chronic thromboembolic pulmonary hypertension (CTEPH) can be defined as pulmonary arterial hypertension (PAH) (mean pulmonary arterial pressure [mPAP] >25 mm Hg) with persistent pulmonary perfusion defects. CTEPH is an underdiagnosed cause of PAH and carries a poor prognosis if untreated (1–3). Acute or recurrent pulmonary emboli may be the initiating event. These are followed by intraluminal thrombus organization, fibrous obstruction of affected proximal arteries, and vascular remodeling in patent distal pulmonary arteries (4,5). CTEPH, therefore, is a disease with a mechanical component potentially amenable to surgery, and a variable degree of small vessel arteriopathy. Pulmonary endarterectomy (PEA) is a potential cure, and the treatment of choice for CTEPH (6,7); therefore, differentiation between CTEPH and PAH is paramount.

From the *St. Vincent's Hospital, Sydney, Australia; †Catholic Academic Hospital, Mainz, Germany; ‡Drexel University College of Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania; §Freeman Hospital, Newcastle upon Tyne, United Kingdom; ‖Marie Lannelongue Hospital, Le Plessis Robinson, France; ¶Baylor College of Medicine, Houston, Texas; #University of California, San Diego, School of Medicine, La Jolla, California; **Medical University of Vienna, Vienna, Austria; ††Papworth Hospital, Papworth Everard, Cambridge, United Kingdom; and the ‡‡National Institute of Cardiology, Mexico City, Mexico. Please see the end of this article for each author's conflict of interest information.

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Diagnosis and Assessment of Operability

Since the 3rd World Symposium on Pulmonary Hypertension held in Venice in 2003 (8), the diagnostic algorithm for CTEPH has not significantly changed. The main diagnostic clue is the presence of 1 or more persistent perfusion defects on ventilation–perfusion scanning. Hemodynamic measurements aid in predicting prognosis and perioperative risk assessment. Multiplanar pulmonary angiography is the gold standard for the confirmation of chronic thromboembolic disease and is recommended for the assessment of operability (6). Multislice computed tomographic scanning (Fig. 1) and magnetic resonance imaging have become valuable complementary investigations (3,9,10). Maximum information regarding pulmonary arterial morphology is required to assess surgical risk and long-term outcome; this information can best be obtained with pulmonary angiography. Patients should be referred for evaluation by a multidisciplinary team experienced in PEA.

There is inadequate evidence that PAH-specific medical therapy is an alternative to surgery (11), and the operation should not be delayed in favor of medical therapy. The best outcomes after surgery are associated with surgeon and center experience; concordance between pre-operative pulmonary vascular resistance (PVR) and anatomic disease; pre-operative PVR <1,000 to 1,200 dynes/s/cm^{-5}; absence of select comor-

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Abbreviations and Acronyms

AS = atrial septostomy
BLTx = bilateral lung transplantation
CI = cardiac index
CO = cardiac output
CTEPH = chronic thromboembolic pulmonary hypertension
DHCA = deep hypothermic circulatory arrest
ECLS = extracorporeal life support
ECMO = extracorporeal membrane oxygenation
HLTx = heart–lung transplantation
IPAH = idiopathic pulmonary arterial hypertension
IVC = inferior vena cava
LV = left ventricle/ventricular
mPAP = mean pulmonary arterial pressure
mRAP = mean right atrial pressure
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PEA = pulmonary endarterectomy
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
RAP = right atrial pressure
RV = right ventricular
6MWD = six-min walk distance
SOT = systemic arterial oxygen saturation

bidities, such as splenectomy or ventriculoatrial shunt; and significant post-operative decrease in PVR (7,12–14).

Surgery does not benefit all CTEPH patients (3). In high-risk patients with a likelihood of having significant distal small vessel disease pre-operatively and limited proximal angiographic pulmonary artery obstruction, a trial of PAH-specific medical therapy may be a reasonable option (3,11). However, the role of medical therapy in CTEPH remains to be further tested and defined.

Currently there is no pre-operative classification system that might allow for better risk stratification (15). In conjunction with PVR, exploratory variables such as pre-operative diffusion capacity, upstream resistance, select biomarkers, and precise assessment of right ventricular (RV) dysfunction may have a role in a future classification system (16–21).

The San Diego surgical classification (22) is based on operative findings of pulmonary artery obstruction, and therefore is not suitable for pre-operative risk stratification. Currently, the recommendation for surgery is based on a careful analysis by an experienced multidisciplinary team.

PEA

The PEA procedure with deep hypothermic circulatory arrest (DHCA) to ensure a bloodless field while providing cerebral protection has been described elsewhere (7,13). Optimal intraoperative visibility of pulmonary artery branches is the prerequisite for complete endarterectomy and maximal RV afterload reduction. The best operative outcome is dependent on a complete endarterectomy and significant early reduction of PVR to <500 dynes/s/cm^{-5} (13). Different techniques for minimizing risk of circulatory arrest have been published (23,24); however, the mortality rates seem worse compared with larger series that included DHCA. Specialists at the University of California, San Diego, reported a 4.4% mortality and 0% neurological morbidity in 500 consecutive PEA operations using DHCA (13). At present, there is no compelling rationale for changing the PEA techniques used by major centers around the world.

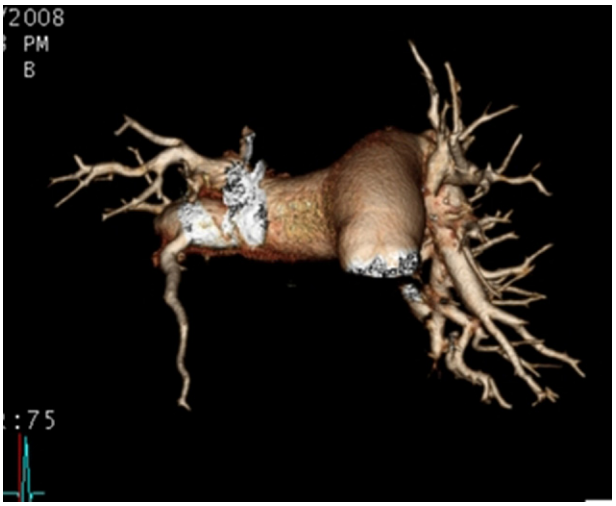

Figure 1 **CT Scan of a Patient With Chronic Thromboembolic Pulmonary Hypertension**

Computed tomographic (CT) scan depicting occlusions of right lobar and segmental pulmonary artery branches without proximal disease of the left pulmonary artery (64-slice CT, 3-dimensional reconstruction of volumetric data set with retrospective electrocardiographic gating). Courtesy of Christopher Ahlers, MD, Department of Radiology, Johannes Gutenberg University Hospital, Mainz, Germany.

