Thorax 1999;54:161–168



# Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension

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Received 9 February 1998
Returned to author 8 May 1998
Revised manuscript received 15 June 1998
Accepted for publication 11 September 1998

The causes of pulmonary hypertension fall into four broad categories: (1) passive increases in pulmonary artery pressure secondary to increased left atrial pressure and left ventricular dysfunction, (2) veno-occlusive disorders, (3) conditions in which the blood flow through the pulmonary arteries is increased beyond the ability of the pulmonary circulation to compensate, and (4) conditions associated with vasospasm or occlusion, resulting in a diminished effective cross sectional area of the pulmonary vascular bed.[1 2] In many cases several factors are present simultaneously. Regardless of the initiating cause, severe prolonged pulmonary hypertension appears to result in largely irreversible changes which involve vascular remodelling and often thrombosis.[3–5]

Because the signs and symptoms of pulmonary hypertension are often very non-specific, patients commonly present late and, until recently, invasive tests were required to establish the diagnosis. Consequently pulmonary hypertension was frequently an important but unrecognised component of other disease states, many of which will be the subject of this discussion.

The main importance of severe pulmonary hypertension is that it may cause right ventricular dysfunction and ultimately death from right heart failure. Pulmonary heart disease, usually associated with pulmonary hypertension, has been estimated to account for at least 10% of all cases of heart disease in the USA.[6] The significance of milder pulmonary hypertension is less clear, but it is probably important. A study in Chicago of 1118 subjects who were undergoing coronary angiography for suspected heart disease showed that the finding of pulmonary hypertension, independent of left ventricular dysfunction, was the single most important predictor of the likelihood of death over the subsequent two years.[7] Pulmonary hypertension also has important prognostic implications in critically ill surgical patients[8] and in those with chronic obstructive pulmonary disease (COPD).[9]

The changes which take place in pulmonary arteries as a result of hypertension have been intensively studied, and numerous pro-inflammatory factors have been identified which can influence these changes.[10] It is often difficult, if not impossible, to distinguish cause from effect. However some factors are frequently present. The aim of the present discussion is to examine the possible role of one such factor, serotonin. This may have added importance since a number of serotonin antagonists are available for oral use. For the purposes of this review pulmonary hypertension is defined as a pulmonary artery pressure of >25 mm Hg at rest.

## Origin of serotonin and causes of elevated levels

Serotonin, also known as 5-hydroxytryptamine, is secreted from neuroendocrine cells in the gut, and tumours of these cells, called carcinoid tumours, are a source of increased production.[11 12] Serotonin from the gastrointestinal tract is normally metabolised by the liver before it reaches the lungs, and it is also effectively removed by the lungs. Both these organs usually localise the effects of serotonin to the circulation of origin, except when abnormal channels of communication exist, as in portal hypertension, or when metabolic capacity is overwhelmed. Lack of removal of vasoactive substances by the liver could help to explain the association between pulmonary hypertension, portal hypertension, and liver diseases.[13 14] The vascular adverse effects of serotonergic amines such as ergotamine are exacerbated in liver disease.[15] The ability of the endothelial cells of the lungs to metabolise amines may also be reduced in disease states, probably because of impairment of amine oxidase enzymes.[16 17] Such impairment results in raised circulating amine levels, which may provide early evidence of endothelial dysfunction in pulmonary hypertension before morphological changes are apparent.[18 19]

Pulmonary neuroendocrine cells secrete vasoactive substances in response to airway hypoxia and hypercapnia.[20 21] For unknown reasons these cells commonly proliferate in patients with pulmonary hypertension, producing a variety of peptides in addition to large amounts of serotonin.[22] In lung transplant recipients with end stage primary pulmonary hypertension the degree of hyperplasia of these cells was found to correlate with the extent of proliferation of myofibroblasts in the pulmonary arteries.[23] In bronchopulmonary dysplasia, a condition strongly associated with pulmonary hypertension, a 34-fold increase in serotonin immunoreactive cells has been demonstrated.[20] Pulmonary neuroendocrine cells, rather than platelets, have been postulated to be the source of increased serotonin production causing acute postoperative pulmonary hypertension in children with congenital heart defects.[24 25] The mast cell also contributes to increased levels of circulating serotonin in the pulmonary hypertension which occurs in rats following exposure to asbestos.[26]

