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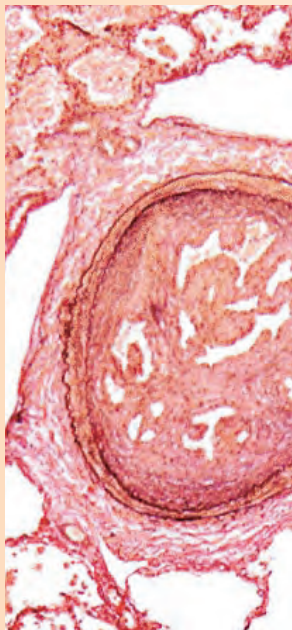
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Attenuated Coronary Collateral Function After Drug-Eluting Stent Implantation

A New Downside of Drug-Eluting Stents?

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Caution has been, and should continue to be, the watchword for coronary artery stent implantation. Astute cardiologists should not be lulled to sleep in the face of the overwhelming everyday success of their expert interventional colleagues' skill in the use of drug-eluting stents (DES). Despite its revolutionary advances, DES implantation has a downside. In addition to the rare complications known to occur during the implantation procedure (extensive dissection, emboli, perforation, side branch occlusion, early abrupt closure, and so on), DES are associated with late subacute thrombosis despite perfect implantation technique and concomitant antiplatelet therapy.

In the issue of the JACC (Vol. 49, No. 1, 2007), Meier et al. identify a new downside to DES: the late attenuation of collateral function. Recall that the most important, if not the only, role of coronary collaterals is to protect the myocardium from ischemia. The rate and type of collateral recruitment with or without angiogenesis vary greatly and for reasons not completely understood. Acute recruitment of collateral flow can be demonstrated in some normal hearts without coronary artery disease. However, in most but not all patients with chronic ischemic heart disease, collaterals are recruited slowly, forming gradually over time. Responding to loss of distal coronary perfusion pressure and intermittent ischemia, angiogenic growth factors and other mediators are postulated to promote formation of new capillary pathways, thus improving perfusion to the challenged myocardial bed. In other patients, for example, some acute myocardial infarction (MI) patients, collaterals are acutely recruited, opening immediately during abrupt arterial occlusion and serving to limit what would otherwise be extensive MI.

It is also important to note that collateral function can change after coronary intervention. Opening a chronic totally occluded vessel with percutaneous angioplasty alters the microcirculatory responses. Abrupt occlusion of a newly recanalized chronic total coronary artery occlusion may result in an MI even though substantial preexisting collaterals protected the myocardium before opening the occlusion. The restored perfusion after percutaneous coronary intervention (PCI) changed the collateral bed responses for the worse.

Collateral function after stenting.

Meier et al. studied 120 patients undergoing repeat PCI 6 months after baremetal stent (BMS, n = 60) and DES (n = 60) implantation, matching patients for clinical and angiographic features including the in-stent stenosis severity. The collateral flow index (CFI = coronary occlusion pressure/aortic pressure - central venous pressure) was measured during stent implantation using a pressure sensor angioplasty guidewire and invasively determined again at a follow-up catheterization. The functional impact of collaterals was also correlated to ischemic tolerance, as measured by intracoronary electrogram ST-segment elevation (≥ 0.1 mV) during ischemia induced by balloon coronary occlusion. Despite similar clinical and angiographic characteristics with equal in-stent stenosis severity ($46 \pm 34\%$ and $45 \pm 36\%$) at follow-up (6.2 \pm 10 months and 6.5 \pm 5 months), CFI was reduced in the DES group compared with the BMS group (0.154 ± 0.097 vs. 0.224 ± 0.142 ; $p \pm 0.0049$). Moreover, CFI failed to prevent ischemia (by intracoronary ECG), which occurred more frequently in the DES group (50 of 60) than in the BMS group (33 of 60, $p = 0.001$). This effect was less



pronounced in sirolimus-DES than paclitaxel-DES.

□ This study points to a new downside of DES (applicable to both sirolimus and paclitaxel): late impairment of collateral function might contribute to an increased ischemic burden in the event of late subacute thrombosis, and this loss could lead to more serious cardiac events when abrupt coronary occlusion occurs.

Why would the drugs on DES have an influence on collateral function?