Post-operative management. Right heart dysfunction caused by residual pulmonary hypertension (PH) and pulmonary vasoconstriction after extracorporeal circulation, and reperfusion edema in endarterectomized segments of the lung can pose significant challenges after PEA (7,25). However, optimal post-operative care has not been defined, and treatment protocols vary among expert centers.

In most patients, RV afterload reduction by removal of obstructive material from the pulmonary vasculature will result in an immediate and significant decrease of pulmonary artery pressures, increase in cardiac index (CI), improved gas exchange, and diuresis. Medical treatment includes cautious fluid administration, maintaining low right atrial pressure (RAP), and administration of vasoconstrictive drugs, if systemic hypotension caused by vasodilatation is present. Reduction of the CI to pre-operative levels may be necessary to minimize flooding of the lungs (reperfusion edema). Although the achievement of adequate gas exchange is a basic tenet of post-operative care after PEA, and pulmonary reperfusion response can be a serious problem, there is no consensus with respect to ventilatory protocols, even in specialized centers. It is uncertain whether mechanical ventilation with high tidal volumes and a limited degree of positive end-expiratory pressure, or nonaggressive pressure-controlled ventilation with high positive end-expiratory pressure, provides better results with regard to gas exchange and hemodynamic effects. Nevertheless, early

extubation 1 or 2 days post-surgery is possible with both protocols in a majority of patients (26).

In a small number of patients, post-operative right heart failure develops because of severe persistent PH caused by incomplete endarterectomy or small vessel disease combined with the effects of extracorporeal circulation, hypothermia, and ischemia (26). Attempts should be made to optimize right heart function with inotropic agents and reduce RV afterload. The role of treatment with specific pulmonary vasodilators in this challenging situation is unclear, although there is limited information that inhaled iloprost might be useful (11,27).

Early reocclusion prophylaxis using intravenous or subcutaneous heparin and subsequent lifelong anticoagulation is mandatory for all post-PEA patients. The routine pre-operative insertion of an inferior vena cava (IVC) filter to reduce the risk of peri-operative or recurrent pulmonary embolism remains a matter of debate. A randomized trial to compare optimal surveillance anticoagulation with or without IVC filter is warranted.

Outcome. The concept of PEA has been transferred from the University of California, San Diego, to an increasing number of centers internationally. A recent report from San Diego included a cohort of 1,100 patients with post-PEA mortality rates of 4.7% (28). With increasing experience, PEA centers should strive for post-operative mortality rates <10%. Since results depend on experience with the procedure, the number of centers per region may have to be limited.

Although the outcome of PEA in patients with CTEPH has not been evaluated in randomized controlled studies, long-term results with respect to survival, functional status, exercise capacity, quality of life, RV function, hemodynamics, and gas exchange are favorable for most patients (7,13,29–31). Maximum benefits of surgery may take 6 months or more. To exclude recurrent disease or residual symptomatic PH, patients should be systematically followed up with hemodynamic re-evaluation 6 to 12 months after surgery. In cases of residual or recurrent PH, specific pulmonary vasodilatory treatment might be beneficial (11,27,32), although further randomized controlled studies are needed.

Consensus

- CTEPH is defined as symptomatic PAH (mPAP >25 mm Hg) with persistent perfusion defects.
- CTEPH has a mechanical component judged amenable to surgery as well as variable small vessel disease.
- Pulmonary endarterectomy is the treatment of choice for CTEPH.
- Once CTEPH is diagnosed, patients should be referred for surgical evaluation by an experienced multidisciplinary team.
- In candidates found to be operable:
  - pulmonary endarterectomy is efficacious and carries a clear survival benefit;
  - there is inadequate evidence that medical therapy (PAH-specific therapy) is an alternative to surgery;
  - surgery should not be delayed in favor of medical therapy;
  - current best practice results in operative mortality rates of 4% to 7%.
- Pre-operative risk stratification requires better definition.
- The best outcomes at present are associated with:
  - surgeon and center experience;
  - concordance between PVR and anatomic disease;
  - pre-operative PVR <1,000 to 1,200 dynes/s/cm^{-5};
  - absence of select comorbidities (e.g., splenectomy, ventriculoatrial shunts);
  - post-operative PVR <500 dynes/cm/s^{-5}.
- Benefits of surgery may not be immediate: full benefits may take ≥6 months.
- Patients should be systematically followed up with hemodynamic re-evaluation at 6 to 12 months after surgery because response may be partial or disease may recur.
- It is unknown whether the current PAH-specific medications are effective in post-operative persistent PH; studies are required.
- In CTEPH patients judged to be inoperable, a randomized, placebo-controlled, double-blind trial with bosentan showed modest improvement in hemodynamics but no change in 6-min walk distance at short follow-up (33).
- No consensus could be reached regarding the role of IVC filters in CTEPH candidates.

Recommendations

- Pre-operative risk stratification requires further development. Variables other than PVR (pre-operative diffusion capacity, pulmonary artery occlusion technique, emerging biomarkers, precise assessment of RV dysfunction) may have a role.
- The collaboration of major centers with experience in PEA is recommended to pool data prospectively for comprehensive analysis of risk factors and best-practice guidelines.
- A pre-operative classification system should be developed for future use.
- A randomized trial of optimal surveillance anticoagulation with or without an IVC filter is warranted.
- The role of medical therapy in patients deemed to be inoperable needs to be further tested and defined.

