Alternatives to Lung Transplantation: Treatment of Pulmonary Arterial Hypertension

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KEYWORDS

- Pulmonary arterial hypertension
- Chronic thromboembolic pulmonary hypertension
- Lung transplantation • Pulmonary endarterectomy
- Atrial septostomy

The Dana Point International Consensus Meeting in 2008 reclassified the clinical presentation of pulmonary hypertension into 5 categories. The first category comprises an intrinsic precapillary pulmonary arteriopathy called pulmonary arterial hypertension (PAH), including idiopathic PAH (IPAH) and familial/inherited pulmonary arterial hypertension, as well as pulmonary hypertension associated with connective tissue disease, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV), and the use of anorexigens. The second category includes pulmonary hypertension as a consequence of left heart disease and increased left heart filling pressures. The third category is related to lung airway or parenchymal diseases with capillary destruction and hypoxic pulmonary vasoconstriction. The fourth category consists of chronic thromboembolic pulmonary hypertension (CTEPH) and is a consequence of pulmonary embolism. The fifth category is pulmonary hypertension of unclear or multifactorial etiologies associated with a mix of rare diseases.

For categories 2 and 3, treatment consists of improving the cardiac or pulmonary abnormalities by reducing left ventricular filling and afterload or by correcting hypoxemia. For categories 1 and 4, specific therapeutic approaches have been developed and are described here. In some patients, these targeted therapies may be very successful and may put off the need for transplantation indefinitely, while in other patients they will be insufficient to stabilize the disease and can only be considered as a bridge to transplantation. Overall, the proportion of lung transplantations performed for IPAH has decreased from about 12% in the 1990s to 2% in 2006.[1] The recent evolution toward a more aggressive approach driven by therapeutic goals derived from prognostic factors has led to consideration of transplantation earlier in disease course when it becomes clear that medical interventions are failing.

PAH

Prognostic Factors in PAH

In the preprostacyclin era, the median survival of untreated patients with IPAH was 2.8 years. However, patients with much better survival could be identified on the basis of favorable clinical indices. A low functional class (New York Heart Association [NYHA] 1 and 2) and better hemodynamics (right atrial pressure <10 mm Hg, cardiac index >2.5 L/min/m^2 and mixed venous oxygen

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saturation >63%) were first identified as important good prognostic factors.[2,3] Subsequently, other factors were described comprising:

- A relatively preserved exercise capacity: 6-minute walk distance greater than 332 m,[4] peak oxygen uptake greater than 10.4 mL/min/kg, and systolic blood pressure greater than 120 mm Hg[5]
- Preserved right ventricular contractile function: Tei index greater tan 0.8,[6] or tricuspid annular tricuspid annular plane systolic excursion greater than 18 mm[7]
- Less right ventricular strain: brain natriuretic peptide (BNP) lower than 150 pg/mL,[8] N terminal brain naturetic peptide (NTproBNP) lower than 1400 pg/mL,[9] or troponin C lower than 0.01 ng/mL.[10]

Similarly, factors have been identified that can predict outcome in patients treated with specific disease-targeted drugs. Sitbon and colleagues[11] showed that an NYHA class 1 or 2, a 6-minute walk distance greater than 380 m, or a 30% decrease in total pulmonary vascular resistance, obtained within 3 months of epoprostenol therapy, were associated with a good outcome (>80% survival at 3 years). This was confirmed by McLaughlin and colleagues,[12] showing a higher survival rate in patients in NYHA class 1 or 2 after 1 year of epoprostenol therapy. More recently, Provencher and colleagues[13] also showed that 6-minute walk distance and total pulmonary vascular resistance after 4 months of bosentan therapy were predictive for long-term survival. The use of these prognostic factors, both before and after the initiation of specific PAH therapy, can help to stratify patients according to their disease severity and to decide whether and when patients should be listed for lung transplantation.

Medical Treatment for PAH

This section describes the randomized controlled studies (RCTs) performed in PAH and summarized in **Table 1**.

Prostacyclin analogs

Prostacyclin or prostaglandin I_2 (PGI_2), first described in 1976, is still considered as the most potent pulmonary vasodilator. It is produced by endothelial cells, binds to specific membrane receptors of smooth muscles cells, and activates adenylate cyclase to increase intracellular cyclic adenosine monophosphate. Beside its vasodilator action, PGI2 also inhibits platelet aggregation and smooth muscle proliferation, both of which are abnormal in PAH.[14,15] Moreover, PGI_2 production has been shown to be insufficient in IPAH, providing a rationale for therapeutic use.[16]

