Role of endothelial and smooth muscle cells in the physiopathology and treatment management of pulmonary hypertension

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Abstract

Pulmonary hypertension can occur either as primary or secondary disease following cardiac or pulmonary illnesses. In either cases, histological lung biopsies reveal vascular remodelling i.e. smooth muscle cells proliferation with medial hypertrophy, arteriolar muscularization and endothelial cell proliferation. Subsequent intimal thickening, fibrosis and in situ thrombosis, altogether lead to vaso-occlusive alterations referred to as plexiform lesions.

Theories concerning the detailed physiopathology of pulmonary hypertension have focused on endothelial and smooth muscle cells' chemical factors production and response to different mediators. The endothelium produces vasoconstrictor and growth-promoting factor such as endothelin-1 (ET-1) as well as vasodilator and growth-inhibitor factors like prostacyclin and nitric oxide (NO). ET-1 has been noted in high concentrations in some clinical cases and experimental models of pulmonary hypertension, coupled with ET-1 receptors' modulation and altered endothelin converting enzyme activities, suggesting their active role in both arteriolar vasoconstriction and occlusion. Vascular thrombosis which has been noted by pathologists in pulmonary hypertension, could be related to an imbalance between thrombotic inducing factors (such as anti-phospholipid antibodies, ET-1 and thromboxane) and decreased fibrinolytic activity and antiaggregant endothelial factors (like prostacyclin, NO, thrombomodulin). The discovery of an endothelial cells' monoclonal proliferation in plexiform lesions of patients with primary pulmonary hypertension may reinforce the cellular proliferation hypothesis to understand the histopathology of this disease. In view of these new findings, the treatments available for pulmonary hypertension have been expanded from the previously employed oxygen therapy, calcium-channel blockers and anticoagulants, to intravenous prostacyclin analogues (epoprostenol) and inhaled nitric oxide. © 1999 Elsevier Science B.V. All rights reserved.

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1. Definition-causes

Pulmonary hypertension is defined by a mean pulmonary arterial pressure exceeding 25 mm Hg at rest or 30 mm Hg during exercise [1]. Contrasting the normally low-pressure pulmonary vascular circuit, it is due to increased pulmonary vascular resistance's. It occurs either as a primary or secondary disease following pulmonary or cardiac illnesses. The initial cardiac diseases include both high pressure diseases (i.e. left ventricular failure) and high blood flow diseases (i.e. congenital heart defects) [2]. In cases of initial pulmonary diseases, pulmonary hypertension can be directly related to hypoxia such as in chronic pulmonary obstructive disease and sleep apnea syndrome, or to a mechanical obstruction to vascular flow for example in post-thrombotic diseases [3]. The recognised causes of secondary pulmonary hypertension are listed in the Table 1. There are also some clinical conditions associated with an increased incidence of pulmonary hypertension i.e. diffuse connective tissue diseases, HIV infection, anorectic drugs and portal hypertension secondary to liver cirrhosis [4] (Table 1). The precapillary pulmonary hypertension often noted in these conditions is considered as a primary form of pulmonary hypertension.
Table 1
Causes of secondary pulmonary hypertension and diseases associated with primary pulmonary hypertension

<table>
<thead>
<tr>
<th>Causes of secondary pulmonary hypertension</th>
<th>Diseases associated with primary pulmonary hypertension</th>
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<tr>
<td>obstruction to venous flow (postcapillary pulmonary hypertension)</td>
<td>Connective tissue diseases</td>
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<tr>
<td>- left ventricular failure</td>
<td>- HIV infection</td>
</tr>
<tr>
<td>- valvular heart disease (mitral-aortic)</td>
<td>- Anorectic drugs</td>
</tr>
<tr>
<td>- congenital heart disease</td>
<td>- Cirrhosis with portal hypertension</td>
</tr>
<tr>
<td>- mediastinal adenopathy or fibrosis</td>
<td></td>
</tr>
<tr>
<td>- pulmonary disease: increased resistance to vascular flow through pulmonary small vessels or sustained hypoxia:</td>
<td></td>
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<tr>
<td>- parenchymal disease: fibrosis, emphysema</td>
<td></td>
</tr>
<tr>
<td>- bronchial disease: obstructive bronchopneumopathy</td>
<td></td>
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<tr>
<td>- thoracic cage abnormalities, sleep apnea syndrome</td>
<td></td>
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<tr>
<td>- obstruction of arterial flow: pulmonary thromboembolism</td>
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given its identical prognosis and histopathology as that of isolated primary pulmonary hypertension. For diffuse connective tissue diseases (i.e. systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus), pulmonary hypertension is considered to be primary once certain causes of secondary pulmonary hypertension such as pulmonary fibrosis and thromboembolic events, have been eliminated [4,5]. Only a minority of patients who have taken appetite suppressant drugs [6], have an HIV infection [7], liver cirrhosis with portal hypertension or connective tissue disease, will develop pulmonary hypertension [6,8]. This may suggest an inherent predisposition to pulmonary hypertension, with HIV infection or anorectic drugs acting as mere triggering factors [4]. Familial cases of pulmonary hypertension have been described via an autosomal dominant transmission mode with incomplete penetrance. The gene has been localised on chromosome 2 [9].