Atrial Septostomy (AS) in Severe PAH

Rationale. In advanced idiopathic pulmonary arterial hypertension (IPAH), either normal RV function or compensated hypertrophy is critical for survival (34). Patients with Eisenmenger syndrome have better survival rates than patients with IPAH (35,36) and the concept that AS successfully decompresses the failing RV and left ventricle (LV) is well accepted. Atrial septostomy represents a strat-

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egy for the treatment of RV failure where medical therapy is failing and there is limited access to lung donors. It allows right-to-left shunting, as permitted by the presence of tricuspid regurgitation, and increased systemic output, which allows increased systemic oxygen transport, in spite of a decrease in systemic arterial oxygen saturation (SOT) (37,38).

Global experience. Based on the worldwide literature, we presented an updated analysis at the Dana Point meeting comprising 223 cases, including children, with a mean age of 28 ± 17 years. Seventy percent of patients were female, 82% had IPAH, and mean New York Heart Association (NYHA) functional class was 3.6 ± 0.4 (J. Sandoval, unpublished written communication, February 2008). Other etiologies were PAH associated with surgically corrected congenital heart disease (8%), collagen vascular disease (5%), distal CTEPH not amenable to surgery (3%), and miscellaneous (3%). Congestive heart failure (43%), syncope (38%), or both (19%) were the principal indications for the procedure, with bridge to transplantation in 14% of cases. Of patients who underwent AS, 96 were nonresponsive to maximal medical treatment, including intravenous prostacyclin infusion (n = 57), bosentan (n = 18), sildenafil (n = 8), beraprost (n = 6), subcutaneous treprostinil (n = 4), inhaled iloprost (n = 3), or combination therapy (n = 10). The simultaneous use of pharmacologic therapy and AS in these reports, as well as the evidence for the safe administration of intravenous epoprostenol, subcutaneous treprostinil, or bosentan in the setting of PAH associated with Eisenmenger syndrome (39–41), support the safety of a combination of medical and surgical treatment.

Procedures. Two techniques have been used. Stepwise balloon dilatation is the procedure of choice. In stepwise balloon-dilation AS, the interatrial orifice is created by puncture with a Brockenbrough needle, then dilated using progressively larger balloon catheters. A 10% decrease in arterial oxygen saturation (SaO_2%) and an increase in LV end-diastolic pressure to 18 mm Hg preclude further dilatation (42). No prospective hemodynamic evaluation has been performed. There are no guidelines for the optimal size of the defect. Anecdotally, a defect size of 8.5 ± 2 mm is said to increase cardiac output (CO) by 20% to 25%. The defect may close and require a repeat procedure.

The choice between balloon-dilation AS or blade balloon AS depends on center expertise and should include both interventional cardiology and PH expertise. Alternative techniques with a custom-made fenestrated Amplatzer (AGA Medical, Golden Valley, Minnesota) device or a butterfly stent at the end of the procedure to keep the AS patent have met with modest success (43,44).

Immediate outcome after AS. In most reports, AS was performed in severe PAH with RV failure with an overall procedure-related mortality of 16% (45). Recommendations to minimize risk have been established (Table 1). In our analysis of 223 cases, mortality was 7.1% at 24 h and 14.8% at 1 month. Factors significantly associated with procedure-related mortality at 1 month are shown in Table 2. The most common cause of death within 24 h was refractory hypoxemia. Less common were progressive right heart failure, procedural complications, multiple organ failure, hemoptysis, and withdrawal of dialysis. From a total of 186 reported surviving patients with early follow-up, syncope and right heart failure improved in 88%, and 12% were unimproved. In all, 16.6% were transplanted. The 6-min walk distance (6MWD) improved 30% to 100% (46–48).

Immediate hemodynamic response. In our updated analysis of 223 cases, hemodynamic results before and after AS were reported in 117 patients. There was a significant decrease in mRAP (14.6 ± 8 mm Hg to 11.6 ± 6.3 mm Hg; $p < 0.0001$), SaO_2% (93.3 ± 4.1% to 83 ± 8.5%), and NYHA functional class (3.49 ± 0.6 to 2.1 ± 0.7), accom-

Table 1 Recommendations for Minimizing Procedure-Related Mortality of Atrial Septostomy

1. Only perform in a center experienced in pulmonary hypertension.
2. Contraindications to AS (unchanged from 2003) are severe right ventricular failure on cardiorespiratory support, mRAP >20 mm Hg, PVRI >55 U/m^2, resting O_2 saturation <90% on room air, and LVEDP >18 mm Hg.
3. Pre-procedure, optimize cardiac function with adequate right heart filling pressure and additional inotropic support if needed.
4. During procedure:
   a. Supplemental oxygen
   b. Appropriate sedation to prevent anxiety
   c. Monitoring variables (LAP, SaO_2%, and mRAP)
   d. Tailor the defect to <10% decrease in O_2 saturation.
5. Post-procedure, optimize oxygen delivery with transfusion of packed red blood cells or darbepoetin before and after.

AS = atrial septostomy; LAP = left atrial pressure; LVEDP = left ventricular end diastolic pressure; mRAP = mean right atrial pressure; PVRI = pulmonary vascular resistance index; SaO_2% = arterial oxygen saturation.

Table 2 Variables Associated With 1-Month Mortality, Univariate Analysis

Variable	Hazard Ratio (95% Confidence Interval)	p Value
RAP >20 mm Hg	30.5 (3.8–244)	0.001*
NYHA functional class	8.53 (0.89–81.2)	0.062*
RHF	5.97 (0.75–47.2)	0.089
Mean RAP, mm Hg	1.19 (1.1–1.29)	0.0001*
Septostomy type, blade	1.19 (0.30–4.6)	0.800
Age >18 yrs	1.12 (0.29–4.34)	0.865
Mean LAP, mm Hg	1.11 (0.86–1.43)	0.420
Baseline PVRI, U/m^2	1.04 (0.98–1.09)	0.148
Mean PAP, mm Hg	1.01 (0.98–1.05)	0.321
Age, yrs	0.99 (0.96–1.03)	0.966
Baseline SaO_2%	0.97 (0.83–1.14)	0.773
Mean SAP, mm Hg	0.96 (0.92–1.01)	0.148
SaO_2% after procedure	0.90 (0.84–0.96)	0.001*
Gender, female	0.73 (0.18–2.8)	0.635
Baseline CI, l/min/m^2	0.38 (0.09–1.6)	0.189
Syncope	0.14 (0.03–0.66)	0.013*

*p values are statistically significant.