Epoprostenol In 1987, Higenbottam and colleagues[17] reported the first chronic use of a prostacyclin analog, epoprostenol, in a patient with IPAH. Two RCTs, from Rubin and colleagues[18] in 1990 and Barst and colleagues[19] in 1996, confirmed that substantial improvements in symptoms, exercise tolerance, and pulmonary hemodynamics could be seen. The second study randomized 81 IPAH patients with NYHA functional class 3 and 4 to receive either continuous epoprostenol or conventional therapy. The mean epoprostenol dose at the end of the 12-week study was 9.2 ng/kg/min. The 6-minute walk distance, the primary end-point of the study, was significantly improved in epoprostenol-treated patients, while it deteriorated in patients under conventional therapy. Significant improvements were also seen in pulmonary hemodynamics, NYHA functional class, and quality of life. This pivotal study led to expanded use of epoprostenol, and, as a consequence of having an effective medical alternative, up to 70% of patients initially listed for lung transplantation were removed from the list as a result of improvement.[20,21] Epoprostenol has since been shown to improve hemodynamics and exercise capacity in patients with PAH related to scleroderma disease.[22] Uncontrolled studies also suggest improvement in patients with PAH related to congenital heart disease,[23,24] portal hypertension,[25] HIV infection,[26] and distal CTEPH.[24]

Because of its short half-life (3–5 minutes), epoprostenol has to be administered intravenously as a continuous infusion. This requires a tunneled central venous catheter and a portable infusion pump. The drug needs to be reconstituted daily and stored in refrigerated reservoirs connected to the portable pump. Patients and relatives need appropriate training by expert nurses to learn how to manage the system safely at home and how to solve the most frequent technical problems. The treatment is started at a dose of 2 ng/kg/min and progressively increased at a rate limited by side effects, including hypotension, flushing, headache, diarrhea, restlessness, jaw pain, leg pain, backache, abdominal discomfort, and nausea. Periodic dose increases are required to maintain efficacy because of tolerance to the drug. Adverse effects are ascites, probably related to increased permeability of the peritoneal membrane, hyperthyroidism, and thrombocytopenia. Complications related to the delivery system are pump malfunction, catheter obstruction and dislocations, local infection, and bacteremia. Excessive dosage can induce high cardiac

Table 1
Summary of randomized controlled trials in pulmonary arterial hypertension: efficacy results

Drug	Indication	NYHA	Borg	QoL	6MWD	PVR	NTproBNP	TTCW	Hospitalization	Progression
Epoprostenol	IPAH-CTD	√	—	√	√	√	—	Survival	—	—
Treprostinil	IPAH-CTD-CHD	√	√	NS	√	√	—	—	—	—
Iloprost	IPAH-CTD-CTEPH	√	—	√	√	√	—	—	—	—
Bosentan	IPAH-CTD	√	√	—	√	√	—	√	√	√
Bosentan	CHD	√	—	—	√	√	—	—	—	—
Bosentan	NYHA II	—	NS	√	$P = .08$	√	√	√	NS	√
Bosentan	CTEPH	NS	√	NS	NS	√	√	NS	NS	—
Sitaxentan	IPAH-CTD-CHD	√	NS	—	√	√	—	NS	NS	NS
Ambrisentan	IPAH-CTD-HIV	√	√	√	√	—	√	√	(↓)	(↓)
Sildenafil	IPAH-CTD-CHD	√	NS	—	√	√	—	NS	(↓)	NS
Tadalafil	IPAH-CTD-HIV-CHD	NS	NS	√	√	√	—	√	—	—

Abbreviations: BNP, brain natriuretic peptide; Borg, Borg dyspnea score at the end of the 6-minute walk disatance (6-MWD); CHD, PAH associated with congenital heart disease; CTD, pulmonary arterial hypertension (PAH) associated with connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, PAH associated with the human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; NS, not significant; NTproBNP, N terminal brain naturetic peptide; NYHA, modified New York Heart Association functional class; PVR, pulmonary vascular resistance; QoL, quality of life; TTCW, time to clinical worsening.

output states, unnecessarily increasing cardiac work.[27]

Treprostinol Treprostinil is a chemically stable tricyclic benzidine analog of prostacyclin, stable at room temperature and with a longer half-life (30–80 minutes, depending on the administration route), suitable for intravenous and subcutaneous administrations. It was developed as a potential successor of epoprostenol. A large 12-week RCT enrolled 469 patients with NYHA class 2 through 4 IPAH, PAH related to congenital heart disease, and PAH related to connective tissue diseases.[28] As with epoprostenol, significant improvements in exercise capacity, functional class, and hemodynamics were reported. The effect on 6-minute walk distance was, however, much smaller than for epoprostenol, except for the patients receiving the highest doses. US Food and Drug Administration (FDA) approval was granted in 2002 because of substantial safety and convenience advantages over intravenous epoprostenol. Unfortunately, pain and redness at the infusion site are encountered by 85% of the patients when the drug is administered subcutaneously, and 8% of patients find the pain intolerable. This has clearly limited the use of the drug. Subcutaneous administration requires small subcutaneous catheters and microinfusion pumps similar to those used to administer insulin to diabetic patients. The initial infusion rate is 1.25 ng/kg/min and gradually increases twice weekly by 1.25 ng/kg/min. Pain seems to be unrelated to the dose, is maximal 4 days after insertion, and decreases afterwards. Patients therefore maintain the catheter at the same place for 1 to several weeks. Patients on intravenous epoprostenol can be transitioned to subcutaneous treprostenil over 1 to 4 days, with no major adverse effects and without clinical deterioration.[29]