2. The primary stimuli of pulmonary hypertension

The most frequent initial stimuli of pulmonary hypertension are hypoxia and mechanical obstruction to pulmonary arterial flow. Acute hypoxia increases pulmonary arterial pressure almost instantly, but the phenomenon is reversible with the recovery of a normal oxygen concentration. Sustained hypoxia leads to durable elevated pulmonary arterial pressure, with partly irreversible vasoconstriction, which is only partially improved by oxygen supplementation [10]. During sustained hypoxia, pulmonary arterial pressure also rises as a result of progressive small vessels’ obliterator changes. The reasons why chronic hypoxia leads to these effects are not clearly understood [10] except in cases of pulmonary hypertension secondary to thromboembolism: in cases of large pulmonary (main, lobar or segmental) vessels’ chronic obliteration, the initial arterial emboli which are not completely dissolved by local fibrinolysis, become endothelialized and the vessel recanalized. These new vessels lack the main physiological properties of normal pulmonary arteries. Vascular dysfunction and increased shear stress may partly explain the pulmonary hypertension observed following pulmonary embolism.

3. Histopathology: cellular mechanisms leading to the so-called plexiform lesions within the pulmonary arterial vasculature

In chronic pulmonary hypertension, although the entire pulmonary vascular tree undergoes histological alterations, it is the smaller vessels (arterioles and venules) which are primarily affected. These alterations include smooth muscle cells proliferation with medial hypertrophy and arteriolar muscularization, fibrosis, in situ thrombosis and endothelial cells proliferation with subsequent intimal thickening [11–13]. In cases of primary pulmonary hypertension, endothelial cells proliferation is monoclonal [14,15]. Concentric endothelial cell proliferation and smooth muscle cell migration leads to so called plexiform lesions which seem to be unique to the pulmonary circulation. These plexiform lesions were initially exclusively associated with primary pulmonary hypertension but are in fact a feature of both primary and secondary pulmonary hypertension.

3.1. Smooth muscle cell proliferation

Sustained pulmonary hypertension leads to enhanced muscularization of small arterioles, whose wall usually consists of a single elastic layer. This process is found even in very distal arteries (15 μm in diameter). The newly formed muscular layer is situated between the former elastic (outer) layer and a de novo elastic (inner) layer which is bordered by intimal cells [13,16]. Since this muscularization also occurs in pulmonary venules and in adults born at high altitude, who are free of cardiac and pulmonary diseases, alveolar hypoxia is suspected to be
responsible for the remodelling of the vessels closest to the alveolar spaces [17]. The arterial medial thickening due to this proliferation correlates with the pulmonary arterial pressure level [1]. In these modified, exceedingly muscularized arterioles, smooth muscle cells undergo morphological and functional changes [13]. Whereas normally they are purely contractile, these arterial smooth muscle cells mature and acquire abnormal proliferative, migratory and synthetic properties. The conversion of smooth muscle cells from a contractile to a migratory phenotype seems to depend upon growth factors (transforming growth factor β and basic fibroblast growth factor) [18] released by the action of vascular elastase on elastin and proteoglycans which stores these growth factors [19]. Elastin peptides also stimulate the change from contractile to migratory phenotype [19]. Consecutively, the smooth muscle cells migrate through the outer elastic layer into the intima where they proliferate and may invade the vascular lumen altogether forming concentric layers referred to as ‘onion-skin lesions’. The final stage with vessel occlusion is called plexiform lesions.