CI = cardiac index; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; RAP = right atrial pressure; RHF = right heart failure; SAP = systemic arterial pressure; other abbreviations as in Table 1.

Table 3 Hemodynamic Effects of Atrial Septostomy Related to Baseline Resting Mean Right Atrial Pressure

	mRAP <10 mm Hg (n = 42)			mRAP 11–20 mm Hg (n = 49)			mRAP >20 mm Hg (n = 26)		
Variable	Before	After	p Value	Before	After	p Value	Before	After	p Value
mRAP, mm Hg	6.6 ± 2.4	5.9 ± 3.2	0.214	14.8 ± 2.8	11.9 ± 3.5	0.0001	26.6 ± 4.4	19.9 ± 3.8	0.0001
mPAP, mm Hg	62 ± 16	64 ± 19	0.329	66.4 ± 17	66.4 ± 16	1.000	63.4 ± 20	67.5 ± 20	0.102
mLAP, mm Hg	5.0 ± 2.7	6.8 ± 2.4	0.005	5.3 ± 3.6	7.8 ± 4.5	0.0001	7.9 ± 3.0	10.9 ± 4.0	0.029
SaO_2%	93.8 ± 4	85.8 ± 7	0.0001	93.0 ± 4.0	82.8 ± 7.2	0.0001	93.1 ± 4.3	78.6 ± 10.3	0.0001
CI, l/min/m^2	2.36 ± 0.6	2.89 ± 0.7	0.0001	2.04 ± 0.7	2.65 ± 1.0	0.0001	1.55 ± 0.5	2.14 ± 0.6	0.0001
mSAP, mm Hg	83 ± 15	83 ± 13	0.931	84.5 ± 14	88.8 ± 15	0.065	78 ± 20	81 ± 18	0.254
NYHA functional class	3.25 ± 0.6	2.00 ± 0.7	0.0001	3.63 ± 0.5	2.21 ± 0.8	0.0001	3.71 ± 0.5	2.00 ± 0.0	0.0001

mLAP = mean left atrial pressure; mPAP = mean pulmonary arterial pressure; mSAP = mean systemic arterial pressure; other abbreviations as in Tables 1 and 2.

panied by an increase in mean left atrial pressure (5.7 ± 3.3 mm Hg to 8.1 ± 4.0 mm Hg; $p < 0.0001$) and CI (2.04 ± 0.69 l/min/m^2 to 2.62 ± 0.84 l/min/m^2).

Hemodynamic improvement is contingent on baseline mRAP (42,45,49) (Table 3). In patients with an mRAP <10 mm Hg, the decrease in mRAP was not significant (−10.6% from an already-low baseline reading), yet there was a 22.5% increase in CI. In patients with an mRAP >20 mm Hg (in whom procedural mortality is highest), mRAP and SaO_2% decreased 25% and 15%, respectively, and CI increased 38% from baseline. Patients with a baseline mRAP between 11 and 20 mm Hg had an intermediate response but a better risk/benefit ratio (47). These measurements represent only the resting state and are likely to be different with exercise, explaining the increase in 6MWD (46–48). Post-AS hemodynamics during exercise have not been established.

An increase in PVR, low mixed venous PO_2, and refractory hypoxemia after AS have been successfully managed with inhaled iloprost (50). The increase in CO with no change in PAP or PVR suggests that the mechanism may be RV decompression and improved LV filling. Clinical improvement occurs despite resting desaturation and further desaturation with exercise.

Mechanisms for hemodynamic and clinical benefit include decompression of the RV at rest, prevention of further RV dilation and dysfunction during exercise, and an increase in CO and SOT, both at rest and during exercise (via right-to-left shunt). The increase in SOT and delivery also produces beneficial effects on peripheral oxygen utilization and decreased muscle sympathetic nerve activity (42,51–53).

Long-term hemodynamics and survival. Evaluation of long-term hemodynamics showed a higher CI and lower RAP in patients at repeat catheterization after a mean of 2 years post-septostomy (36). Echocardiography at 5.5 months after AS showed a significant decrease in right atrial and RV systolic and diastolic areas (54).

Of the 223 cases presented at Dana Point, follow-up information was available for 128. For these 128 patients, median survival was 60 months and mean survival time was 52.3 months. The mean survival after AS (excluding procedural deaths) was 63.1 months. Mortality after septostomy (excluding procedure-related mortality) was dictated by older age (hazard ratio [HR]: 1.04), scleroderma (HR: 8.32), NYHA functional class (HR: 4.71), NYHA class III and IV (HR: 6.24), CI (HR: 0.179), left atrial pressure (HR: 0.737), and SOT (HR: 0.99). The impact of baseline mRAP on survival, which is relevant before septostomy, disappears once the procedure has been performed. A diagnosis of scleroderma negatively impacts survival after AS.

Post-septostomy survival of patients with severe PH and right heart failure seems at least comparable to that achievable with current pharmacologic agents. However, given that a significant proportion of patients were receiving medications before and after the procedure, it is difficult to separate the relative benefits.

Summary. Atrial septostomy stands as an additional promising strategy in the treatment of severe PAH. It can be performed successfully in selected patients with advanced pulmonary vascular disease. In patients with PAH who have undergone successful AS, the procedure has resulted in a significant clinical improvement, beneficial and long-lasting hemodynamic effects at rest, and a trend toward improved survival. Procedure-related mortality is still high but seems to be decreasing since recommendations to minimize risk were implemented. However, because the disease process in PAH is unaffected, AS is considered a palliative procedure.

Indications for AS include: 1) failure of maximal medical therapy, persisting RV failure, and/or recurrent syncope; 2) as a bridge to transplantation; and 3) when no other therapeutic options exist (8,55).

Consensus

- The concept that AS decompresses the RV is accepted.
- Uptake has been limited. Impediments may be lack of a training pathway or the terminology “palliative procedure.”
- Patients known to benefit from AS have IPAH with syncope or persistent RV failure or have received failed medical therapy.
- Atrial septostomy has a role in health care systems without drug access.
- Atrial septostomy has been used to bridge to lung transplantation and might prolong survival for patients on a waiting list.
- Stepwise balloon dilatation is the procedure of choice.

