State of the Art

Recent Advances in the Treatment of Pulmonary Hypertension

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Although for decades clinicians have had little to offer their patients with pulmonary arterial hypertension (PAH), exciting biomedical research has now begun to shed new light on a rare but important clinical topic. Research has led to a better understanding of the mechanisms behind this common final pathway of many conditions and promising therapies are emerging. Indeed, the number of clinical trials published yearly has quadrupled over the last decade (Figure 1). Though many unanswered questions remain, these exciting breakthroughs give both patients and carers much to hope for.

Overview of the illness

PAH is a chronic, persistent elevation in pulmonary artery pressure without evidence of left heart failure. It is defined as any elevation of mean pulmonary artery pressure greater than 25 mmHg at rest or 30 mmHg with exercise, although clinical studies usually focus on patients with moderate to severe pressure elevations. Every year one new person in 1,000,000 will be diagnosed. It is more prevalent in women and often affects them in early adult life. Irrespective of cause, in later stages it has a relatively homogenous clinical picture.

The disorder arises from a variety of aetiologies, and classification schemes have recently been redefined based on better understanding of the initial pathologic insult. General categories include connective tissue disorders, systemic sclerosis, chronic pulmonary embolism, congenital heart defects (namely Eisenmenger syndrome, or pulmonary hypertension due to left-to-right shunts), drugs, and familial forms.[1] Though schemes are in constant modification,[2] the most recent classification breakdown is the Evian classification shown in table 1.[3] Still, in a large number of cases no clear aetiology is found.

Symptom onset is gradual. Patients usually come to medical attention after the disease has progressed considerably. Often it is first detected by echocardiography. Dyspnoea is the hallmark symptom, though its severity is not necessarily dependent on the degree of pressure elevation. Syncope may also occur, usually from transient drops in cardiac output due to under filling of the left ventricle. Physical manifestations include elevation of the jugular venous pulse, a large v wave of tricuspid regurgitation (TR), a holosystolic murmur at the lower sternal border, and a palpable right ventricular heave. Often a loud pulmonary component of the second heart sound can be heard. Cyanosis and clubbing may be present in hypoxic patients. The lung exam is often normal. Cool extremities from reduced cardiac output may be appreciable late in the course.

Prognosis is universally poor. From a registry started in 1980, median survival was only 2.8 years, with 68% survival at 1 year,