3.2. Fibrosis

An increase of extracellular matrix turn-over and number of vascular fibroblasts, which produce components like elastin and collagen, is demonstrated. The enhanced matrix synthesis versus its destruction leads to vascular stiffness [20]. Peacock et al. hypothesised that this intensified matrix synthesis could be an adaptive response of the arterial vessels in order to maintain prolonged vasoconstriction during sustained hypoxia, without increased energy expenditure [21]. The matrix destruction depends on elastolysis. Enhanced elastolysis occurs early in the pathological process, before vascular remodelling is detected [22], and is secondary to local vascular elastase activity [23,24]. Hypoxia also stimulates the transcription of collagenase IV gene which further contributes to matrix remodelling [24].

3.3. Arterial and arteriolar thrombosis

In primary and secondary pulmonary hypertension, arterial thrombosis of small and medium size arteries has frequently been described by pathologists [25,26]. In cases of classic thromboembolic pulmonary hypertension, it is the thrombosis of major pulmonary artery which is the recognised cause of the disease [3]. It is a distinctive histopathologic process from that of the occlusion of smaller and distal vessels which constitute two-thirds of primary forms of pulmonary hypertension [27] and one-third to a half of all cases of secondary pulmonary hypertension [28]. For some patients, extensive small vessels thrombosis is the main pathological finding [29].

3.4. Endothelial cell proliferation

In some cases of pulmonary hypertension, using immunoperoxidase staining with antibodies to factor-VIII-related antigen, plexiform lesions were related to a process of endothelial cells proliferation [30]. The authors suggested that endothelial proliferation contributes to the final obliteration of small vessels. However, the reason for this stimulation and its mediators remain to be elucidated. Recently, Lee et al. showed that the endothelial proliferation is monoclonal in primary pulmonary hypertension suggesting that a somatic genetic alteration process could be involved in its pathogenesis [14,15].

4. The role of factors produced by endothelial cells and platelets in the pathogenesis of sustained vasoconstriction and vascular remodeling (Fig. 1)

As soon as arterial layers’ remodeling occurs with increased wall thickness and decreased arterial diameter, the pulmonary vessels become less responsive to further vasodilatation stimuli. Concomitant increase in vascular wall shear stress leads to further endothelial functional impairment. While endothelial histological changes can be considered as secondary to a causal disease in secondary pulmonary hypertension, in primary pulmonary hypertension there is still a debate whether the endothelial dysfunction is the cause or merely a marker of the disease [31]. The endothelium normally releases both vasoconstrictor and growth-promoting factors like endothelin, or vasodilator and growth-inhibitor factors such as prostacyclin and NO [21], responsible of local vascular homoeostasis. Endothelial dysfunction or lesions lead to impaired production and/or release of these factors.

4.1. Role of endothelin-1

The potential role of endothelin-1 (ET-1) in the pathogenesis of pulmonary hypertension has recently been evoked [32]. ET-1 is an important vasoactive peptide produced by endothelial cells in pulmonary and systemic circulations. It is released following the stimulation by a variety of substances including: epinephrine, cytokines (such as: transforming growth factor-bêta, interleukin-1), or following altered vascular physical factors (increased shear stress, hypoxia or cold exposure) [24]. ET-1 is produced via the action of an endothelin-converting enzyme (ECE) which converts big ET-1 to ET-1 [33]. Once released, ET-1 may bind to either type A receptors (ET_A receptor) localised mainly in vascular smooth muscle cells, or type B receptors (ET_B receptor) found on endothelial cells. ET_A receptors are usually considered to mediate vasoconstriction while ET_B lead to vasodilatation through the release of NO. McCulloch et al. demonstrated that an anatomical functional heterogeneity exists in the distribu-
Fig. 1. Sustained hypoxia-induced variations in pulmonary vascular tone, cellular proliferation, and thrombosis.
tion of ET-1 receptors. It was hence noted that while ET$_A$ receptors mediate vasoconstriction in the large elastic arteries, in pulmonary resistance arteries of rats it is the ET$_B$ receptors which mediate vasoconstriction [34]. In a lung perfusion system, ET-1 binds to its receptor on vascular smooth muscle cells (mainly ET$_A$) and has no effect on endothelial cells, which could explain sustained pulmonary arterial vasoconstriction [35]. Interaction of ET-1 with its ET$_A$ receptor could therefore explain sustained pulmonary arterial vasoconstriction.