- Data are sparse with Amplatzer devices, blade septostomy, butterfly stents, and cutting-edge balloons.
- Selection guidelines are unchanged from 2003: do not undertake AS if baseline O_2 saturation is <90% on room air or LV end diastolic diameter is >18 mm Hg.
- Procedural deaths relate to inadvertent overly large defect or a decrease in O_2 saturation >10%. Deaths are more common if RAP is >20 mm Hg.
- Procedural mortality is approximately 5%.
- The defect created should be tailored to the end O_2 saturation.
- Use in children could be increased.
- Spontaneous closure of the defect may require a repeat procedure.
- Survival after AS is superior to survival predicted by the National Institutes of Health.
- The benefit on survival differs from that of single-drug therapy in that it is immediately apparent.
- It is unknown how early in the course of PAH AS may be useful.

Recommendations

- The lack of data on exercise and long-term hemodynamics after AS needs to be addressed.
- The role of AS as a bridge to transplantation should be delineated because it may delay transplantation.
- A combination approach of early AS with drug therapy seems attractive in class IV patients.
- A trial of monotherapy patients (stable or deteriorating class III to IV) randomized to AS or no procedure is recommended.

Lung Transplantation

Heart–lung transplantation (HLTx) or bilateral lung transplantation (BLTx) is the final option for selected patients in whom medical therapy fails (56,57). The most common indication is IPAH; less common indications are scleroderma, histiocytosis, and sarcoidosis. Use of BLTx and HLTx for PAH has decreased worldwide as the result of PAH-specific medical treatments (58). Nevertheless, patients in class IV or who remain in class III despite combination therapy should be referred for transplantation assessment.

Patient selection. Published consensus guidelines are used by major transplantation centers, yet many patients with IPAH are still referred at a late stage, when medical therapy has failed and multi-organ failure is present. Because the lack of optimal donor organs is a global problem, death rates on the waiting list are high for patients with end-stage PAH. Post-operative mortality is significantly higher if transplantation is performed in the setting of right heart, renal, and hepatic failure, and marginal organs may also be used.

Potentially eligible class IV patients with IPAH should be referred immediately for transplantation assessment. The etiology of PAH, the functional and hemodynamic status, and the course of the disease in the particular patient must be considered to allow optimal timing of the transplantation listing. Patients with improvements after combination medical therapy over the first 3 months and, in particular, who move to class II, can be withdrawn from the waiting list and closely followed up. In patients remaining in class III on combination therapy, transplantation assessment and listing should not be delayed.

Patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis have the worst prognosis because medical treatment is ineffective (56); these patients must be referred for transplantation assessment at the time of diagnosis. Despite medical treatment, patients with scleroderma-associated PAH have a worse prognosis than do patients with IPAH (59), and the transplantation option should be discussed earlier. In contrast, patients with congenital right-to-left shunts and Eisenmenger syndrome have higher survival rates (37,38). Criteria for transplantation listing for these patients are difficult to define. However, the decision for transplantation for these patients should not be postponed until renal and hepatic failure occur, when patients can become unacceptable candidates.

The 6MWD and peak myocardial oxygen consumption predict survival. Listing algorithms for transplantation in PAH should incorporate hemodynamics because RAP >15 mm Hg and a CI <2.0 l/min/m^2 are primary determinants of poor survival (56).

Type of transplantation. In patients with IPAH, BLTx or HLTx are performed in most centers around the world. Single-lung transplantation for IPAH has been abandoned because of high rates of pulmonary edema and poor outcomes.

In patients with congenital cardiac abnormalities and Eisenmenger syndrome (particularly atrial septal defect), isolated lung transplantation combined with repair of cardiac defects is possible. HLTx provides survival advantages in this group of PAH patients, in whom it should be considered the procedure of choice (60). A HLTx in PAH is technically easier and preserves airway blood supply. The median sternotomy preserves respiratory mechanics, and the post-operative course is simpler.

In other etiologies of PAH, the choice between BLTx and HLTx remains open, and factors such as organ donation shortage, local allocation protocols, and center experience and preference play a role. Patients with PAH requiring 2 or 3 donor organs may be disadvantaged in many systems. Because a definite survival benefit for HLTx in IPAH has not been shown, it may not be appropriate to use the donor organs for 1 recipient rather than 2 if there is no major cardiac disease other than RV dysfunction. There are several advantages and disadvantages of BLTx or HLTx, but none has proven to be a determinant of survival. Post-operative RV dysfunction or high blood flow to the

new lungs with an increased LV pre-load can contribute to primary graft failure (60). These conditions can be stabilized by careful post-operative management, and RV function has been shown to recover following afterload reduction by transplantation in IPAH. Airway ischemia is more common after isolated lung transplantation compared with HLTx, but it was not a significant problem in a recent series of BLTx (57). In HLTx, a shorter ischemic time is mandatory; this may reduce the possible donor pool. Primary cardiac graft failure and accelerated long-term coronary artery disease are drawbacks of HLTx.

Outcome. In selected patients with end-stage PAH, the quality of life, exercise capacity, and long-term survival are profoundly improved by lung transplantation. Survival rates at 3 months after BLTx or combined HLTx for PAH are, however, the lowest among all lung transplant recipients (58). Heart–lung recipients with Eisenmenger syndrome and IPAH had significantly better overall survival than patients with other congenital abnormalities. Poor pre-operative patient status, including multiorgan failure, the complexity of the operation with routine use of extracorporeal circulation, and post-operative hemodynamic instability caused by RV or LV dysfunction after BLTx may result in inferior early survival. However, 5- and 10-year survival rates after BLTx for IPAH are similar to those seen with transplantation for other etiologies (58). Lung transplant recipients with IPAH who survived to 1 year had a significantly better survival at 10 years than transplant recipients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

Retrospective studies from individual centers showed superior early and long-term results after BLTx or combined HLTx for IPAH (57,61). In a retrospective study from Pittsburgh (30 recipients who underwent transplantation between 1994 and 2006), actuarial survival was 86% at 1 year, 75% at 5 years, and 66% at 10 years (57). Early referral to a specialized multidisciplinary lung transplantation center familiar with the unique problems of PAH patients and the complex transplantation procedure is key.