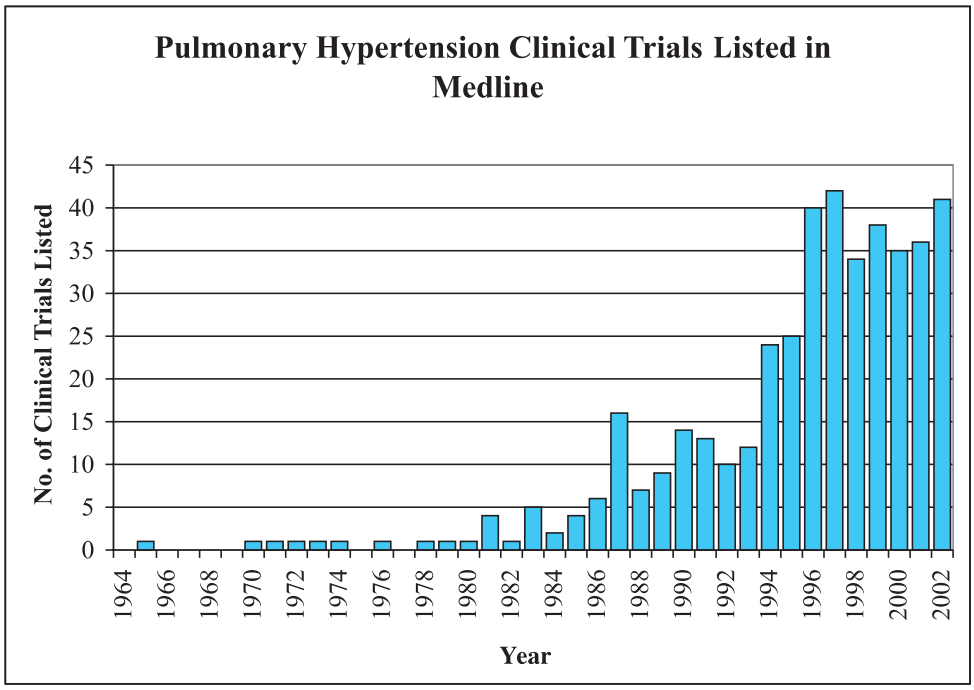

Figure 1. Number of clinical trials on pulmonary hypertension listed in Pubmed Medline index per year, showing explosive growth in the area over the last decade.

48% at 3 years, and 34% at 5 years[4] (Figure 2). Based on this registry, predictors of mortality were pulmonary artery pressure (PAP), right atrial pressure (RAP), and cardiac index (CI).[5] Studies done since have shown a variety of prognostic tools, among them age,[6] oxygen consumption and systolic blood pressure.[7] Other reports have shown the prognostic value of exercise tolerance, functional class, response to adenosine, and sustained improvements of CI and PAP.[8] D-dimer level may also have prognostic importance.[9] Echocardiographically, RA size and TR jet were also predictive of survival.[10]

Established therapies

Oxygen

Because of its vasodilatory effects, oxygen is an acceptable therapy for patients even without hypoxia. Reduction in pulmonary vascular resistance (PVR) from oxygen administration has been demonstrated,[11,12] with more appreciable effects in younger patients.[13] Still, the degree of response depends on disease aetiology.[14] In fact, oxygen may have negative effects in PAH associated with connective tissue disease.[15] In adult patients with Eisenmenger syndrome there is no evidence for its continued use,[16] but it may be beneficial in children.[17] There are no data to support routine oxygen administration for improving long-term outcome in any group.

Warfarin

PAH from any cause is associated with thrombosis in the distal pulmonary vessels.[18] Although the exact mechanism for this is not clear, warfarin plays a role in the treatment of PAH. Warfarin therapy has been shown to reduce mortality, particularly in patients who do not respond initially to calcium channel blockers.[19] Warfarin is therefore recommended in all patients with PAH,[1] although uncertainties exist concerning the routine administration of warfarin for patients with Eisenmenger syndrome.[20]

Calcium channel blockers

Since calcium channel blockers have both systemic and pulmonary vasodilatory action, they have been used in PAH treatment for years. There appears to be a subset of patients (<10%) who respond acutely to calcium blockers (meaning a drop in mean PA pressure of at least 10 mmHg or to <40 mmHg),[21] and in these patients continued therapy is particularly beneficial[1] and thus recommended.[22] However, re-

Table 1. Aetiology of Pulmonary Hypertension (Evian Classification).

1. Pulmonary Arterial Hypertension
    - 1.1 Primary Pulmonary Hypertension
        - Sporadic
        - Familial
    - 1.2 Related to:
        - Collagen Vascular Disease
        - Congenital Systemic to Pulmonary Shunts
        - Portal Hypertension
        - HIV Infection
        - Drugs
            - Anorexigens
            - Other
        - Persistent Pulmonary Hypertension of the Newborn
        - Other

2. Pulmonary Venous Hypertension
    - 2.1 Left Sided Atrial or Ventricular Heart Disease
    - 2.2 Left Sided Valvular Heart Disease
    - 2.3 Extrinsic Compression of Central Pulmonary Veins
        - Fibrosing Mediastinitis
        - Adenopathy/Tumours
    - 2.4 Pulmonary Veno-occlusive Disease
    - 2.5 Other

3. Pulmonary Hypertension Associated with Disorders of the Respiratory System/Hypoxia
    - 3.1 Chronic Obstructive Pulmonary Disease
    - 3.2 Interstitial Lung Disease
    - 3.3 Sleep Disordered Breathing
    - 3.4 Alveolar Hypoventilation Disorders
    - 3.5 Chronic Exposure to High Altitude
    - 3.6 Neonatal Lung Disease
    - 3.7 Alveolar-Capillary Dysplasia
    - 3.8 Other

4. Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease
    - 4.1 Thromboembolic Obstruction of Proximal Pulmonary Arteries
    - 4.2 Obstruction of Distal Pulmonary Arteries
        - Pulmonary Embolism
        - In-situ Thrombosis
        - Sickle Cell Disease

5. Pulmonary Hypertension due to Disorders Directly Affecting the Pulmonary Vasculature
    - 5.1 Inflammatory
        - Schistosomiasis
        - Sarcoidosis
        - Systemic Sclerosis
        - Systemic Lupus Erythematosis
    - 5.2 Pulmonary Capillary Haemangiomatosis

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duced myocardial contractility may result, especially from older dihydropyridines, and their use has been drastically diminished in recent years. Amlodipine and felodipine have fewer negative effects on cardiac contractility and should be used preferentially when heart failure is suspected. Calcium channel blockers are not felt to be efficacious in patients with systemic sclerosis.[23]

Heart failure therapy

Diuretics and digoxin, both utilised extensively for the treatment of congestive heart failure, have been used to treat symptoms of right-sided heart failure. Published data about these drugs in PAH are limited. The immediate effects of digoxin have been studied in pulmonary hypertension, and produced a measurable increase in CI.[24] This warrants its general use, though no long-term data are available. Although diuretics have a role in volume control, caution should be taken. They are potentially harmful if intravascular volume depletion leads to a reduction in ventricular filling and thus reduced cardiac output. In patients with Eisenmenger syndrome, diuretics can also increase right to left shunting as well as worsen symptoms of hyperviscosity, and thus should be used with caution.

Acute testing

When PAH is first suspected, the patient should be offered a right heart catheterisation to confirm the diagnosis, exclude left heart disease, and to test for acute haemodynamic reversibility with vasodilators. Such a trial is often used to stage further therapy. This can be done using intravenous adenosine[25] or inhaled nitric oxide, which some consider to be the gold standard.[26] Since an elevation in cardiac output alone can cause a drop in PVR, a positive response is defined as both a drop in PVR (defined differently by authors but usually at least a 10 mmHg drop in mean PA pressure or a fall of PVR of 20% from baseline) and a rise in CI. However, usually only a fraction of patients will show an acute response, and some of the therapies discussed below are beneficial even in those who do not.

Advanced medical therapies

Prostacyclin

The first drug to offer a significant breakthrough in PAH treatment was intravenous prostacyclin or epoprostenol (Flolan). Primarily a vasodilator, it also has a role in improving CI.[27] Side effects can be limiting and include nausea, vomiting, dizziness, light-headedness, and flushing. An obvious obstacle is the need for constant intravenous access with its inherent risk of line infection, etc. If the infusion is stopped patients may experience rebound symptoms, which can trigger decompensation. Thus, a decision to start therapy must be made with these issues in mind. With any therapy, hard clinical end points can be difficult to demonstrate. But the six minute walk test, where the patient walks for six minutes at their own pace to cover maximum distance, is a simple and reproducible end point often used in clinical trials.[28]