Sirolimus and tacrolimus are potent immunosuppressant and antiproliferative drugs. Tacrolimus reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506-binding protein), creating a new complex (FKBP12-FK506) that interacts with and inhibits calcineurin, thus inhibiting both T-lymphocyte signal transduction and interleukin (IL)-2 transcription and production. In a similar, but not identical, way, sirolimus acts by binding to the cytosolic protein FK-binding protein 12 (FKBP12). However, the sirolimus-FKBP12 complex does not affect calcineurin but rather inhibits the mammalian target of rapamycin (mTOR) pathway through derepression of PP2A, inhibiting lymphocyte proliferation and responses to IL-2 as well as blocking the activation of T- and B-cells. Some of these mechanisms likely affect either the stimuli of or direct response to collateral angiogenesis.

Stimuli to collateral development.

Few pathogenetic factors have been described that favorably or unfavorably influence collateral development and angiogenesis. The duration of myocardial ischemic symptoms and the severity of epicardial stenotic lesions (physiologically speaking) are the best known stimuli to collateralization. In Meier et al. no evident difference in clinical presentations among patient groups was seen. Angiogenesis often accompanies tumor growth and development. Rapamycin inhibits metastatic tumor growth in in vivo mouse models. Does the inhibition of the associated carcinogenic angiogenic mechanisms play a role in collateral growth impairment? The answer is not known. However, the antiangiogenic properties of rapamycin are linked to decreased production of vascular endothelial growth factor (VEGF) and an inhibited response of vascular endothelial cells to stimulation by VEGF. Peripheral blood mononuclear cells from healthy human volunteers were inhibited by sirolimus to outgrow to smooth muscle-like and endothelial cell-like cells (early neointimal hyperplasia). Thus, although sirolimus acts against large-vessel restenosis, it is conceivable that its

inhibitory effect on smooth-muscle progenitor cells affects re-endothelialization or distant angiogenesis. Interestingly, the adverse effects of DES on endothelialization and endothelial function have been shown only for sirolimus-eluting stents, but collateral function attenuation was seen for both sirolimus and paclitaxel in the study by Meier et al. The important new findings that both sirolimus and paclitaxel elicit a negative effect on collateral function, and that the effect of sirolimus appears to be less pronounced than that of paclitaxel, require further exploration into mechanisms of collateral stimulation angiogenesis beyond our current understanding.

Study limitations.

The limitations of the current study are few. The investigators have a long and distinguished track record of successful explorations in the subtleties of directly measured coronary physiologic responses in patients during cardiac catheterization. The technical feat of such data collection, coupled with ischemic quantification, should be acknowledged, and its limitations would be unlikely to yield spurious results. The need to study collateral function over time from the large data bank of BMS- and DES-treated patients did not permit randomization beforehand and limited intra- and intergroup comparisons. It is understandable why the limited applications of BMS precluded such study. Finally, concerns may exist regarding individual propensities to form collaterals that might skew the results. No clinical study can guarantee precise patient matching, but the statistical analysis appeared to discount this factor as an important influence on the results.

Clinical implications.

This study highlights a previously unappreciated downside of DES. Although it is still of largely theoretical concern, should abrupt late occlusion occur after DES, the normal collateral protection would be impaired to some degree, with more ischemia potentially permitting a larger ischemic insult and higher mortality risk than would otherwise occur. No one would question the acceptance of this downside given the superior long-term restenosis results for the vast majority of our patients with DES. The observations from this study serve to focus our attention on how and why collaterals act to protect the heart and what the future might hold for pharmacologic manipulation of collateral function.

Reference: Journal of the American College of Cardiology, 2007, Vol. 49(1), pp: 21-22.



Pulmonary arterial hypertension: classification, diagnosis and contemporary management

Positioned between the two sides of the heart and residing within the lungs, the pulmonary circulation has a central role in cardiopulmonary gas exchange and oxygen transport. Its central position also renders the pulmonary circulation prone to injury as a result of disorders affecting the heart, lungs or systemic circulation. An uncommon, but serious and potentially devastating chronic disorder of the pulmonary circulation is pulmonary hypertension, a haemodynamic abnormality of diverse aetiology and pathogenesis. Over the past decade, several advances have occurred in the understanding, classification and medical management of pulmonary hypertension. This article outlines the approach to the diagnosis of pulmonary arterial hypertension (PAH) and discusses the use of currently available drug treatments and surgical procedures for this condition.

