GENERAL CARDIOLOGY

Pulmonary arterial hypertension:
new ideas and perspectives

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The classic way to describe a disease is to begin with nomenclature, definitions, and classifications. A fortunate coincidence gives us the opportunity today to start from the very early stages of pathophysiologic processes, a gene mutation. In fact, in a recently published paper¹ the gene involved in familial primary pulmonary hypertension (PPH) has been described and the finding has been confirmed by a second independent group.²

Genetics

Familial PPH has an incidence of at least 6% among all cases of PPH; it is an autosomal dominant disorder with reduced penetrance and genetic anticipation, and has been mapped to a locus designated *PPH1* on chromosome 2q33. The mutations interest the gene *BMPR2*, encoding a transforming growth factor β (TGF- β) type II receptor (BMPR-II) that is located in the cell membrane.³ TGF- β is representative of a large family of small polypeptides that have many different effects on growth and development. In fact, depending on the cell type, the TGF- β pathway influences many different processes such as growth, mobility, angiogenesis, immunosuppression, and apoptosis. Interestingly, mutations in the *BMPR-II* gene have also been found in more than 20% of human colorectal cancers. A link between PPH and tumorigenesis has been suspected in the past,⁴ based on exuberant proliferative vascular changes of pulmonary arteries and on monoclonal endothelial cell proliferation of plexiform lesions.⁵ *BMPR2* germline mutations have been detected in 55% of cases of familial PPH and also in 26% of sporadic cases of PPH, raising the possibility that familial cases are more frequent than expected.⁶ Until now 46 different mutations of *BMPR2* have been identified in PPH patients, and most of them produce a loss of function for the *BMPR-II* receptor.⁷ Thus, haploinsufficiency seems to be the molecular mechanism that initiates PPH. On the other hand, the high frequency of “true” sporadic PPH cases and reduced penetrance of familial PPH suggests that additional triggers are required for the development of the disease. Such mechanisms could be a second somatic mutation within an unstable *BMPR-II* pathway⁸ or any stimulus able to dis-

Genetics of primary pulmonary hypertension

- A family history is detectable in at least 6% of cases of primary pulmonary hypertension (PPH)
- Familial PPH is an autosomal dominant disorder with reduced penetrance and genetic anticipation
- Mutations of type II bone morphogenetic protein receptor gene (*BMPR2*) have been detected in 56% of families with PPH and 26% of sporadic cases of PPH
- Mutations are likely to produce a loss of function in the transforming growth factor β (TGF- β) pathway that is involved in cell proliferation and apoptosis
- Reduced penetrance suggests that additional triggers besides genetic mutations are required for the development of the disease

rupt pulmonary vascular cell growth control. It is obvious that the identification of the gene responsible for familial PPH and for some cases of sporadic PPH represents a milestone in our understanding of this severe condition, and it will provide new insights into research strategies in pulmonary hypertension.

Pathology and classification

Even if in the future genetic analysis can help us to identify patients at the very early stages of the disease,⁹ currently when a PPH patients become symptomatic the characteristic obstructive changes of the pulmonary vascular bed are fully expressed. The lesions are characterised by cellular proliferation that involves the intima, media, and adventitia of the small pulmonary arteries and arterioles.¹⁰ Plexiform lesions that are considered as a proliferation of endothelial cells, smooth muscle cells, and myofibroblasts with formation of microvessels, are often present. Thrombosis in situ, typically involving the small arteries or veins, can co-exist with any of the previous findings. This picture has been defined as proliferative pulmonary vascular disease and is characteristic not only of PPH but is present in other conditions with precapillary pulmonary hypertension—for example, collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension, and HIV infection.