In humans, ET-1 was first associated with secondary pulmonary hypertension in children with congenital heart defects [36]. Increased levels of ET-1 in systemic and pulmonary blood in the course of pulmonary hypertension, and evidence for its excessive production within the lungs (following biopsies of patients with pulmonary hypertension compared with healthy subjects), was demonstrated [31,37]. Endothelin-1 systemic concentrations were also found to be greater in primary versus secondary pulmonary hypertension [37]. In lung biopsies of patients with pulmonary hypertension, compared with normal lungs, Giard showed that the pulmonary arteries’ endothelium has a strong immunoreactivity for ECE-1, suggesting that elevated plasma concentrations of this peptide could result from an amplified conversion of big ET-1 to ET-1 [38]. Bialecki et al. suggested that the hypoxia-induced changes in arterial responsiveness to ET-1 might be the cause of increased ET-1 plasmatic concentrations [39]. In hypoxic rats, a treatment with oral ETA receptor antagonist led to a vasodilatation and a decreased right ventricular pressure [40]. This beneficial effect was due to restoration of the nitric oxide-induced smooth muscle cell’s relaxation and endothelium-dependent dilation in response to acetylcholine [41]. These experiments establish a link between ET-1 and nitric oxide roles during hypoxia and in pulmonary hypertension [24].

4.2. Role of vascular growth factors

Vascular endothelial growth factor (VEGF), a protein secreted by endothelial cells and whose only known target is the endothelial cells themselves, could be a factor of intimal proliferation. VEGF is present in the lung vascular smooth muscle cells, macrophages, and epithelial cells [42]. Endothelial cells do not secrete VEGF under physiological conditions. VEGF has however been found in plexiform lesions of patients with primary pulmonary hypertension. Furthermore, in monocytic cell line and isolated lung experiments, the gene encoding for VEGF is stimulated almost instantly following hypoxia [43]. Experimental serial deletions of VEGF gene promoter identified a 28-bp fragment which is necessary for hypoxia induction of VEGF. This fragment is recognised by HIF-1, a transcription factor essential to the hypoxia response [44,45]. The transcriptional activation of the VEGF gene is subsequent to a VEGF promoter and HIF-1 interaction [46]. Transient expression studies showed that nitric oxide exposure suppressed hypoxia-induced VEGF gene transcription [47].

Endothelial cells cultured under low oxygen pressure also release a platelet-derived growth factor (PDGF) [24]. PDGF induces vasoconstriction and stimulates pulmonary artery fibroblasts migration and proliferation [21]. Endothelin, a vasoactive mediator produced by endothelial cells also induces chemotaxis and replication of the fibroblasts [48].

4.3. Role of prostaglandins

Endothelial cells produce a vasodilator and antiagregant prostaglandin, prostacyclin, while platelets produce thromboxane A$_2$, a prothrombotic prostaglandin. In patients with primary pulmonary hypertension, the levels of prostacyclin are reduced compared with those of thromboxane A$_2$ metabolites [49]. These results however were not confirmed by a later study [50]. Prostacyclin modulates the vasoconstrictor response of arteriolar muscular cells in the case of acute hypoxia [51]. This response decreases in cases of prolonged hypoxia [52]. Decreased prostacyclin levels are also partly responsible for the prothrombotic state noted in pulmonary hypertension. Increased platelet activation and decreased platelet survival were reported [28] and are normalised after prostacyclin infusion [53]. However, other studies concerning the circulating levels of stable platelet activation markers (such as: thromboxane B$_2$, β-thromboglobulin and platelet factor 4) show conflicting results [54].

4.4. Role of nitric oxide

Nitric oxide (NO) usually contributes to maintain a low blood pressure in the pulmonary circulation. NO is produced by endothelial cells through the action of nitric oxide synthase (NOS). Three isotype of this enzyme have been described. One (iNOS or type II) is induced and secreted by various cells following cytokine stimulation. The two others are secreted one by endothelial cells (eNOS or type III) and the other by neurones (nNOS or type I) [55].