Conditions associated with the destruction of platelets are likely to cause the release of serotonin and other contents which may cause

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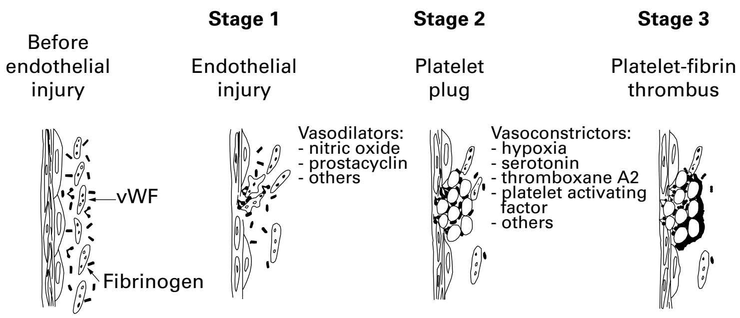


*Figure 1 Stages in the interaction of platelets with the walls of pulmonary arteries following trauma. Stage 1: adhesion of platelets following endothelial injury mediated by von Willebrand factor (vWF). Stage 2: formation of the platelet plug with aggregation and degranulation (some of the most important vasoconstricting and vasodilating substances are listed, many of which are released from platelets). Stage 3: fibrin clot formation (mediated by fibrinogen). Modified from reference 186 with permission.*

pulmonary hypertension.[27] Immune mediated acute thrombocytopenia is one such condition.[28] The aggregation of platelets also releases serotonin, and when the process occurs in pulmonary arteries this causes vasospasm.[29] Binding of platelets to arteries is mediated largely by von Willebrand factor and factor VIII.[30] Increased aggregation of platelets and decreased platelet survival time are regularly observed in most forms of primary and secondary pulmonary hypertension.[4 31] Abnormalities of endothelial factor VIII have been observed in cases of pulmonary hypertension in both humans and sheep,[32–34] and adherence of platelets to the pulmonary arteries in pulmonary hypertension is likely to be pathologically enhanced by the increases in endothelial von Willebrand factor which result from increased shear stress (fig 1).[35] These changes may lead to pulmonary arteriosclerosis, which is usual in pulmonary hypertension.[36]

Circulating serotonin is taken up by endothelial cells, and even more so by platelets, where it is stored in dense (delta) granules.[30] When the endothelial cells or platelets are unable to take up serotonin because of damage or as a result of congenital abnormalities, circulating serotonin levels are increased and pulmonary hypertension may result. The increases in serotonin levels in patients with these problems persist following normalisation of pulmonary artery pressures after lung transplantation, indicating that the platelet abnormality is not caused by pulmonary hypertension.[37]

## Effects of serotonin

A number of biogenic and synthetic amines are capable of causing endothelial disruption and platelet stimulation. Serotonin is somewhat unique in that these changes occur at levels which are not much higher than the "resting levels" which are observed in mammalian blood.[38] The opening of junctions between endothelial cells causes oedema.[39] On a molar basis, serotonin is the most potent pulmonary vasoconstrictor identified to date in humans,[40] but in the systemic vasculature it causes profound vasodilation.[41] These differing effects on the two circulations are similar to those of hypoxaemia and the effects of serotonin are intensified under hypoxaemic conditions and by the administration of catecholamines.[41] In conditions characterised by stimulation of the sympathetic nervous system, such as cardiopulmonary bypass, subthreshold doses of serotonin can have significant vasoconstrictor effects.[42] The vasoconstrictor effects of serotonin have been found to be synergistic with other concomitant variables which are too numerous to list.[43] Serotonin is also a bronchoconstrictor.[41 44]