In 2004, the FDA also approved treprostinil for intravenous administration. Although this therapy shares with epoprostenol the risk of line infection and sepsis, it offers advantages of longer half-life and easier drug preparation. Three small uncontrolled studies, 1 after slow transition from intravenous epoprostenol,[30] 1 after rapid switch[31] and 1 for de novo treatment,[32] suggest similar efficacy for intravenous treprostinil and epoprostenol. However, the dosing of intravenous treprostinil is generally at least twice that of epoprostenol.

Inhaled treprostinil has been studied in a phase 3 trial, which showed significant but moderate improvements in exercise capacity.[33] An oral form of treprostinil is under investigation.

Iloprost Iloprost is another stable prostacyclin analog with an intermediate half-life (20–25 minutes) available for intravenous and inhaled administration. The inhalation route is attractive, because it delivers medication to ventilated lung areas exclusively, thereby limiting ventilation mismatch and hypoxemia. A 12-week RCT included 203 patients with NYHA class 3 and 4 IPAH, PAH related to connective tissue disease, and CTEPH.[34] The primary composite endpoint (improvement in NYHA class plus at least 10% improvement in the 6-minute walk distance plus no deterioration or death) was reached by 16.8% of the patients on iloprost treatment versus 4.9% on placebo. Fewer patients in the iloprost group died or deteriorated compared with the placebo group (4.9% vs 11.8%). Iloprost benefits also included hemodynamic, functional, and quality-of-life improvements. Adverse effects were increased cough, headache, flush, and jaw pain. The major limitation of this therapy is the short duration of effect requiring repetitive inhalations up to 9 times a day, each lasting 4 to 15 minuts, depending on the nebulizer type.[35]

Iloprost has also been studied as add-on therapy in patients treated with bosentan. Sixty-five patients were included in a 12-week RCT.[36] Significant improvements in functional class, hemodynamics, and time to clinical worsening were observed in the combination therapy group.

Endothelin receptor antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor and pro-proliferative substance. It is produced by endothelial cells and binds to two different receptors, ET_A and ET_B. Excessive production of endothelin in IPAH provides a rationale for receptor blockade. Selective ET_A and nonselective ET_A and ET_B receptor antagonists (ERA) have been developed.

Bosentan Bosentan, an orally active dual receptor antagonist, has been evaluated in two RCTs including NYHA-class 3 patients with IPAH and patients with PAH related to connective tissue disease. In the first study, significant improvements in exercise capacity, hemodynamics, and functional class were documented.[37] In the second one, bosentan (125 mg and 250 mg twice daily) significantly increased exercise capacity, delayed the time to clinical worsening, and improved Borg dyspnea score and functional class.[38] More recently, bosentan was shown to improve hemodynamics and time to clinical worsening but not 6-minute walk distance in NYHA class 2 patients with IPAH and PAH related to connective tissue disease.[39] Finally, in a RCT performed in patients with PAH related to congenital heart disease, bosentan significantly improved hemodynamics and 6-minute walk distance.[40]

Bosentan is well tolerated, except for a reversible, dose-related increase in liver enzymes in about 10% of the patients. This hepatotoxicity is attributed to inhibition of the canalicular bile salt export pump.[41] Significant drug interactions have been reported with cyclosporine, tacrolimus, gliburide, ketoconazole, itraconazole, and ritonavir. FDA approval was obtained in 2002.

Sitaxentan Sitaxetan is a highly selective ET_A receptor blocker. It has been evaluated in 2 large RCTs that included NYHA class 2 and 3 patients with IPAH and PAH related to connective tissue disease and to congenital heart disease. In the first trial, drug dosage was 100 mg and 300 mg once daily.[42] Sitaxentan significantly improved exercise capacity (6-minute walk distance but not peak oxygen consumption), functional class and pulmonary hemodynamics. In the second RCT, dosage was 50 and 100 mg for sitaxentan, and there was an additional open-label arm with bosentan.[43] Significant improvements in 6-minute walk distance and functional class were reported for the 100 mg and bosentan arms but not for the 50 mg arm. Notably, sitaxsentan has very recently been withdrawn by Pfizer from clinical use because of unpredictable acute hepatic failure.

Ambrisentan Ambrisentan is a modestly selective ET_A receptor blocker that has been studied in 2 large RCTs.[44] Significant improvements in 6-minute walk distance, functional class, Borg dyspnea score, quality of life, and time to clinical worsening were reported for all 3 dosages. No significant liver function abnormalities were reported. Peripheral edema was a common adverse effect, particularly in the 10 mg arm. FDA approval was obtained in 2007. No drug interactions have been reported to date.