In hypoxic rats lungs, northern blot analysis show that the level of eNOS mRNA increases significantly, as well as the two mRNA detected for iNOS [56]. Western blot analysis confirm a significant increase in eNOS and iNOS proteins. De novo eNOS immunostaining is revealed in small and medium-sized arteries of hypoxic rats compared with staining nearly exclusively limited to large-sized arteries in normoxic rats [57]. Increased NOS expression does not necessarily correspond to an increased NO activity. However, in chronically hypoxic rats, NO-synthesis blockade with L-arginine analogue enhances pulmonary vasoconstriction induced by acute hypoxia [56] and increased NOS activity was noted to coincide with the beginning of the vascular remodelling process during
chronic hypoxia [58]. In hypoxic bovine endothelial cells, Palmer et al. showed that the interaction of HIF-1 with iNOS gene promoter regulated transcription of i-NOS gene [59].

In humans, nNOS is found in normal vascular endothelium [60] but its immunostaining is not increased in patients with pulmonary hypertension as compared with controls [61]. eNOS showed strong immunostaining in almost all plexiform lesions in cases of pulmonary hypertension when compared with normal lung tissue [62]. These results however contradict Giad’s et al. previous findings of a reduced expression of eNOS mRNA and immunoreactivity in the lungs of patients with pulmonary hypertension [63]. Therefore, if chronic hypoxia leads to an up-regulation of iNOS and eNOS in hypoxic rats, the results in humans are still conflicting [62,63].

4.5. Other prothrombotic factors

As reported in isolated cases [64,65] and in a prospective study [66], anti-phospholipid antibodies may be implicated in the pulmonary arterial thrombotic process. In a study of 38 patients, anti-phospholipid antibodies were found in 44% of the precapillary pulmonary hypertension cases, where in situ thromboses are frequently observed [66]. Decreased levels of thrombomodulin, an antithrombotic factor present on the luminal part of endothelial cells, were found in secondary pulmonary hypertension [67,68]. Decreased fibrinolytic activity with elevated plasminogen activator inhibitor-1 activity was shown in primary pulmonary hypertension [69].

In sum, an imbalance due to increased thrombotic factors (endothelin-1, thromboxane A2, antiphospholipid antibodies) with diminished fibrinolytic activity and antiaggregant endothelial factors (prostacyclin, thrombomodulin, nitric oxide) favours thrombosis in pulmonary hypertension.

4.6. Role of inflammation

In some patients with pulmonary hypertension, plasma pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-1β and interleukin-6, are elevated [70]. Interleukin-1β which stimulates both ET-1 and PDGF production may act as a link between endothelial dysfunction, increased matrix synthesis and inflammation [70]. Interleukin-8, whose gene expression is stimulated by hypoxia, could be another link between hypoxia and inflammation [71]. A local pro-inflammatory enzyme like 5-lipoxygenase, abundantly present in alveolar macrophages, shows more intense immuno-histochemical staining in small arteries of patients with primary pulmonary hypertension as compared with controls [72]. The role of the mediators of local and general inflammation is probably underestimated in the pathogenesis of pulmonary hypertension [15].