Serotonin is a mitogen, causing hyperplastic and hypertrophic changes in smooth muscles.[45] The most readily identifiable clinical manifestation of this effect is valvular heart disease.[46] These effects are mediated by a variety of cellular processes, including cyclic nucleotides and protein kinase C activation.[47 48] A complex interplay exists at a systemic and local level between inflammation, thrombosis, fibrinolysis, vasospasm, and vascular remodelling. Many of the important mitogens implicated in remodelling have a vasoconstrictor and prothrombotic effect, and vasodilators such as nitric oxide inhibit platelet aggregation, thrombosis, and remodelling.[49] The histological changes which occur during pulmonary vascular remodelling have been reviewed elsewhere.[3–5] Remodelling has many features in common with the changes that occur in arteriosclerosis, except that arteriosclerosis generally involves larger vessels with a high elastin content.[50] Endothelial proliferation may also be more exuberant in some varieties of pulmonary hypertension than in arteriosclerosis.[32] Hypoxia and stretching of the pulmonary vessels are believed to be important stimuli for these processes which involve phenotypic changes in endothelial cells, myofibroblasts, and numerous types of inflammatory cells.[51 52] The end result of these changes are structural and functional changes which result in an increased pulmonary vascular resistance. These changes were accelerated by the administration of serotonin to rats exposed to chronic hypoxia.[53 54]

## Serotonin receptors

At least five classes of serotonin receptor have been identified, each with numerous subclasses, and different receptors have been implicated in the pathogenesis of a number of vascular disorders.[55] $S_1$ and $S_2$ are the principal receptors relevant to the pulmonary arteries.[56] The vascular response to serotonin is determined by a large number of concomitant variables, and also varies between vasodilation and vasoconstriction in different segments of the same artery, which makes generalisation difficult.[57] However, under most experimental conditions, stimulation of $S_1$ pulmonary receptors causes vasodilation and $S_2$ receptors often mediate vasospasm.[56] Functional imbalance of this system may result in hypertension, as in pre-eclampsia.[58] With arteriosclerosis, numbers of $S_2$ receptors are increased, causing increased sensitivity to serotonin.[59–61] Arteriosclerosis also appears to predispose to vasospasm due to deficiencies of endothelial vasodilation.[62]

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## Serotonergic agents

Pulmonary hypertension can be caused in most mammalian species by numerous serotonergic drugs, many of which are sympathomimetic anorexients. These include aminorex[63] and dexfenfluramine.[64] In rabbits, aminorex and other anorexients cause release of serotonin from platelets.[65] In dogs, intravenous dexfenfluramine augments hypoxic pulmonary vasoconstriction and, with long term oral use, pulmonary vascular resistance is increased.[66] In rats phentermine and phenmetrazine cause pulmonary vasoconstriction by prolonging the vasoconstrictive influence of serotonin.[67 68] More recently three other anorexient agents were found to cause pulmonary vasoconstriction by inhibiting potassium current in pulmonary vascular smooth muscle, an action which mimicked the effect of hypoxia.[69] Other drugs with direct or indirect serotonergic effects[70] have been associated with pulmonary hypertension—namely, cocaine,[71] dopamine,[72] doxapram,[73] fluoxetine,[74] lithium,[75] methamphetamine,[76] methysergide,[77] pentazocine,[78] phenmetrazine,[73] protamine,[79] sertaline,[80] and tryptophan.[81] Most of these reactions are infrequent, implying individual variations in susceptibility, and for several of these agents possible alternative mechanisms of toxicity exist, but the common feature of serotonergy suggests that these may often be synergistic. In the case of pentazocine, for example, there are numerous reports concerning the illicit intravenous use of tablets containing talc, which cause a granulomatous arteritis, frequently resulting in chronic pulmonary hypertension. Crushed pentazocine tablets injected into dogs also cause transient pulmonary hypertension.[82] However, other more common illicit drugs which are used in a similar way appear to cause these problems less frequently,[83] and acute pulmonary hypertension is also a well established effect of pure pentazocine.

The pulmonary vasodilator urapidil is primarily an alpha-1 adrenoreptor blocker, but may also act by stimulating $S_1$ receptors.[84]

## Specific pulmonary hypertensive diseases which may involve serotonin

### THE CARCINOID SYNDROME

Investigators have found that about 25% of patients with the carcinoid syndrome have pulmonary hypertension which is often relatively mild.[85] This is probably because of liver metabolism, since liver dysfunction is a prerequisite for the production of cardiac lesions in the guinea pig model of this disease.[86] In addition to valve disease, pulmonary hypertension may contribute to the commonly observed tricuspid regurgitation.[87] More severe valvular disease is found in patients with higher serotonin levels.[88 89] Similar valvular lesions have frequently been observed during the use of ergotamine and methysergide, both of which are partial serotonin agonists, and have recently been reported in association with diet pills which also have serotonergic properties.[90] Carcinoid tumours secrete peptides which also characteristically provoke florid vascular fibroproliferative reactions.[91 92] Ketanserin provides relief of many of the symptoms of the carcinoid syndrome and, when used during anaesthesia, consistently reverses systemic hypertension,[43] but the effects on pulmonary hypertension have not been studied.