Phosphodiesterase 5 inhibitors

Cyclic guanosine monophosphate (cGMP), the intracellular second messenger of nitric oxide (NO), is a potent vasodilator and inhibitor of smooth muscle cell proliferation. Inhibitors of cGMP phosphodiesterase (PDE) increase intracellular concentrations of cGMP, thereby enhancing the effects of endogenous NO. The cGMP-specific PDE5 is the predominant PDE isoenzyme in the pulmonary arteries.

Sildenafil Sildenafil is an orally active, selective PDE5 inhibitor with a half-life of 3 to 5 hours. One large RCT randomized NYHA class 2 to 4 patients with IPAH or PAH related to connective tissue disease and congenital heart disease to receive 20 mg, 40 mg, or 80 mg of sildenafil versus placebo three times daily for 12 weeks.[45] Significant improvements in 6-minute walk distance and pulmonary hemodynamics were demonstrated, of similar magnitude for the 3 dose regimens. FDA approval was obtained in 2005. Because of the absence of a dose–response effect, only the 20 mg dosage was approved.

Adverse effects include headache, flushing, dizziness, dyspepsia, abnormal vision, back pain, myalgia, and epistaxis. A potentiation of the hypotensive effects of nitrates has been reported. Concomitant administration with bosentan causes a decrease in the plasma level of sildenafil and an increase in the level of bosentan; however, no dose adjustment has been recommended. Coadministration with ketoconazole, itraconazole, or ritonavir is discouraged.

Tadalafil Tadalafil is a newer, longer-acting PDE5 inhibitor. A recent 16-week RCT included patients with IPAH and PAH associated with connective tissue disease, congenital heart disease, and HIV who were randomized to placebo or tadalafil 2.5 mg, 10 mg, 20 mg, or 40 mg orally once daily.[46] Treatment was given as monotherapy, or, in 53% of patients, as add-on therapy to bosentan. Tadalafil 40 mg increased 6-minute walk distance and quality of life, delayed the time to clinical worsening, and improved hemodynamics. The most common treatment-related adverse event reported with tadalafil was headache.

Long-term survival data

With the exception of the original epoprostenol study,[19] all the previously mentioned 12- to 16-weeks RCTs were unable and not powered to show survival benefits. In a meta-analysis, Macchia and colleagues[47] could not demonstrate survival benefits for the PAH-specific therapies. However, in 2009, Galie and colleagues,[48] combining data from 21 studies involving 3140 patients, showed a 43% mortality reduction over 14.3 months, on average. Survival data have also been collected from long-term observational studies and compared against historical controls from a period when no therapy was available for PAH in the United States (**Table 2**).[2] These historical data were confirmed by more recent survival data from China, where these therapies are not widely available.[49]

Only a small number of IPAH patients with an acute vasodilator response to NO or epoprostenol demonstrate a beneficial response to calcium channel blockers (CCBs), but this characteristic is associated with a long-term survival advantage.[50] Recommended doses are up to 240 mg/d for nifedipine and 900 mg/d for diltiazem, but the effect of smaller doses has not been evaluated. It is

Table 2
Summary of large cohorts treated with epoprostenol, treprostinil, iloprost, and bosentan in comparison with conventional treatment

References	Drug	n	Type	NYHA	6MWD	OA	1-y	2-y	3-y	Comb[a]
D'Alonzo et al,[2] 1991	—	194	IPAH	—	—	20%	68	—	48	—
Christie et al,[1] 2008	LTx	710	IPAH	—	—	—	69	63	59	—
Barst, 1994	epo	18	IPAH	3.17	264 ± 160	100%	87	72	63	—
Sitbon et al,[11] 2002	epo	178	IPAH	—	240	—	85	70	63	—
McLaughlin et al,[12] 2002	epo	162	IPAH	—	—	—	88	76	63	—
Barst et al,[43] 2006	trepro	860	—	—	—	—	87	78	71	15%
Lang et al,[51] 2006	trepro	122	PAH/CTEPH	3.20 ± 0.04	305 ± 11	95%	89	—	71	18%
Opitz et al,[52] 2005	ilo inh	76	IPAH	—	—	47%	79	70	59	54%
Hoeper, 2008	ilo inh+iv	79	IPAH-CTD-CHD-PoPH	3.23	287 ± 112	—	86	73	59	—
McLaughlin et al,[55] 2005	bos	169	—	—	345 ± 87	—	96	89	86	30%
Hoeper, 2005	bos	123	—	—	308 ± 133	88%	93	83	80	43%
Provencher et al,[13] 2006	bos	103	IPAH	—	319 ± 105	99%	92	89	79	44%
Sandoval et al,[63] 1998	BDAS	14	IPAH	3.57 ± 0.6	107 ± 127	—	92	92	92	—
Rich et al,[50] 1992	CCB	17	IPAH (R)	2.39 ± 0.5	—	—	94	94	94	—
Sitbon, 2005	CCB	38	IPAH (LT R)	2.42	380 ± 112	—	97	97	97	—

Abbreviations: BDAS, baloon dilation atrial septostomy; bos, bosentan; CCB, calcium channel blockers; CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; epo, epoprostenol; ilo inh, inhaled iloprost; iv, intravenous; (I)PAH, (idiopathic) pulmonary arterial hypertension; LTx, lung transplant; PoPH, portopulmonary hypertension; trepro, treprostenil; 6-MWD, 6-min walking distance.