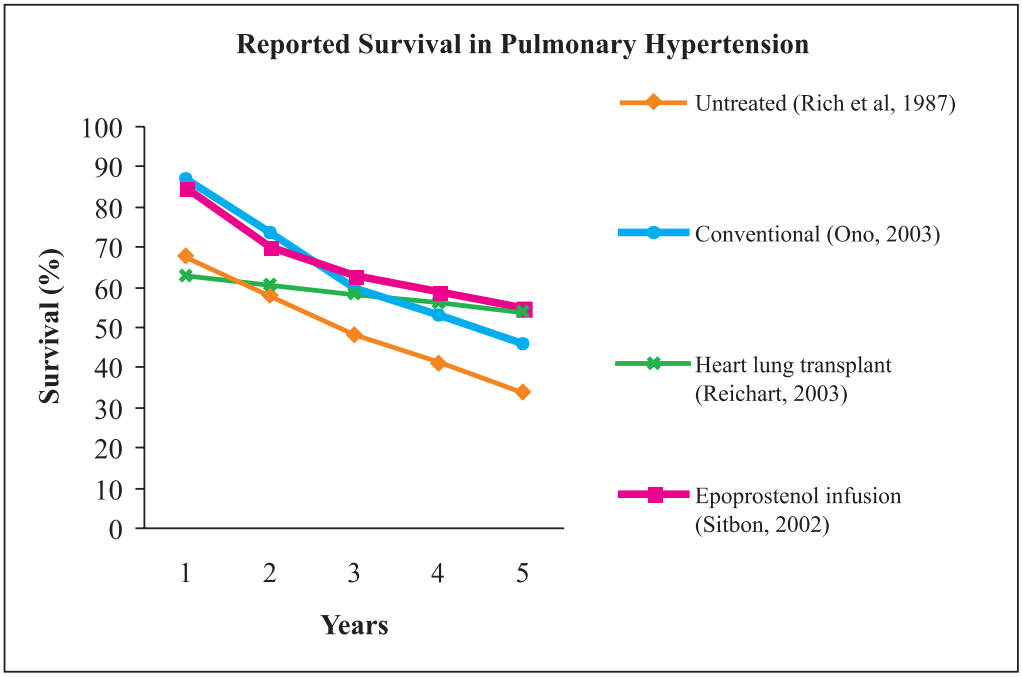

Figure 2. Comparison of reported survival curves of various treatment regimens for pulmonary arterial hypertension.

Prostacyclin has been shown to improve exercise performance, haemodynamics, and quality of life[29] in patients with primary PAH and those in whom it is secondary to scleroderma.[30] Similar results have also been reported in children.[31] In patients with systemic lupus erythematosus, prostacyclin may stop disease progression but otherwise there is little improvement.[32] After a year of treatment the change in PVR may even be lower than that measured acutely,[33] though these findings have been contradicted by other investigators.[34] Furthermore, long-term improvement in survival versus historical controls has been clearly demonstrated[6,8] even up to 5 years after initiation of therapy[35] (Figure 2). At least one study has shown better long-term outcome from prostacyclin than lung transplant,[36] even when there had been no response to vasodilators before starting treatment. Because of the above evidence, patients in NYHA class III or IV should be offered intravenous therapy, but there is no role for this in patients with few or no symptoms.

Other delivery methods for prostacyclin

To avoid the shortcomings of intravenous administration, newer forms of prostacyclin are being developed including inhaled (iloprost/treprostinil), subcutaneous (uniprost/treprostinil) and oral forms (beraprost). Iloprost was compared to epoprostenol and had similar effects in 21 patients.[37] However, frequent inhalations are required because of its short half-life. Subcutaneous prostacyclin has been shown to improve 6-minute walk distance,[38] but erythema and induration at the site of injection can be problematic.

Oral prostacyclin has obvious advantages in delivery. It has also been shown to increase short-term exercise tolerance.[39] However, in a separate study of 116 patients, the initial improvement in 6-minute walk test was not seen after 9-12 months and side effects were abundant.[40] Overall, however, in a group of 20 patients with chronic thromboembolism, beraprost reduced PVR and improved 5-year mortality compared to 23 similar patients on conventional therapy.[41] These were patients to whom surgery could not be offered, and the study was not randomised. Still, the study reported the best survival data in PAH to date in this subset (76% after 5 years). It is not known whether the same degree of survival advantage will be applicable to other patient groups.[42]

Inhaled nitric oxide

The vasodilator properties of inhaled nitric oxide (NO) have definite clinical utility in PAH.[43] It is cumbersome for long term use, but often finds use in the intensive care setting,[44] including the treatment of neonates.[45] It may have a role in the peripartum management of pregnant women with PAH, although pregnancy remains a high risk endeavour for these patients and is thus strongly contraindicated.