### MONOCROTALINE INDUCED PULMONARY HYPERTENSION

The plant *Crotalaria spectabilis* (the source of monocrotaline) is often used to induce pulmonary hypertension in experimental animals, most commonly the rat, and also has this effect in man. Endothelial injury is the first change observed, followed by hypertrophy of arterial smooth muscle and right ventricular hypertrophy.[93 94] Plasma serotonin levels are increased, coinciding with platelet accumulation in the lungs, the vasoconstrictor response to serotonin is enhanced, and both pulmonary artery pressure and the severity of histological changes are reduced by selective serotonin blockade and by inhibition of serotonin synthesis with chlorophenylalanine.[53 95 96] The hypertensive effect of monocrotaline was reduced in rats made moderately thrombocytopenic with antiplatelet serum,[97] and by the platelet modifying drug sulphinpyrazone.[98] Prednisolone was also beneficial.[99] However, the thromboxane inhibitor dazmegrel was ineffective, suggesting a less important role for thromboxane A2 in this disorder.[100]

### PULMONARY EMBOLISM

The pulmonary hypertension associated with acute pulmonary embolism (PE) is sometimes disproportionate to the degree of physical vascular occlusion, and some of this has been attributed to the vasoconstrictive effects of platelet derived serotonin.[101–103] Bronchoconstriction following PE may have the same cause.[104 105] Platelets adhere to the thrombus which has lodged in the pulmonary arteries[106 107] and this commonly results in depletion of circulating platelet levels.[108] Experimental embolisation in animals with fresh thrombotic material containing large amounts of platelet derived serotonin generates a more profound pulmonary vasoconstrictor response than embolisation with barium, glass beads, and other objects which do not contain platelets or stimulate thrombin mediated platelet degranulation.[41 109] The degree of vasoconstriction is also proportionate to the extent of endothelial damage caused by the embolus.[110] If experimental animals are rendered thrombocytopenic prior to embolisation, the pulmonary hypertension is significantly attenuated and inhibition of the platelet release reaction with sulphinpyrazone or heparin has a similar effect.[111 112] A significant average reduction of approximately 5 mm Hg in the pulmonary hypertension generated by PE was observed in humans after the administration of ketanserin.[113] Ketanserin and other serotonin blockers also reduce post embolic pulmonary hypertension in dogs.[112 114]

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RADIATION PNEUMONITIS AND ANTITUMOUR DRUGS

Irradiation of tissues causes release of serotonin as evidenced by direct measurement,[115] and indirectly by the well established beneficial effects of $S_3$ receptor antagonists in the treatment of radiation induced side effects.[116] Endothelium is a rapidly dividing tissue which suffers the early effects of radiation,[117] and pulmonary hypertension often results.[118 119] Serotonin levels were also increased significantly following treatment with vinblastine and other antitumour drugs.[120]

ADULT RESPIRATORY DISTRESS SYNDROME AND SHOCK

Pulmonary hypertension is observed in almost all cases of adult respiratory distress syndrome (ARDS),[40] and vascular remodelling is pronounced in patients who survive longer than 10 days.[121] Progressive thrombocytopenia occurs in 50% of cases, and often parallels the course of worsening hypoxia.[122 123] Platelet activation and intrapulmonary platelet aggregation are also common.[124 125] Sibbald *et al* observed a correlation between raised serotonin levels and pulmonary hypertension in patients with ARDS related to sepsis.[126] Serotonin contributed to pulmonary hypertension in dogs during haemorrhagic shock, and this hypertension was prevented with serotonin antagonists.[127] Administration of ketanserin to patients with acute respiratory failure following circulatory shock also caused significant haemodynamic improvements.[128]