[a] Proportion of patients started with combination therapy during the course of the study.

recommended that treatment with CCBs only be considered for patients whose fall in mean pulmonary arterial pressure and pulmonary vascular resistance is dramatic and sustained.

Two single-center reports on the long-term follow up of patients with IPAH treated with epoprostenol showed an overall survival of 63% at 3 years and 55% at 5 years.[11,12] Treprostinil seems to have an effect on survival which is similar to that of epoprostenol.[51] This is clearly not the case for inhaled iloprost[52] nor for intravenous iloprost.[53] The improvement in prognosis observed with the oral agents (bosentan, sitaxentan and sildenafil) is clearly related to inclusion of less sick patients, and to the significant proportion of combined therapies in the most recent series. It is also quite remarkable that different series across different countries or continents provide similar survival data within each drug category.

A few observational studies have looked at the long-term outcome in specific PAH subgroups. In a subgroup of 66 patients with PAH related to connective tissue disease previously included in the two bosentan RCTs, Denton and colleagues[54] showed 1- and 2-year survival rates of 86% and 73%, respectively. These data, compared with the 96% and 89% survival reported for patients with IPAH by McLaughlin and colleagues,[55] emphasize again the poorer prognosis of patients with PAH related to connective tissue disease. However, in the recently published, open-label TRUST-study investigating the long-term effects of bosentan in PAH related to connective tissue disease, the authors reported 92% survival at 48 weeks with stabilized quality of life.[56] These results are in agreement with the significant improvement in survival reported by Williams and colleagues[57] in a cohort of 45 patients with PAH related to systemic sclerosis treated with bosentan as first-line therapy compared with a historical group of 47 patients from the prebosentan era. Similarly, Adriaenssens and colleagues[58] analyzed the effects of new therapies (mainly treprostinil and bosentan) in a cohort of patients with PAH related to congenital heart disease. The authors were able to show a prolonged time to clinical worsening (defined by death or inscription on the active list for transplantation) in patients receiving new therapies compared with patients on conservative therapy.

Patients with IPAH listed for lung transplantation have demonstrated a 50% reduction in mortality while on the list (33% vs 64%) when treated with iloprost or bosentan compared with non targeted therapy.[59] It is, however, important to emphasize the better survival of transplanted patients compared with those still waiting for transplantation and treated with iloprost or bosentan. Timely referral of these patients for transplantation centers should therefore be reinforced.

It also appears that a high proportion of patients who are dying from PAH nowadays receive monotherapy with oral agents.[60] This is suggested by the recent report of an American care provider on 821 patients initiated on bosentan between Oct. 1, 2004, and Dec. 31, 2004, and followed over 3 years. Overall survival at 3 years was only 64%. Of 190 patients who died, 169 were on bosentan monotherapy, and only 11% were escalated to prostanoid therapy before death. The vast majority of them had never been referred to an expert center.

In conclusion, it is important to realize that even if meta-analyses of RCTs are not able to demonstrate improved survival with new therapies for PAH, there is a large body of evidence for improved survival to be found in long-term observational studies. However, about 30% of the patients fail to respond even to epoprostenol therapy, and those who remain in NYHA class 3 and 4 have 3-year survival rates of about 30%.[11,12]

Atrial Septostomy for PAH

Rationale

Atrial septostomy has been used for a long time as a palliative procedure for certain congenital cardiac anomalies in children. Its use in patients with PAH is supported by the observation that IPAH patients with a patent foramen ovale live longer than those without intracardiac shunting.[61] Likewise, patients with Eisenmenger syndrome live longer and have heart failure less frequently than patients with IPAH.[62] Shunting decreases right ventricular afterload and increases left ventricular preload, inducing an increase in cardiac output. The drop in systemic arterial oxygen saturation induced by right–left shunting is compensated by increased cardiac output, systemic oxygen transport, and mixed venous oxygen saturation. There is also a decompression of the right ventricle and decreased symptoms of heart failure.