Bosentan

Bosentan is a non-specific dual endothelin (ET) receptor antagonist, the first of several drugs that are now included in its class. Endothelin is raised in PAH and causes vasoconstriction, smooth muscle proliferation and hypertrophy, and raises renin-angiotensin activity leading to fluid retention. Bosentan causes vasodilatation in both the pulmonary and systemic circulation.[46] Several studies in patients with rheumatic disease or scleroderma have shown improvements in functional class and 6-minute walk test after six to twelve months of therapy,[47] as well as improved preliminary haemodynamics and improved echocardiographic parameters (including RV size) when compared to placebo.[48] The drug has a good safety and efficacy profile in both adults and in children.[49] It has been associated with improved survival in rats.[50] Bosentan is non-selective for both endothelin receptor subtypes, ET-a and ET-b. Other drugs with selective receptor affinity have been developed, but there is uncertainty as to which subtype is more important. BQ-123 is selective for ET-a, and has been studied in 26 patients with good results except in those with congenital heart disease.[51] Sitaxsentan is another ET-a selective antagonist and can improve both exercise capacity and haemodynamics after 12 weeks.[52] On the other hand, the ET-b receptor may be involved in an important negative-feedback loop that blocks ET production.[53]

Sildenafil

Sildenafil is an inhibitor of phosphodiesterase (PDE), an enzyme that breaks down cAMP and cGMP, which play a role in cell signalling pathways leading to vasoconstriction. The PDE family of enzymes consists of at least 11 subtypes found in many different organs, especially vascular smooth muscle and myocytes.[54] The net effect of their inhibition is vasodilatation. Sildenafil has been shown to block the vasoconstrictive effects of hypoxia in normal patients.[55] Acutely, sildenafil reduces PAP and increases CI.[26] Sildenafil has also been shown to be equally as effective as inhaled NO in acutely improving haemodynamics.[26] Importantly, no negative in-

otropic effects have been demonstrated, which is a potential problem given that PDE 5 is also found in cardiomyocytes. Experience with sildenafil in paediatric patients with primary PAH is so far limited.[56] As yet, no long-term survival benefits following sildenafil treatment have been demonstrated.

Combination therapy

Since several diverse classes of therapy show great potential in the treatment of PAH, will there be a role for combination therapy? Though little is known yet about combined effects, studies are under way. Importantly, there do not seem to be adverse effects from combination vasodilator therapy. Sildenafil has been combined with epoprostenol and shown to improve acute haemodynamics[57] and 6-minute walk distance[58] without adverse effects. The combination of sildenafil and inhaled NO was more effective at raising CI than either therapy alone.[26] Tolafentrine, another PDE antagonist, when combined with inhaled iloprost, enhanced the effects of iloprost without ill effects.[59] Iloprost and sildenafil have been combined safely in other studies.[60] However, no long-term survival benefits from such combinations have been demonstrated so far.

Future pharmacological targets

The fact that vasodilators do not fully reverse the disease underscores the understanding that its pathogenesis involves more than just vasoconstriction. Cellular proliferation and vascular remodelling explain the lack of complete reversibility with vasodilatation. Numerous reports speculate about other potential targets for therapy. These include thrombopoietin,[61] 5-HTT,[62] vasoactive intestinal peptide,[63] adrenomedullin,[64] arginine in sickle cell patients[65] and various signalling peptides.[66] In addition, there are possible associations between PAH and human herpes virus 8,[67] hyperhomocystinaemia,[68] and the ACE-DD genotype.[69] With so many avenues currently being explored, there is great hope for additional pharmacological options in the near future for patients with PAH.