COLLAGEN DISORDERS

Pulmonary hypertension is a complication of most varieties of collagen disease, particularly systemic lupus erythematosus (SLE), a disease in which pulmonary artery pressures were raised in over 30% of consecutive cases in several series.[129–131] Patients with SLE and Raynaud's syndrome appear to be particularly susceptible.[132] Intraplatelet and circulating serotonin levels were found to be significantly higher in patients with calcinosis, Raynaud's phenomenon, and oesophageal dysmotility (the CREST variant) than in controls.[133 134] Stachow *et al* found evidence of impaired monoamine oxidase activity in scleroderma, and the increased levels of serotonin observed were normalised by treatment with ketanserin.[135] In a multicentre trial oral ketanserin reduced the frequency of episodes of Raynaud's symptoms from 34% to 18% among 222 patients[43] and, in a study of 14 patients with systemic sclerosis and relatively severe pulmonary hypertension, Seibold *et al* found that intravenous ketanserin decreased pulmonary artery pressure by 13–44% in five patients but caused a paradoxical increase in one, with no change in the other eight.[136]

PORTAL HYPERTENSION

Hadengue *et al* found that 2% of 507 patients with portal hypertension also had pulmonary hypertension and the portal hypertension usually preceded the pulmonary hypertension.[137] These authors postulated that either microemboli or unspecified vasoactive substances were bypassing the liver to reach the lung by way of portosystemic shunts Thrombocytopenia was present in most cases of portal hypertension with plexogenic pulmonary arteriopathy.[138]

HYPOXIC DISORDERS

Because of the prevalence of chronic lung disease, hypoxia is probably the commonest of all causes of pulmonary hypertension apart from diseases caused by parasites.[2] The mechanisms of hypoxic vasoconstriction have been reviewed elsewhere, but much remains unknown.[139] Hypoxia complicates many of the other diseases which have already been discussed, and modifies the effects of many vasoactive substances.[140 141] In healthy subjects hypoxia per se does not appear to increase circulating serotonin levels,[142] but levels are increased in patients with several types of chronic lung disease and associated pulmonary hypertension.[143 144] Patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension show evidence of greater activation of platelets in pulmonary vessels than those with normotensive COPD,[145 146] and a reduced platelet survival time is also found.[147] In animal models platelets release their contents into the lung during hypoxic vasoconstriction.[148] The release of platelet contents and the progression of pulmonary hypertension in patients with COPD may be slowed with the use of the platelet-inhibiting drug dipyridamole.[149 150] This agent also reduced pulmonary artery pressure and the thickness of pulmonary arteries in rats exposed to chronic hypoxia.[151 152]

## Inherited and acquired platelet disorders

PLATELET STORAGE POOL DISEASES

As noted above, patients with a deficiency of dense granules in platelets are unable to take up serotonin from the blood, often resulting in increased circulating levels of the amine. One such case of "platelet storage pool disease" has been described in which the patient developed severe pulmonary hypertension long after the platelet disorder was diagnosed.[153] Ketanserin alleviated the pulmonary hypertension in this case. An experimental model of platelet storage pool disease exists in the fawn hooded rat, an animal which is studied for its propensity to develop pulmonary hypertension.[154] In this species pulmonary vascular smooth muscle proliferates more rapidly in response to epidermal growth factor than in normotensive rats,[155] there is increased vasoconstrictor sensitivity to serotonin,[156] and decreased biogenic amine removal by lung tissue.[157] These rats also appear to have a genetic propensity to overproduce endothelin-1, another mitogen and vasoconstrictor.[158]

An acquired form of platelet storage pool disease, associated with disordered uptake of serotonin, occurs commonly in patients with myeloproliferative disorders.[159] Portal hypertension is a well recognised complication of these disorders and, in one series, a 13% incidence of pulmonary hypertension was also observed.[160] Platelets in patients with

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myeloproliferative disorders have also been found to have a selectively exaggerated serotonin release induced by immune complexes.[161]

PLATELET CELL MEMBRANE DISORDERS

In addition to myeloproliferative disorders, other diseases are characterised by platelet cell membrane abnormalities, thrombocytopenia, increased circulating serotonin levels, portal hypertension, and pulmonary hypertension. These include paroxysmal nocturnal haemoglobinuria[162–164] and the antiphospholipid syndrome.