Consensus

- Lung transplantation is the final effective treatment for selected patients with IPAH.
- The procedure of choice is BLTx or HLTx. Single-lung procedures have been abandoned. Living lobar transplants put donors at risk.
- In choosing BLTx versus HLTx, organ donation rates, local allocation protocols, and unit preference play a role.
- Patients with PAH require 2 or 3 organs and may be disadvantaged in some allocation systems.

Recommendations

- Although drug therapy may delay transplantation, a class IV patient who fulfills criteria should be referred for transplantation assessment.
- Patients with veno-occlusive disease must be referred for transplantation assessment at diagnosis.
- Listing algorithms for transplantation in PAH must incorporate hemodynamics because hemodynamics are the primary determinant of survival, in addition to functional class, exercise capacity, and failure to respond to other therapies (Guidelines of the International Society for Heart and Lung Transplantation define RAP >15 mm Hg, CO <2.0 l/min) (58).

Extracorporeal Support

Extracorporeal life support (ECLS) has been successfully used for cardiorespiratory support in neonates and children (62). Common indications for ECLS in adults are respiratory failure and acute respiratory distress syndrome (63). Possible indications for ECLS in PAH are acute RV failure and hypoxemia caused by massive pulmonary embolism (63), bridge to lung transplantation, support after lung transplantation (64–66), and treatment of severe reperfusion edema after PEA for CTEPH (67).

Extracorporeal life support is considered for patients with PH and potentially reversible right heart failure in whom conventional support is failing, including optimized ventilation and fluid management, prone positioning, inhaled nitric oxide, prostanoid agents, and pharmacologic therapy for right heart function (62).

The modes of ECLS are venovenous or venoarterial systems using the internal jugular or common femoral veins and/or common femoral, common carotid, or right axillary arteries for cannulation (62,68). Venovenous ECLS is useful for carbon dioxide removal, oxygenation, and RV afterload reduction. Venoarterial ECLS is preferred for RV decompression and after lung transplantation (although having high mortality rates) because it provides more effective oxygenation.

Bleeding, neurological, infectious, and thromboembolic complications limit widespread use of ECLS (62,67). Controlled randomized studies are not available and are unlikely to be performed. However, ECLS can be a lifesaving option in critically ill PAH patients and should be at hand in specialized PH centers.

Extracorporeal membrane oxygenation (ECMO) is a valuable tool in lung transplantation, providing the potential to bridge patients to transplantation, to replace cardiopulmonary bypass with at least equal results, and to overcome severe post-operative complications. Favorable survival rates can be achieved despite the fact that ECMO is used in the more complex patient population undergoing lung transplantation (69).

Conclusions

- When conventional support for the RV is ineffective, ECLS may take several forms. Established modalities are:

  - venovenous: useful for carbon dioxide removal, oxygenation, RV afterload reduction
  - venoarterial: preferred for RV decompression and support and after lung transplantation (although high mortality if needed), providing more effective oxygenation
- Devices include membrane oxygenators, centrifugal pumps, and heparin-bonded systems.

Consensus

- Extracorporeal life support can be lifesaving in critically ill patients with RV failure, but no data are available from randomized controlled trials.
- Many questions remain regarding indications, timing, and cannulation choice.

Ventricular Assist Devices

Mechanical circulatory support for the RV has been used for patients refractory to medical therapy. The usual goal of mechanical circulatory support involving the RV is to bridge the patients to lung transplantation.

Patients with end-stage right heart failure secondary to IPAH have fared poorly with pulsatile assist systems in anecdotal reports. The PAP typically increases markedly with pulsatile mechanical support because of the high energy imparted to blood by a pulsatile mechanical device, even with pumps that are pneumatically driven and set to deliver the lowest possible dP/dT. The high dP/dT of pulsatile ventricular assist devices results in damage to the pulmonary microcirculation, with increased PVR and PAP often resulting in intraparenchymal pulmonary hemorrhage, hemoptysis, and death. The challenge is to increase flow through a circulatory bed with inherently high resistance and high impedance attributable to derangements of smooth muscle proliferation and vascular collagen accumulation. Such patients may be best served by a support device that incorporates a gas exchange function in addition to a circulatory function, taking blood from the venous circulation and delivering it directly to the left atrium or arterial circulation, thereby excluding the diseased RV and lungs from the patient's circulatory system. Unfortunately, ECMO provides only short-term support in adults, and an inflammatory response associated with the large prosthetic surfaces of an oxygenator have limited its success.

Nonpulsatile flow axial or centrifugal flow devices—for example, roller pumps inserted percutaneously—may have promise, with the potential for vascular remodeling, but they are largely untested.

Consensus

- There is little literature on RV assist devices.
- Right ventricular assist devices are effective in RV failure secondary to LV failure.
- Right ventricular assist devices with pulsatile flow cause high distension pressure, and flow characteristics are less adjustable than with nonpulsatile axial or centrifugal flow devices.
- In addition to short-term survival benefit, long-term support may permit vascular remodeling.
- There is a strong rationale for the development of such devices.

Other Interventional Modalities

Novalung®. The Novalung® interventional Lung-Assist (iLA) membrane ventilator device (Novalung, GmbH, Germany) is a pumpless extracorporeal lung-assist device used in acute lung failure. It is driven by the patient's CO and does not require extracorporeal pump assistance. A membrane gas exchange system with optimized blood flow is integrated in an arteriovenous bypass established by vascular cannulation. Novalung® has been applied in 4,000 patients for artificial lung assistance with easy use and low cost (70).

Stem cell transplantation. Circulating endothelial progenitor cells instigate angiogenesis in PAH and home to the location of endothelial damage, providing endothelial repair. Autologous endothelial progenitor cell transplantation may be explored in PAH in the future.

RV synchronization. In PAH, significant interventricular dyssynchrony occurs because of a right bundle branch block with prolonged RV systolic contraction time, compared with the LV (71). This is probably caused by a decrease of electrical conductivity over the RV caused by high prestretch of the RV myocardial fibers and the large force these fibers must generate to shorten. Dyssynchrony is known to impede LV diastolic filling (72).