The identical pathologic features represent a strong rationale for categorising all the above conditions in a single group of diseases defined according to the new World Health Organization classification as pulmonary arterial hypertension (PAH) (table 1).¹¹ In addition, all these patients share a similar clinical picture and are treated medically in the same way. These aspects underscore the philosophy of the new

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WHO classification that is intended to group diseases with similar pathologic, pathophysiologic, clinical, and therapeutic features. The second category—pulmonary venous hypertension—identifies all the conditions characterised haemodynamically by postcapillary pulmonary hypertension that are usually caused by left heart diseases. The third category includes cases in which pulmonary hypertension is associated with disorders of the respiratory system and/or hypoxaemia. The fourth category—pulmonary hypertension caused by chronic thrombotic and/or embolic disease—lists the states characterised by mechanical obstruction situated in the main, lobar, and segmental pulmonary arteries. Interestingly, patients with chronic thromboembolic pulmonary hypertension (CTEPH) seem to develop in the unobstructed arteries and arterioles, submitted to high flow-high pressure stress, pathological changes similar to those considered specific for PAH. Those changes are probably responsible for progressive haemodynamic deterioration, despite the absence of recurrent embolic episodes. The final category—pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature—comprises inflammatory diseases such as sarcoidosis, schistosomiasis, and a rare condition called pulmonary capillary haemangiomatosis.

The new WHO classification will help the diagnostic process as well as the definition of categories to be included in treatment trials. Interestingly the term “secondary” pulmonary hypertension, widely used in the past, is no longer recommended as pathophysiologic links between the underlying conditions remain unproven beyond epidemiological clustering of some diseases with pulmonary hypertension. Recent genetic advances give insights and new impetus to research into why patients with similar associated conditions may or may not develop pulmonary hypertension.

Diagnosis and assessment

Relatively early detection of pulmonary hypertension would be possible in the era of Doppler echocardiography if only appropriate diagnostic work up was not so commonly delayed, especially in “healthy” young individuals stubbornly complaining of unexplained mild functional impairment. New classification and uniform treatment for patients with PAH, together with availability of non-invasive imaging tests, greatly simplified the diagnostic procedures required for therapeutic decision making. Venous and hypoxic pulmonary hypertension are readily diagnosed within the framework of routine clinical tests such as chest radiography, echocardiography, and pulmonary function tests. A perfusion lung scan is essential for identifying patients with chronic thromboembolic disease who should follow different diagnostic pathways towards assessing the indications for surgical intervention. In PAH patients right heart catheterisation is still

Table 1 World Health Organization new diagnostic classification¹¹

1. Pulmonary arterial hypertension
1.1 Primary pulmonary hypertension
(a) Sporadic
(b) Familial
1.2 Related to:
(a) Collagen vascular disease
(b) Congenital systemic to pulmonary shunts
(c) Portal hypertension
(d) HIV infection
(e) Drugs/toxins
(1) Anorexigens
(2) Other
(f) Persistent pulmonary hypertension of the newborn
(g) Other
2. Pulmonary venous hypertension
2.1 Left sided atrial or ventricular heart disease
2.2 Left sided valvar heart disease
2.3 Extrinsic compression of central pulmonary veins
(a) Fibrosing mediastinitis
(b) Adenopathy/tumours
2.4 Pulmonary veno-occlusive disease
2.5 Other
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
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 caused by chronic thrombotic and/or embolic disease
4.1 Thromboembolic obstruction of proximal pulmonary arteries
4.2 Obstruction of distal pulmonary arteries
(a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
(b) In situ thrombosis
(c) Sickle cell disease
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
5.1 Inflammatory
(a) Schistosomiasis
(b) Sarcoidosis
(c) Other
5.2 Pulmonary capillary haemangiomatosis

considered mandatory for initial prognostic evaluation and assessment of pulmonary vasoreactivity.