Antiphospholipid antibodies occur in about 10% of patients with chronic thromboembolic pulmonary hypertension.[165] Other pulmonary manifestations include: (1) pulmonary emboli, (2) adult respiratory distress syndrome, (3) alveolar haemorrhage, (4) pulmonary capillaritis, and (5) primary thrombosis of the lung vessels.[166] These antibodies are also commonly found in association with collagen diseases. They may interact with phospholipids and phosopholipid-bound proteins in blood vessel walls and platelets causing damage to vessel walls and platelet aggregation, resulting in thrombocytopenia.[167 168]

THROMBOCYTOPENIA IN PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Platelets have been also implicated in the pathophysiology of persistent pulmonary hypertension of the newborn. Segall *et al* identified 90 newborn infants with perinatal asphyxiation and found that only the 12 infants with thrombocytopenia had proven pulmonary hypertension.[169] These authors suspected that platelet derived thromboxane $A_2$ may have caused the hypertension, but were unable to find a correlation between pulmonary artery pressures and prostaglandin metabolites. In another study it was determined prospectively that infants who developed persistent pulmonary hypertension as a result of meconium aspiration could be identified by the onset of thrombocytopenia prior to the hypertension.[170]

## Serotonin antagonists

The $S_2$ receptor antagonist ketanserin is the best studied agent of this type for reducing pulmonary hypertension or vascular resistance. Inhibition of platelet aggregation is another effect.[43] Like most vasodilators this drug has varying efficacy, reflecting the complex pathophysiology of the disease. In the treatment of primary pulmonary hypertension, McGoon *et al* detected an average reduction of pulmonary vascular resistance of 18% with intravenous use in 10 patients.[171] In a later study of 20 patients, eight of whom had not previously responded to other vasodilator therapy, the same authors found a small but significant decrease in pulmonary vascular resistance in the group as a whole, with a clinically significant response in three patients.[172] In addition to conditions previously discussed, studies showing haemodynamic benefits with ketanserin have involved patients with protamine induced pulmonary hypertension,[79] respiratory failure,[128] and valve surgery.[173 174] In comparison to nitroprusside, ketanserin usually improved gas exchange.[175] However Hamet *et al* could detect no change following administration of ketanserin in patients with hypoxic COPD.[176] Animal studies involving different species have shown decreases in pulmonary artery pressure following pulmonary oedema after acid injury,[177] serotonin induced pulmonary hypertension,[178] and endotoxaemia.[179] In the latter condition there is a phasic response. In several species serotonin was found to mediate the pulmonary hypertension occurring three hours after endotoxin injections, but not the more severe pulmonary hypertension which occurred earlier. Ketanserin had no effect in the first two hours, but was effective after three hours at a time when platelet counts ceased to fall.[180–182] Droperidol has been observed to prevent serotonin-induced bronchospasm and pulmonary hypertension in humans and dogs.[183 184]

Numerous pulmonary vasodilators are available, but their influence on survival has not been adequately demonstrated. Ketanserin is seldom mentioned in reviews of these agents, although in the short term it appears to be as efficacious as many other agents that have been more extensively studied. The effects of ketanserin on pulmonary hypertension suggest that serotonergic mechanisms may be contributing to the problem.

## General conclusions

The pathophysiology of pulmonary hypertension cannot be fully understood in terms of a traditional single cause and effect model. The concept of a balance of factors is probably more helpful. Under different circumstances three general, often interrelated, types of response are apparent: vasodilation/vasospasm, mitogenesis/cytostasis, and thrombosis/fibrinolysis. Although the vascular response to insult often appears relatively stereotyped, causes are invariably multifactorial. Genetic, environmental, nutritional, gender related factors and comorbidities are all likely to influence the final outcome. Serotonin is clearly an important and pervasive proinflammatory influence in these processes. Most authorities are now in agreement that serotonergic mechanisms are important in the pathogenesis of dietary pulmonary hypertension.[63 64 80 185] The role of serotonin in other varieties of pulmonary hypertension has been unjustly neglected.

The evaluation of effective therapies for this serious disorder demands a much better understanding of the precise mechanisms involved in different clinical situations and in different stages of the disease. In many variants the patients are young, the prognosis is very poor, and the clinical management is difficult. Vasodilator therapy in isolation is frequently ineffective. A multifaceted approach to treatment including antiserotonin agents or platelet modifying drugs may prove to be more successful.

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