Techniques

The criteria to perform atrial septostomy are an NYHA class of 3 to 4, recurrent syncopal episodes, severe ascites, or clinical deterioration despite maximum medical treatment. The procedure is performed under sedation or light anesthesia, ideally under control of transesophageal echocardiography and careful hemodynamic monitoring titrated for a fall in arterial saturation of 5% to 10%. Once a hole is punctured using a Brockenbrough needle or a radiofrequency catheter, the

fenestration can be made by different techniques: balloon dilation only, a self-expandable stent, a balloon-expandable stent with special technique to get a diabolo shape, or a fenestrated atrial septal defect occluder. In the first case, the hole is progressively dilated with increasingly larger balloons until an arterial saturation of 80% to 85% with FiO_2 21% is obtained.[63] A blade balloon can be used to get a better initial opening with tears, which subsequently can be enlarged.[64] Balloon dilatation is easy and relatively inexpensive. However, the disadvantages are multiple:

- The final size of the connection is difficult to predict
- Multiple sizes of balloons may be needed
- Spontaneous closure of such a connection is usually observed over days to weeks.[65]

Redo-dilation after some weeks with a balloon is dangerous; the fenestration will have fibrous walls, which usually will resist dilation and can rupture with very big balloons, potentially resulting in a broad tear and excessive right to left shunt. By using a stent, it is possible to resize the hole at any time during the course of the disease. After release of the stent, the opening inside can be increased by balloon dilation. A diabolo shape has recently be used to improve stent stability.[66]

Results

In an early review of 62 cases, Rothman and colleagues[67] documented a mortality of 15%. Severe and refractory arterial hypoxemia, due to excessive communication, was the leading cause of death. This emphasizes the need for controlled fenestration. High right atrial pressure and pulmonary vascular resistance were associated with poor outcome, suggesting that septostomy should be performed earlier in the course of the disease. Improvement was reported in 70% of the patients, with resolution of ascites, edema, and syncopal episodes. Sandoval and colleagues[63] reported, in a series of 15 patients, that right atrial pressure decreased by about 5 mm Hg; cardiac index increased by more than 0.5 L/min/m^2, and the 6-minute walk distance was almost doubled. Kerstein and colleagues[64] noted further improvements in hemodynamics 7 to 27 months after septostomy. The complications were transient hypotension, femoral pseudo-aneurysm/arteriovenous fistula, and spontaneous closure in 20% of the cases. Overall, atrial septostomy seems to be a safe procedure in well selected PAH patients. In the modern era, mortality rates are in the range of 0% to 6% for balloon dilatation atrial septostomy[63,65] and for stent fenestration.[66]

Current therapeutic algorithms for PAH all position atrial septostomy as a late therapy and often consider it as a bridge to transplantation.[68,69] It is, however, crucial to have this procedure in mind from the diagnosis on, and certainly when medical treatment is not as satisfactory as it should be according to the already identified prognostic factors.

CTEPH

CTEPH is probably caused by single or recurrent embolization of thrombi that obstruct the pulmonary vascular bed. A history of symptomatic pulmonary embolism, however, is absent in up to 50% of patients who develop CTEPH. The reasons for incomplete resolution of the emboli are not fully understood. During the course of the disease, a distal vessel arteriopathy, caused by overperfusion in nonoccluded lung areas, sometimes becomes predominant. As the only potentially curable cause of pulmonary hypertension, CTEPH should be recognized so that appropriate interventions can be undertaken. The differential diagnosis between PAH and CTEPH is sometimes complicated, as central in situ thrombosis related to low flow can be seen in PAH. The presence of segmental perfusion defects on lung scan is a strong argument for CTEPH. Assessment of operability can be challenging, even when employing modern imaging procedures such as pulmonary angiography, computed tomography (CT) angiography or magnetic resonance tomography.

Pulmonary Endarterectomy

Procedure

Pulmonary endarterectomy (PEA) was introduced in 1958 but not commonly performed until 1985. Most of the procedures have been performed at the University of California at San Diego, but other centers worldwide are now performing the operation. Mortality of PEA has decreased from 22% originally to 4% to 8% in experienced centers.

The technique of bilateral PEA was originally described by Daily[70] and then further refined by Jamieson.[71] PEA is performed through a median sternotomy with cardiopulmonary bypass and periods of deep hypothermic (18°–20°C) circulatory arrest lasting 20 minutes. The superior vena cava is dissected free; the right pulmonary artery is incised, an endarterectomy plane is established and right endarterectomy is performed. The left pulmonary artery is then incised and left endarterectomy is performed. The atrial septum is inspected and a patent foramen ovale, if present, is closed. Recent modifications of the surgical

approach include the use of intraoperative video-assisted angioscopy to enhance visibility in the distal pulmonary arteries[72] and selective antegrade cerebral perfusion with moderate rather than deep hypothermia.[73]

Although pulmonary hemodynamics improve immediately after surgery in most patients, the postoperative course can be complicated. In addition to the common complications of cardiac surgery, patients undergoing PEA can experience severe reperfusion edema and persistent pulmonary hypertension with hemodynamic instability.