5. Therapeutic applications of prostacyclin and NO based on their roles in pulmonary hypertension

Pulmonary hypertension considered for a long time as a dreadful and hopeless disease is now under better medical and surgical management [73]. Non specific therapy (diuretics and digoxin) were initially used with nondrug treatment such as oxygen supplementation. The latter remains the main treatment when pulmonary hypertension is due to chronic obstructive pulmonary disease. Present treatments ensue from the roles of vasoconstriction and thrombosis in pulmonary hypertension. Initial evaluation of a patient with pulmonary hypertension includes a detailed medical history and clinical examination in order to identify possible causes of secondary pulmonary hypertension. It is followed by right heart catheterization for precise pressure measurements and testing of calcium antagonists or short-acting molecule such as NO, or prostacyclin analogue such as epoprostenol [74]. The anticipated response to these substances is pulmonary arterial vasodilatation with a subsequent reduction in pulmonary vascular resistance. It only occurs in 25% of all patients tested and is considered as favourable because long term treatment with calcium antagonists is effective in such cases. In a 5-years prospective study of 64 patients with primary pulmonary hypertension, 17 patients responded to calcium-channel antagonists with a 20% decrease in pulmonary-artery pressure [75]. They received a long-term (5 years) and high dose calcium-channels antagonists treatment (mean daily dose of nifedipine: 172 mg). Five years later, patients who responded to the vasodilator treatment had an increased survival (94%) as compared with the patients who did not (55%). The effect of lower doses of calcium-channel antagonists was not examined in this study. Anticoagulation increased survival of patients with primary pulmonary hypertension who did not respond to calcium-channel antagonists [75] and a retrospective study demonstrated an increased survival of patients with pulmonary hypertension treated with anticoagulants [26]. Anticoagulation is therefore a recommended treatment of pulmonary hypertension with a target INR (international normalised ratio) between 2 and 3. When these treatments do not improve clinical and hemodynamic parameters, a prostacyclin analogue infusion or inhaled NO is used. The prostacyclin analogue epoprostenol is delivered via continuous intravenous infusion. Long-term infusion (3 months) has favourable hemodynamics effects with a decrease of mean pulmonary artery pressure (-4.8 mmHg) and pulmonary vascular resistance (-3.4 mmHg/l/min) [74]. Most patients (39 among 41 patients) received the full 3 months treatment. The main complications of epoprostenol treatment, due to its exclusive intravenous delivery, were catheter-related infectious or thrombotic events. The beneficial effects of epoprostenol are independent from the causal disease [76,77] or from the effects of brief infusions used during hemodynamic explorations.
These seemingly contradictory results of long versus short term prostacyclin infusions, led to the hypothesis that additional therapeutic effects of prostacyclin apart from vasodilatation, such as platelet aggregation inhibition or action on vascular growth and remodelling, may be activated following prolonged infusions [51,53]. Continuous epoprostenol intravenous infusion was used in a few patients for 3 years with an increased survival but epoprostenol doses were increased during treatment [78]. This is probably due to its rapid metabolism and/or to the increased production of vasoconstrictors to counteract prostacyclin beneficial effects. These mechanisms may also explain pulmonary hypertension rebound following abrupt discontinuation of epoprostenol infusions. Inhaled nitric oxide is also an effective arteriolar vasodilator, mainly in cases of acute pulmonary hypertension or in children. It has been used for shorter periods than prostacyclin analogue with good results [79] and its long-term use awaits further studies. In the worst cases, when pulmonary hypertension remains refractory to all of these treatments, the patient can be inscribed on the waiting list for lung transplantation [73,80]. The waiting time of up to two years led to the death of 30% to 40% of patients before the availability of continuous prostacyclin infusion. However, with the vasoactive treatments (calcium-channel antagonists, prostacyclin analogue, NO), fewer patients now need lung transplantation.

To conclude, although the primary cause of pulmonary hypertension is still unknown and it remains without a cure in advanced and irreversible forms, exciting findings regarding the pathology and physiology of pulmonary hypertension has led to progress in its management with treatments providing a prolonged survival and a better quality of life. Present treatments result from the understanding of the role of vasoconstriction and thrombosis in vascular remodelling. Anticoagulation now belongs to the standard treatment of pulmonary hypertension while calcium antagonists are used in patients where a pulmonary arterial vasodilatation is observed after short acting vasodilator infusion. Increased production of vasoconstrictor effectors such as endothelin-1 during hypoxia while prostacyclin levels are decreased led to the use of prostacyclin analogue infusions and inhaled nitric oxide in cases of pulmonary hypertension refractory to standard treatment. Future therapeutic innovations could depend on the use of other vasoactive treatments such as endothelin receptor blockers or nitric oxide donors or other antithrombotic drugs such as thromboxane synthase inhibitors. Neither the role of cytokines or proliferative and chemotactic factors, nor the mechanism of facilitating agents such as anorexigen, have yet been used to develop future therapeutics. It seems however that the finding of more effective or new treatments will rely on the better understanding of the relative roles of endothelial dysfunction, local inflammation and cellular proliferation in the development of pulmonary hypertension.

References