Definition and classification

Pulmonary hypertension (PHT) is defined as sustained increase in mean pulmonary arterial (PA) pressure to a level greater than 25 mmHg at rest or greater than 30 mmHg during exercise, with a normal pulmonary artery wedge pressure <15 mmHg and an increased PVR to greater than three Wood units.

There are many causes of PHT but it is most commonly seen (and previously referred to as secondary PHT) complicating left heart disease and parenchymal lung disease. To further confuse things, the previous classification system also used the term secondary PHT to describe a larger heterogenous group of diseases, where a casual agent (e.g. anorexigen) or associated disease (e.g. connective tissue disease, Eisenmenger's physiology, liver cirrhosis) was identified. This was distinguished from an unclassified condition, where PHT was present with no identified cause or association- referred to as primary PHT (PPH). In response to an increasing understanding of the biology and physiology of PHT, the World Health Organization (WHO) sponsored an expert working group to develop a new classification (Table 1). This classifies PHT by a combination anatomical site of principal lesion (e.g. PAH, pulmonary veno-occlusive disease (PVOD)) and aetiology (e.g. thromboembolic PHT, PAH secondary to connective tissue disease). This new classification system is much more useful when considering the natural history, prognosis and potential therapies of the different causes of PHT. Group 1 in the classification includes PHT, where the lesion is primarily of the arterial bed (particularly the pulmonary arteriole)-PAH, including idiopathic PAH (iPAH) and familial PAH (fPAH) (terms which have replaced the old term PPH). PAH can also occur with known associations, including connective tissue diseases especially the limited cutaneous form of scleroderma (commonly referred to as CREST syndrome) and in association with anorexigen and other drug or toxin use, portal hypertension (portoPHT), HIV disease, myeloproliferative disorders, in

poorly controlled thyrotoxicosis and in some rare metabolic diseases. PAH can also occur secondary to congenital systemic to pulmonary shunts (Eisenmenger syndrome). These syndromes are significantly different from iPAH in terms of their pathogenesis and natural history; however, there is increasing evidence that the specific PAH therapies may also be effective. Two rare conditions namely PVOD and pulmonary capillary haemangiomatosis (PCH) are characterized by similar changes in the pulmonary arterioles, but additional significant venous or capillary involvement. It is important to differentiate them from iPAH as selective pulmonary arteriolar dilators may cause severe pulmonary oedema. PHT may also arise as a result of chronic thromboembolic disease (CTEPH). This is defined separately in the classification as many patients may be amenable to surgical correction (pulmonary thromboendarterectomy), although medical therapy may have some efficacy. PHT complicating left heart disease and lung disease are classified separately as treatment is directed primarily at the underlying cause and correction of hypoxaemia.

Table 1 : World Health Organization classification of pulmonary hypertension

Group 1: pulmonary arterial hypertension
<ul style="list-style-type: none"> Idiopathic Familial Known associations <ul style="list-style-type: none"> Connective tissue disease Portopulmonary hypertension HIV Anorexigens, drugs and toxins Thyrotoxicosis Haematological abnormalities Splenectomy Congenital systemic to pulmonary shunts (Eisenmenger syndrome) Persisting pulmonary hypertension of the newborn Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis
Group 2: pulmonary hypertension in association with left heart disease
<ul style="list-style-type: none"> Left ventricular disease Aortic or mitral valve disease
Group 3: pulmonary hypertension in association with hypoxic respiratory disease
<ul style="list-style-type: none"> Sleep apnoea Chronic obstructive pulmonary disease Interstitial lung disease
Group 4: pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group 5: miscellaneous
<ul style="list-style-type: none"> Sarcoidosis Histiocytosis X