Patient selection

Although PEA is the treatment of choice for CTEPH, not all patients are eligible for this surgery. Patients with very high pulmonary vascular resistance (>1200 dyne/s/cm^5) have a high perioperative mortality. The proportion of large vessel obstruction versus small vessel obliteration is a crucial determinant of the response to surgery. A discrepancy between angiographic obstruction and pulmonary hemodynamics should be handled with caution. Partitioning pulmonary vascular resistance by analyzing the pulmonary arterial pressure curve after inflation of the balloon of the Swan Ganz catheter gives information on the presence of small vessel disease and can help to predict postoperative pulmonary arterial pressure and outcome of PEA.[74] Comorbidities, such as morbid obesity, severe interstitial or obstructive pulmonary disease, chronic renal insufficiency, diabetes mellitus, inoperable coronary artery disease, hepatic dysfunction, and advanced age contribute to increased risk and should be considered. Age is not a contraindication to PEA if health status is otherwise good. If PEA is not an option or if an inadequate functional status is obtained after PEA, lung transplantation can be considered.

Long-term outcome

The untreated prognosis of advanced CTEPH is poor, with a 5-year survival of about 20%.[75–77] In contrast, 5-year survival following PEA is around 75%.[78] Most patients undergoing PEA also experience long-term improvements in functional class, exercise capacity and pulmonary hemodynamics.

Medical Treatment

In addition to the mechanical occlusion of a large part of the pulmonary circulation, remodeling of the nonoccluded vasculature—exposed to elevated pressure-related and flow-related physical forces—may contribute to a worsening of pulmonary hypertension. This observation has served as a rationale for the use of PAH-specific treatments in CTEPH.

Preoperative medical treatment

In patients with very high pulmonary vascular resistance and thereby a potentially high risk of perioperative mortality, pretreatment with epoprostenol[79] has been proposed. However, no RCT is available, and there is no clear consensus view other than that PEA should not be delayed by a trial of medical therapy. Any preoperative use of disease-modifying therapy should be within the context of an RCT.

Medical treatment for inoperable patients

Medical therapy is even more widely used for patients with inoperable disease or with persistent pulmonary hypertension after PEA. A recent 16-week large RCT showed significant decrease in pulmonary vascular resistance (24% from baseline) and in NTproBNP in CTEPH patients treated with bosentan, without change in the 6-minute walk distance.[80] A small RCT with sildenafil similarly showed significant improvement in pulmonary vascular resistance without effect on 6-minute walk distance,[81] but in an open-label trial including a larger number of patients, Reichenberger and colleagues[82] were able to show simultaneous improvements in hemodynamics and exercise capacity. A recent paper by Skoro-Sajer and colleagues[75] demonstrated a significant improvement in survival after 1 to 5 years of therapy with subcutaneous treprostinil compared with a matched historical control group. Five-year survival did not, however, reach the value obtained with PEA.

SUMMARY

Lung transplantation used to be the only hope for patients presenting with advanced PAH. The last 20 years has seen the development of disease-targeted drugs, directed toward different pathways of importance to the pathobiology of PAH. Favorable response to medical therapy frequently delays or obviates the need for transplantation. For refractory cases, atrial septostomy can provide significant palliation and serve as a bridge to transplant. For patients with CTEPH and proximal clot, PEA rather than transplantation is usually the surgical option of choice. The diagnosis, assessment, and management of PAH remain complex, underpinning the need to provide care for such patients via specialist centers.

REFERENCES

1. 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.
2. D'Alonzo 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.
3. Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and importance of thrombosis. Circulation 1984;70:580–7.
4. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000; 161:487–92.
5. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002;106:319–24.
6. Yeo TC, Dujardin KS, Tei C, et al. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 1998;81:1157–61.
7. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006;174: 1034–41.
8. Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202–8.
9. Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest 2006;129:1313–21.
10. Torbicki A, Kurzyna M, Kuca P, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation 2003;108:844–8.
11. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780–8.
12. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–82.
13. Provencher S, Sitbon O, Humbert M, et al. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006;27:589–95.
14. Friedman R, Mears JG, Barst RJ. Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997; 96:2782–4.
15. Mandegar M, Fung YC, Huang W, et al. Cellular and molecular mechanisms of pulmonary vascular remodeling: role in the development of pulmonary hypertension. Microvasc Res 2004;68:75–103.
16. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992;327:70–5.
17. Higenbottam T, Wheeldon D, Wells F, et al. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). Lancet 1984;1:1046–7.
18. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med 1990;112:485–91.
19. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296–302.
20. Robbins IM, Christman BW, Newman JH, et al. A survey of diagnostic practices and the use of epoprostenol in patients with primary pulmonary hypertension. Chest 1998;114:1269–75.
21. Conte JV, Gaine SP, Orens JB, et al. The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. J Heart Lung Transplant 1998;17:679–85.
22. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000;132:425–34.
23. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999; 99:1858–65.
24. Higenbottam T, Butt AY, McMahon A, et al. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. Heart 1998;80:151–5.
25. Kuo PC, Johnson LB, Plotkin JS, et al. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997;63:604–6.
26. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care Med 2000;162:1846–50.
27. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol 1999;34:1184–7.
28. Simonneau G, Barst RJ, Galie N, et al. 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.