In animal studies, opening the pericardium facilitates LV filling, increases LV end-diastolic volume and output, and reduces septal bowing. Because a relationship exists between pericardial pressure and RAP, and RAP is increased in patients with severe PAH, diastolic interaction may theoretically be improved.

Consensus

- Right ventricular resynchronization therapy has potential and is likely to be safe enough for a pilot study in humans with IPAH.

Novel shunts for PAH: Potts anastomosis or "de novo ductus arteriosus," a hypothetical exercise. The rationale for creating new right-to-left shunts is that PAH patients with Eisenmenger physiology or patent foramen ovale survive longer than IPAH patients. Atrial septostomy is accepted as a mechanism for unloading the RV and reducing RV area, syncope, ascites, and edema. This occurs despite an 85% resting desaturation and a further 68% desaturation with exercise. A potential alternate decompression technique is to create a Potts anastomosis (side-to-side anastomosis from left pulmonary artery to descending aorta) (73).

Seven children with varying etiology (IPAH or corrected transposition) and suprasystemic PA pressure failing drug therapy underwent Potts anastomosis (73). There was 1 technical death. Follow-up at 26 ± 22 months in the remainder showed a tripling of 6MWD, improved functional class, freedom from syncope, upper limb SaO_2 97%, lower limb 80%, and pulmonary artery and aortic pressures equalized (74,75). In theory, this technique might be applicable in adults with IPAH, although some operative risk is likely.

Purely hypothetical is the idea of creating a de novo ductus arteriosus with conduit, which might perhaps be valved to prevent aortic backpressure surges into the pulmonary artery. Possible materials might be derived from LV assist device circuitry or arteriovenous fistulae formation for dialysis, radial artery graft (used in coronary artery bypass surgery), valved saphenous vein grafts, or new polymers.

Consensus. There is no consensus, given the paucity of data. The idea, however, is quite an exciting one, particularly if it can be applied in adults in whom other therapies have failed.

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Reprint requests and correspondence: Prof. Anne M. Keogh, St. Vincent's Hospital, Victoria Street, Darlinghurst 2010, Sydney NSW, Australia. E-mail: amkeogh@stvincents.com.au.

REFERENCES

1. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257–64.
2. Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001;119:818–23.
3. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation 2006;113;2011–20.
4. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685–92.
5. Yi ES, Kim H, Ahn H, et al. Distribution of obstructive intimal lesions and their cellular phenotypes in chronic pulmonary hypertension: a morphometric and immunohistochemical study. Am J Respir Crit Care Med 2000;162:1577–86.
6. Auger WR, Kim NH, Kerr KM, Test VJ, Fedullo PF. Chronic thromboembolic pulmonary hypertension. Clin Chest Med 2007;28:255–69.
7. Dartevelle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2004;23:637–48.
8. Klepetko W, Mayer E, Sandoval J, et al. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:73S–80S.
9. Ley S, Kauczor HU, Heussel CP, et al. Value of contrast-enhanced MR angiography and helical CT angiography in chronic thromboembolic pulmonary hypertension. Eur Radiol 2003;13:2365–71.
10. Coulden R. State-of-the-art imaging techniques in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006;3:577–83.
11. Bresser P, Pepke-Zaba J, Jaïs X, Humbert M, Hoeper MM. Medical therapies for chronic thromboembolic pulmonary hypertension: an evolving treatment paradigm. Proc Am Thorac Soc 2006;3:594–600.
12. Hartz RS, Byrne JG, Levitsky S, Park J, Rich S. Predictors of mortality in pulmonary thromboendarterectomy. Ann Thorac Surg 1996;62:1255–9.
13. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003;76:1457–64.
14. Bonderman D, Skoro-Sajer N, Jakowitsch J, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation 2007;115:2153–8.
15. Kim NH. Assessment of operability in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006;3:584–8.
16. Kim NH, Fesler P, Channick RN, et al. Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Circulation 2004;109:18–22.
17. Langer F, Bauer M, Tscholl D, et al. Circulating big endothelin-1: an active role in pulmonary thromboendarterectomy? J Thorac Cardiovasc Surg 2005;130:1342–7.
18. Suntharalingam J, Goldsmith K, Toshner M, et al. Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension. Respir Med 2007;101:2254–62.
19. Skoro-Sajer N, Mittermayer F, Panzenboeck A, et al. Asymmetric dimethylarginine is increased in chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2007;176:1154–60.
20. Hardziyenka M, Reesink HJ, Bouma BJ, et al. A novel echocardiographic predictor of in-hospital mortality and mid-term haemodynamic improvement after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension. Eur Heart J 2007;28:842–9.
21. Condliffe R, Kiely D, Gibbs JS, et al. Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension. Eur Respir J 2009;33:332–8.
22. Thistlethwaite PA, Mo M, Madani MM, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. J Thorac Cardiovasc Surg 2002;124:1203–11.
23. Hagl C, Khaladj N, Peters T, et al. Technical advances of pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Eur J Cardiothorac Surg 2003;23:776–81.