Surgical therapies

Atrial septostomy

Since patients with Eisenmenger physiology and chronic right to left shunting seem to have better survival than patients with isolated PAH, the idea of creating such a shunt has obvious merits. Atrial septostomy, usually through a transseptal catheter approach, unloads the right atrium, improves left ventricular filling and raises cardiac output, albeit at the expense of cyanosis. Results are mixed, partly because the procedure is still largely only offered to end-stage patients. An early series of 12 patients demonstrated improved ascites and syncope in 6, but no improvement in the remainder.[70] Atrial septostomy in this setting is seen as a bridge to transplantation.[71] In a recent publication, out of 17 patients undergoing the procedure electively, 5 died in follow-up, 5 underwent heart-lung transplant, and 7 survived with some symptomatic improvement.[72] Thus, certain patients may benefit greatly from the procedure. However, tertiary expertise is clearly required as the atrial septostomy procedure carries a significant mortality (roughly 16%)[73] and procedural morbidity (renal dysfunction, catheter related vascular injury, acute hypoxia).

Thrombectomy

For patients with known chronic thromboembolic pulmonary hypertension, surgical removal of embolised clot has been developed as a solution. The procedure is complex and only performed in a handful of institutions worldwide.[74] It involves circulatory arrest and thus surgical morbidity and mortality are not trivial. Still, a centre of excellence has recently reported an operative mortality of 4.4% regardless of extent of clot or degree of RV dysfunction,[75] underscoring the need for centralised services in this rather challenging field. After a successful thrombectomy clinical results can be excellent. Prostacyclin is still beneficial when given before thrombectomy.[76]

Transplantation

Despite the therapeutic advances discussed above, inevitably some patients will have significant limitation despite the optimal pharmacological treatment. In these patients, lung transplantation should be seriously considered. Whether a recipient should receive one or both donor lungs is still debated. Bilateral lung transplant may be preferred over single lung in primary PAH recipients, especially those with higher PAP, whereas in secondary PAH there is no clear advantage to either.[77] Heart-lung transplant is offered for patients with right heart failure or complex congenital heart disease. Heart- lung transplant has a 54% survival at 5 years[78] (Figure 2). At one German centre, survival was best in those with Eisenmenger syndrome (74% at 5 years)

versus thromboembolic PAH (60% at 5 years) and primary PAH (35% at 5 years).[79] Elsewhere in the literature it has been difficult to demonstrate any mortality advantage of heart-lung transplant in Eisenmenger syndrome,[80] since many of these patients have fairly good survival. Generally, waiting times are long, however, due to organ shortage. In a survey involving 35 centres worldwide, waiting times were 16.8 months for lung, and 21.3 months for heart-lung,[81] with the longest waits occurring in the United States. Survival is most often limited by chronic allograft rejection including bronchial obstruction.[82]

Congenital heart disease (Eisenmenger syndrome)

Though patients with PAH and associated congenital heart disease, particularly Eisenmenger syndrome, are often considered jointly in studies of PAH, they represent a distinct patient group, while additional data are required. Limited conclusions can be drawn from preliminary studies. Oxygen therapy has not been shown to convey survival benefits.[16] Prostacyclin has been shown to improve pulmonary haemodynamics and functional capacity in patients with intracardiac shunts. However, many of these patients were not cyanosed,[83] and in general there is uncertainty as to the selection criteria and timing of intervention. Selective endothelin A receptor antagonists also have a favourable acute haemodynamic response in Eisenmenger patients.[51] Early safety data on Bosentan are encouraging and show distinct promise.[84] Results from a larger multicentre randomised study are anticipated. Some advocate that patients with congenital heart disease should be treated in much the same way as those with other forms of PAH,[85] although this is not universally accepted.

Conclusions

Pulmonary arterial hypertension has been associated with limited therapeutic options and poor prognosis for decades. We are, however, witnessing exponential growth in both pathologic understanding and therapeutic success. Although results from clinical trials may still be in the early stages and the long-term outcomes have not yet been fully elucidated, recent research has generated much confidence in therapeutic interventions. Future improvements are likely, and will involve specific molecular targets, advanced methods of drug delivery, and combination therapies. Furthermore, it is reasonable to expect that advances in the prevention and early detection of PAH will also arise from today's advances in the biochemical lab and imaging modalities. Without a doubt, patients with PAH and their caring physicians can maintain an optimistic outlook.

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