Of the various drugs available, inhaled iloprost and inhaled nitric oxide are increasingly used for this purpose in referral centres. Nitric oxide is particularly interesting because it does not affect systemic circulation and hardly modifies cardiac output, despite significant pulmonary vasodilatation observed in some responders. Therefore, calculation of the true effect on vascular tone is more reliable. However, with emerging potent oral and inhaled drugs, combining vasodilatory and antiproliferative properties, the issue of invasive testing for pulmonary vasoreactivity in selecting treatment may lose its importance. “True” responders, represented by patients in whom the acute fall of both pulmonary artery pressure and pulmonary vascular resistance is in the range of 30–50%, will likely be identified by real time Doppler echocardiography performed during inhalation of nitric oxide or iloprost. There is a tendency to avoid treatment with calcium channel blockers in patients with severe pulmonary hypertension, because of concern that the potentially detrimental side effects of this class of drugs will outweigh their benefits in less responsive patients.

In the prostanoids era the main challenge is now to assess the results of long term treatment. This is especially important for intravenous epoprostenol in order to steer between, on the one hand, unnecessary dose escalation leading to side effects, faster tachyphylaxis, and excessive costs, and on the other, ineffective doses of the active substance. Repeated catheterisation is clearly a poor option, while the six minute walk test has a growing importance, especially in the light of recent data indicating the prognostic implications of this test in patients with PPH.¹² While standard echocardiography virtually failed as a non-invasive test for long term monitoring of effects of treatment in severe pulmonary hypertension,¹³ new ideas based on Doppler assessment of indices of pulsatile right heart haemodynamics offer some promise.¹⁴ There is no alternative to Doppler echocardiography when screening high risk populations. Importantly, recent WHO recommendations allow the diagnosis of mild pulmonary hypertension based on systolic pulmonary pressure exceeding 40 mm Hg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of 3.0–3.5 m/s.¹¹ However, anecdotal reports on false positive Doppler diagnosis of pulmonary hypertension as well as the risk of missing early stages of the condition, apparent only during exercise, must be taken into account.¹⁵ On the other hand, stress Doppler echocardiography seems to be able to identify genetically predisposed subjects with normal rest haemodynamics and an abnormal rise in systolic pulmonary artery pressure on exercise.⁹ However, evaluation of the level and changes in mean pulmonary pressure is virtually impossible using the Doppler method.

Therapeutic strategy

Medical treatment

The treatment of PPH until a few years ago was only symptomatic and based on the experiences of few specialised centres. In fact, the evidence of the favourable effect of oral anticoagulation and calcium channel blockers came from studies experiencing methodological problems. In any case, anticoagulation may not be enough to revert or even stabilise vascular changes, and calcium channel blockers are effective in only a small proportion of PPH patients that respond to acute pharmacological challenges (15–25% according to response definition).¹⁶

The 1990s can be considered as the prostacyclin era, even if the first experiences with this compound started a decade earlier. Two randomised studies showed that continuous intravenous infusion of epoprostenol, a stable preparation, improved functional capacity, haemodynamics, and survival of New York Heart Association (NYHA) functional class III/IV PPH patients when compared to “conventional” treatment.^{17 18} Epoprostenol treatment can be considered “unconventional” because its very short half life (3–5 minutes)

Diagnosis and assessment

- Non-invasive early detection of pulmonary hypertension is possible by traditional Doppler echocardiography at rest or on exercise
- Venous and hypoxic pulmonary hypertension are diagnosed with routine clinical tests such as chest radiography, echocardiography, and pulmonary function tests
- Segmental defects on perfusion lung scan suggest chronic thromboembolic pulmonary hypertension and require a different diagnostic pathway addressing the feasibility of surgical thromboendarterectomy
- Right heart catheterisation is still considered mandatory for initial prognostic evaluation and assessment of pulmonary vasoreactivity in patients with PAH
- Nitric oxide is the substance of choice to test for acute vasoreactivity
- The current tendency is to define acute responders as patients in whom the acute fall of both pulmonary artery pressure and resistance is in the range of 30–50%
- Six minute walk test is useful in the assessment of functional impairment and prognosis, and in the evaluation of long term therapeutic response
- The usefulness of Doppler parameters of pulsatile right heart haemodynamics as indices of prognosis and treatment effect is under scrutiny

means it has to be administered intravenously, which requires “tunnelled” central venous catheters and portable pumps for the continuous administration of the drug. However, significant clinical and functional improvement may be expected, also in patients not responding to pulmonary vasodilatation during acute tests and previously considered to have irreversible vascular changes.