24. Thomson B, Tsui SS, Dunning J, et al. Pulmonary endarterectomy is possible and effective without the use of complete circulatory arrest—the UK experience in over 150 patients. Eur J Cardiothorac Surg 2008;33:157–63.
25. Mayer E, Klepetko W. Techniques and outcomes of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006;3:589–93.
26. Fedullo PF, Auger WR, Dembitsky WP. Postoperative management of the patient undergoing pulmonary thromboendarterectomy. Semin Thorac Cardiovasc Surg 1999;11:172–8.
27. Kramm T, Eberle B, Krummenauer F, Guth S, Oelert H, Mayer E. Inhaled iloprost in patients with chronic thromboembolic pulmonary hypertension: effects before and after pulmonary thromboendarterectomy. Ann Thorac Surg 2003;76:711–8.
28. Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Techniques and outcomes of pulmonary endarterectomy surgery. Ann Thorac Cardiovasc Surg 2008;14:274–82.
29. D'Armini AM, Cattadori B, Monterosso C, et al. Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: hemodynamic characteristics and changes. Eur J Cardiothorac Surg 2000;18:696–702.
30. Archibald CJ, Auger WR, Fedullo PF, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 1999;160:523–8.
31. Condliffe R, Kiely D, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008;15:1122–7.
32. Hughes R, Jaïs X, Bonderman D, et al. The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. Eur Respir J 2006;28:138–43.
33. Jaïs X, D'Armini AM, Jansa P, et al., for the BENEFiT Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52:2127–34.
34. D'Alonso GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991;115:343–9.
35. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;15:100–5.
36. Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. Coron Artery Dis 2005;16:19–25.
37. Nihill MR, O'Laughlin MP, Mullins CE. Effects of atrial septostomy in patients with terminal cor pulmonale due to pulmonary vascular disease. Catheter Cardiovasc Diagn 1991;24:166–72.
38. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation 1995;91:2028–35.
39. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999;99:1858–65.
40. Simonneau G, Barst RJ, Galiè N, et al., for the Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:800–4.
41. Galiè N, Beghetti M, Gatzoulis MA, et al., for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48–54.
42. Sandoval J, Gaspar J. Atrial septostomy. In: Peacock AJ, Rubin LJ, editors. Pulmonary Circulation. 2nd Edition. London: Edward Arnold, 2004:319–33.
43. Micheletti A, Hislop AA, Lammers A, et al. Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension. Heart 2006;92:969–72.
44. Prieto LR, Latson LA, Jennings C. Atrial septostomy using a butterfly stent in a patient with severe pulmonary arterial hypertension. Catheter Cardiovasc Interv 2006;68:642–7.
45. Sandoval J, Rothman A, Pulido T. Atrial septostomy for pulmonary hypertension. Clin Chest Med 2001;22:547–60.
46. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension: a therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998;32:297–304.
47. Vachiéry JL, Stoupel E, Boonstra A, Naeije R. Balloon atrial septostomy for pulmonary hypertension in the prostacyclin era (abstr). Am J Respir Crit Care Med 2003;167:A692.
48. Allcock RJ, O'Sullivan JJ, Corris PA. Atrial septostomy for pulmonary arterial hypertension. Heart 2003;89:1344–7.
49. Rich S. Dodin E, McLaughlin VV. Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. Am J Cardiol 1997;80:369–71.
50. Kurzyna M, Dabrowski M, Bielecki D, et al. Atrial septostomy in treatment of end-stage right heart failure in patients with pulmonary hypertension. Chest 2007;131:977–83.
51. Ciarka A, Vachiéry JL, Houssière A, et al. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. Chest 2007;131:1831–7.
52. Velez-Roa S, Ciarka A, Najem B, Vachiéry JL, Naeije R, van de Borne P. Increased sympathetic nerve activity in pulmonary artery hypertension. Circulation 2004;110:1308–12.
53. Bristow MR, Zisman LS, Lowes BD, et al. The pressure-overloaded right ventricle in pulmonary hypertension. Chest 1998;114:101S–6S.
54. Espínola-Zavaleta N, Vargas-Barrón J, Tazar JI, et al. Echocardiographic evaluation of patients with primary pulmonary hypertension before and after atrial septostomy. Echocardiography 1999;16:625–34.
55. Doyle RL, McCrory D, Channick RN, Simonneau G, Conte J. Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:63S–71S.
56. Orens JB, Estenne M, Arcasoy S, et al., for the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745–55.
57. Toyoda Y, Thacker J, Santos R, et al. Long-term outcome of lung and heart-lung transplantation for idiopathic pulmonary arterial hypertension. Ann Thorac Surg 2008;86:1116–22.
58. Christie JD, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report—2008. J Heart Lung Transplant 2008;27:957–69.
59. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest 2003;123:344–50.
60. Waddell TK, Bennett L, Kennedy R, Todd TR, Keshavjee SH. Heart-lung or lung transplantation for Eisenmenger syndrome. J Heart Lung Transplant 2002;21:731–7.
61. de Perrot M, Chaparro C, McRae K, et al. Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. J Thorac Cardiovasc Surg 2004;127:1493–501.
62. Conrad SA, Rycus PT, Dalton H. Extracorporeal Life Support Registry Report 2004. ASAIO J 2005;51:4–10.
63. Maggio P, Hemmila M, Haft J, Bartlett R. Extracorporeal life support for massive pulmonary embolism. J Trauma 2007;62:570–6.
64. Vlasselaers D, Verleden GM, Meyns B, et al. Femoral venoarterial extracorporeal membrane oxygenation for severe reimplantation response after lung transplantation. Chest 2000;118:559–61.
65. Fischer S, Bohn D, Rycus P, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. J Heart Lung Transplant 2007;26:472–7.
66. Pereszlenyi A, Lang G, Steltzer H, et al. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Eur J Cardiothorac Surg 2002;21:858–63.
67. Thistlethwaite PA, Madani MM, Kemp AD, Hartley M, Auger WR, Jamieson SW. Venovenous extracorporeal life support after pulmonary endarterectomy: indications, techniques, and outcomes. Ann Thorac Surg 2006;82:2139–45.
68. Kahn J, Müller H, Marte W, et al. Establishing extracorporeal membrane oxygenation in a university clinic: case series. J Cardiothorac Vasc Anesth 2007;21:384–7.

69. Aigner C, Wisser W, Taghavi S, et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. Eur J Cardiothorac Surg 2007;31:468–74.
70. Walles T. Clinical experience with the iLA Membrane Ventilator pumpless extracorporeal lung-assist device. Expert Rev Med Devices 2007;4:297–305.
71. Gan CT, Lankhaar JW, Marcus JT, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. Am J Physiol Heart Circ Physiol 2006;290:H1528–33.
72. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ. The relationship between pericardial pressure and right atrial pressure: an intraoperative study. Circulation 1986;73:428–32.
73. Zipes D, Libby P, Bonow R, Braunwald E, editors. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 5th edition. Philadelphia, PA: WB Saunders, 2005.
74. Blanc J, Vouhé P, Bonnet D. Potts shunt in patients with pulmonary hypertension (letter). N Engl J Med 2004;350:623.
75. Serraf A, Petit J, Belli E, et al. Potts anastomosis for severe pulmonary arterial hypertension in children. Presented at: American Thoracic Society International Conference; May 2007; San Diego, CA.

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