29. Vachiery JL, Hill N, Zwicke D, et al. Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. Chest 2002; 121:1561–5.
30. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med 2005;172:1586–9.
31. Sitbon O, Manes A, Jais X, et al. Rapid switch from intravenous epoprostenol to intravenous treprostinil in patients with pulmonary arterial hypertension. J Cardiovasc Pharmacol 2007;49:1–5.
32. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. Chest 2006;129: 683–8.
33. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 2010; 55:1915–22.
34. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322–9.
35. Gessler T, Schmehl T, Hoeper MM, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J 2001;17:14–9.
36. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006;174:1257–63.
37. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358: 1119–23.
38. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
39. Galie N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008;371:2093–100.
40. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48–54.
41. Fattinger K, Funk C, Pantze M, et al. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. Clin Pharmacol Ther 2001;69: 223–31.
42. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004;169:441–7.
43. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006;16(47):2049–56.
44. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010–9.
45. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148–57.
46. Barst RJ, Brundage BH, Ghofrani A, et al. Tadalafil improves exercise capacity, health-related quality of life and delays time to clinical worsening in patients with symptomatic pulmonary arterial hypertension. Chest 2008;134:s39003.
47. Macchia A, Marchioli R, Marfisi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007;153:1037–47.
48. Galie N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394–403.
49. Jing ZC, Xu XQ, Han ZY, et al. Registry and survival study in chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 2007;132: 373–9.
50. Rich S, Kaufmann E, Levy PS. The effects of high doses of calcium channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76–81.
51. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest 2006; 129:1636–43.
52. Opitz CF, Wensel R, Winkler J, et al. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Eur Heart J 2005;26:1895–902.
53. Hoeper MM, Gall H, Seyfarth HJ, et al. Long-term outcome with intravenous iloprost in pulmonary arterial hypertension. Eur Respir J 2009;34(1):132–7.
54. Denton CP, Humbert M, Rubin L, et al. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Ann Rheum Dis 2006;65:1336–40.
55. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244–9.
56. Keogh AM, McNeil KD, Wlodarczyk J, et al. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. J Heart Lung Transplant 2007;26:181–7.

57. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart 2006;92:926–32.
58. Adriaenssens T, Delcroix M, Van Deyk K, et al. Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome. Eur Heart J 2006;27:1472–7.
59. Dandel M, Lehmkuhl HB, Mulahasanovic S, et al. Survival of patients with idiopathic pulmonary arterial hypertension after listing for transplantation: impact of iloprost and bosentan treatment. J Heart Lung Transplant 2007;26:898–906.
60. Tankersley MA, D'Albini LD, Ozanich AN, et al. A 36-month survival analysis of patients beginning oral PAH monotherapy: an indication for escalation of therapy? Houston (TX): PHA; 2008.
61. Glanville AR, Burke CM, Theodore J, et al. Primary pulmonary hypertension. Length of survival in patients referred for heart–lung transplantation. Chest 1987;91:675–81.
62. Hopkins WE, Ochoa LL, Richardson GW, et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;15:100–5.
63. 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.
64. Kerstein D, Levy PS, Hsu DT, et al. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation 1995;91: 2028–35.
65. 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.
66. Troost E, Delcroix M, Gewillig M, et al. A modified technique of stent fenestration of the interatrial septum improves patients with pulmonary hypertension. Catheter Cardiovasc Interv 2009;73:173–9.
67. Rothman A, Sklansky MS, Lucas VW, et al. Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. Am J Cardiol 1999;84:682–6.
68. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007;131:1917–28.
69. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243–78.
70. Daily PO, Dembitsky WP, Iversen S. Technique of pulmonary thromboendarterectomy for chronic pulmonary embolism. J Card Surg 1989;4:10–24.
71. Jamieson SW, Auger WR, Fedullo PF, et al. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29-month period. J Thorac Cardiovasc Surg 1993;106:116–26.
72. Dartevelle P, Fadel E, Chapelier A, et al. Angioscopic video-assisted pulmonary endarterectomy for postembolic pulmonary hypertension. Eur J Cardiothorac Surg 1999;16:38–43.
73. 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.
74. 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.
75. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. J Thromb Haemost 2007;5:483–9.
76. Riedel M, Stanek V, Widimsky J, et al. Long-term follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest 1982;81:151–8.
77. Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001;119:818–23.
78. Archibald CJ, Auger WR, Fedullo PF, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 1999;160: 523–8.
79. Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. Eur Respir J 2004; 23:595–600.
80. Jais X, D'Armini AM, Jansa P, et al. 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.
81. Suntharalingam J, Treacy CM, Doughty NJ, et al. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest 2008;134:229–36.
82. Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. Eur Respir J 2007;30: 922–7.