Initially, epoprostenol treatment was viewed as providing a bridge to transplantation in advanced cases of PPH, but recent experience has established this approach as a possible alternative to transplantation. In fact, the improvement in some patients is so great that they no longer fulfil the criteria for being put on a waiting list for transplantation. A reasonable approach may therefore be to consider patients in NYHA functional class III/IV for initiation of epoprostenol treatment and concurrent listing for transplantation, and then maintain on the waiting list only those patients who do not improve substantially or who deteriorate after an initial improvement. By limiting the number of waitlisted patients in this way, it may be possible to reduce the waiting time for lung transplantation.

The favourable effects of epoprostenol have been shown not only in PPH patients but also in almost all the conditions in the PAH category according to the WHO classification (table 1).¹¹ Nevertheless, epoprostenol treatment requires that patients and relatives are given adequate training for the appropriate management of the delivery system, in order to minimise severe side effects such as sepsis and pump malfunctions, which may be life threatening. Moreover, the development of tolerance to the drug means that the doses must be increased over time in order to maintain efficacy, thus increasing both side effects and costs. Alternative ways of administering prostacyclin are under active investigation in order to improve the risk-benefit profile and cost effectiveness of treatment. Currently, three stable prostacyclin compounds—uniprost, iloprost, and beraprost, administered by the subcutaneous, inhaled and oral routes, respectively—are under scrutiny by controlled clinical trials.

Uniprost is infused subcutaneously by small portable pumps similar to those used for administering insulin to diabetic patients; the system requires no more than 15 minutes every three days for management. A randomised, placebo controlled, double blinded study involving 470 patients with NYHA class III/IV PAH has been recently completed and preliminary results have been reported in recent meetings of the European Society of Cardiology and American Heart Association. Favourable and significant effects were observed on functional capacity (as assessed by the six minute walk test), symptoms, and haemodynamics. The most frequent side effect was pain and redness at the infusion site, which limited the dose increase in a proportion of cases and prevented use of the drug in about 8% of patients.

Iloprost is a stable analogue of prostacyclin available for intravenous, oral, and inhalation use. Several open, uncontrolled studies have reported favourable effects of inhaled iloprost on functional capacity and haemodynamics of patients with PAH.^{19, 20} Administration of iloprost requires a special inhalation device in order to produce particles of a certain diameter and to limit ambient spillover of the drug. A major limitation of this administration method is the short duration of effect, requiring up to 12 inhalations a day to achieve consistent clinical efficacy in some patients. A randomised, placebo controlled, double blind study is currently underway in Europe in patients with PAH. The results should be available in 2001 and they will indicate definitively the extent of the long term effects of this new treatment.

Beraprost sodium is the first chemically stable and orally active prostaglandin I₂ analogue available for clinical studies. Preliminary, uncontrolled experiences mainly in Japan have shown that long term treatment with this compound is able to determine favourable clinical haemodynamic and prognostic effects in patients with PPH.²¹ Currently, two randomised, placebo controlled, double blind studies in PAH patients are in progress in the USA and Europe.

Recently, endothelin-1 (ET-1) receptor antagonists, a class of drug available for oral administration, have undergone evaluation in PAH patients. The rationale for using these drugs is linked to the raised concentrations of ET-1, a potent vasoconstrictor and mitogenic substance, both in plasma²² as well as in lung tissue²³ of PAH patients. A pilot, randomised, placebo controlled, double blind phase III study on bosentan, an ET-A and ET-B receptor antagonist, administered orally in PAH patients has been recently completed. Preliminary reports show favourable effects on functional capacity and haemodynamics, leading to the initiation of a larger trial currently underway in the USA and Europe.

A phase II open study on the acute haemodynamic effects of intravenous sildenafil, a type V cGMP phosphodiesterase inhibitor, in patients with pulmonary arterial hypertension is in progress in Europe. The drug is available also for oral administration and, if supported by preliminary findings,²⁴ a long term study could be initiated in the future.

Other substances to be evaluated in phase I, II, and III studies include nitric oxide, L-arginine, and elastase inhibitors. Finally, gene transfection strategies for the treatment of pulmonary hypertension are in preclinical phase of development. Encouraging results have been shown in animal models promoting the expression of both prostacyclin and nitric oxide synthase.

Non-drug treatment

Besides medical treatment and lung transplantation, two additional procedures have been utilised in patients with PAH and CTEPH—balloon atrial septostomy (BAS) and pulmonary artery thromboendarterectomy.

BAS is an invasive procedure that is intended to create an interatrial defect in order to produce a right to left shunt. Experimental and clinical observations suggest that such intervention can reduce right atrial pressure and increase systemic output, improving exercise capacity and survival in PAH patients.²⁵ Balloon atrial septostomy is performed by the transeptal Brockenbrough technique and stepwise multiple balloon dilatation of increasing size, tailored to produce a maximal systemic oxygen saturation fall of 5–10%. The procedure related failure and death rates are not negligible and therefore BAS should be performed in centres experienced in both interventional cardiology and pulmonary hypertension. Even if BAS may represent a real alternative or a bridge to transplantation for selected patients with severe PAH who are unresponsive to medical treatment, the procedure is still considered investigational.

Pulmonary circulation in patients with CTEPH is affected both by gross central obstructive lesions caused by unresolved organised thrombi, as well as by proliferative changes similar to those found in PAH, involving remaining unobstructed small arteries and arterioles.²⁶ Pulmonary thromboendarterectomy in deep hypothermia is the treatment of choice. In survivors it offers excellent long term

Therapeutic strategies

- Oral anticoagulation is indicated if no contraindication is present, while the use of calcium channel blocking agents is restricted to the minority of patients (15–25%) who are responders to the vasoreactivity test
- Continuous intravenous infusion of prostacyclin is indicated in NYHA class III/IV patients
- Lung transplantation is currently indicated in the case of failure of prostacyclin treatment
- Stable prostacyclin analogues for subcutaneous, inhaled, and oral routes and endothelin-1 receptor antagonists are in the advanced stages of clinical development
- Balloon atrial septostomy is an investigational procedure that can be effective in selected cases unresponsive to other therapeutic options
- Pulmonary artery thromboendarterectomy is indicated in patients with chronic thromboembolic pulmonary hypertension and proximal obstructive lesions

results, with sustained improvement in haemodynamics and exercise tolerance.^{27–29} Unfortunately, not all patients are appropriate candidates for this operation. Advanced age and severe functional impairment, as well as severe pulmonary hypertension and high pulmonary vascular resistance, increase the risk of procedure related mortality. More importantly, some patients with coexisting distal lesions inaccessible to surgery may in fact fail to improve despite removal of the central lesions.³⁰ Because chronic distal changes are difficult to either confirm or exclude, even with angiography and angioscopy, the overall mortality related to pulmonary thromboendarterectomy has not decreased below 7% even in the most experienced centres.

In patients with documented isolated distal organised post-thromboembolic obstructions, new prostanoid derivatives are currently tested in the hope of preventing progression or even reversing proliferative changes affecting the patent part of the pulmonary circulation.

A recent paper reports on successful percutaneous balloon dilatation of surgically inaccessible organised thrombotic lesions. This would open new perspectives for patients who are not good candidates for surgical treatment.

In conclusion, with the beginning of the third millennium a wide range of new treatment modalities for pulmonary hypertension are expected in a relatively short time. Our knowledge of the pathophysiology, diagnosis, assessment, and treatment of this condition will probably advance rapidly in the coming years. Compared to the very slow rate of progress previously in this field, we can consider to have entered a totally new era.

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