Epidemiology and genetics

The incidence and prevalence of PAH is uncertain. A recent study examining iPAH in Scotland found that in adults between 16-65 years of age, there was an incidence of 2.5/million per year in men and 4.0/million per year in women. The point prevalence of iPAH is likely to be approximately 15-20/million. As patients with PAH tend to be equally distributed between the idiopathic and associated categories, 40/million is a reasonable prevalence estimate in the community. Physicians have often considered iPAH in women (often peripartum) presenting with unexplained dyspnoea in their third or fourth decade of life. It is increasingly apparent that iPAH can present in both genders at all ages. The fPAH shows an autosomal dominant inheritance but with genetic anticipation (presenting earlier in successive generations) and only 10-20% penetrance (i.e. a low rate of disease even in those carrying the defective gene). The best described genetic mutation causing PAH is in the transforming growth factor- β receptor family (e.g. the bone morphogenic protein receptor type 2 (BMPR-II)).

Pathogenesis and rationale for specific PAH therapies

The pathobiology of PAH is focused on the pulmonary arteriole due to a combination of vasoconstriction, vascular remodelling (particularly intimal and medial proliferation), formation of plexiform lesions and thrombosis. It is assumed that the very low rates of response to acute vasodilator challenge reflects the small contribution of vasoconstriction relative to vascular remodelling. Progressive narrowing of the pulmonary arteriole leads to increase in PVR, hypertrophy of the right ventricle (RV) with the progressive rise of PA pressure. The physiological consequences are poor cardiac output response to exercise (with the cardinal symptom exertional dyspnoea); impaired ventilation perfusion matching may cause hypoxaemia (although shunting through a patent foramen ovale is another important cause), but ultimately as the disease progresses, right ventricular dysfunction and failure develop. Bowing of the intraventricular septum may cause compression (with dysfunction) of the left ventricle. The high pressure within the RV may impede blood flow down the right coronary artery with the development of right ventricular angina. Within the pulmonary arterioles, the main cellular changes involve the endothelium, platelets, smooth muscle cells and adventitial fibroblasts. At least three major signalling pathways are important in the course of PAH: (i) the prostacyclin (PGI₂) pathway, (ii) the nitric oxide (NO)-cGMP-phosphodiesterase 5 (PDE-5) pathway and (iii) the endothelin pathway. An imbalance between the upregulated vasoconstrictive/pro-proliferative endothelin system and downregulated vasodilatory/antiproliferative /antithrombotic NO and PGI₂ system is felt to be a key contributor to initiation and progression of disease. Platelets may have an important role, as pro-coagulant, by increasing platelet release of serotonin (contributing to smooth muscle vasoconstriction and proliferation), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF,

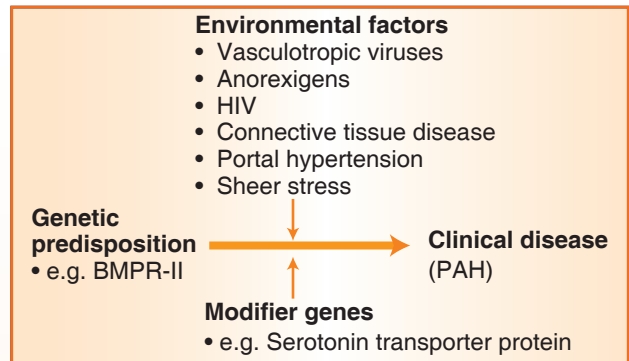


Figure 1 : Multiple hit hypothesis of pathogenesis of pulmonary arterial hypertension (PAH). BMPR-II, bone morphogenic protein receptor type 2.

PDGF as well as other growth factors, such as epidermal growth factor and insulin-like growth factor-1, are upregulated in PAH. These may contribute to endothelial cell dysfunction and proliferation as well as abnormal smooth muscle and adventitial proliferation. Ion channel abnormalities within the smooth muscle cells may also play a role. The loss of some of the normal voltage-gated potassium (K⁺) channels leading to increased intracellular calcium and resultant vasoconstriction and smooth muscle proliferation has been reported. Vasculitis may be important in certain forms of PAH (e.g. systemic lupus erythematosus (SLE)), with immunosuppressive medications shown to be effective in some forms of PAH.

Clinical Presentation

Although PAH may be asymptomatic in its early stages, exertional dyspnoea is the most frequent presenting symptom and occurs virtually in all patients as the disease progresses. Fatigue and weakness are also common and a minority of patients may report angina or syncope. As PAH may be associated with a variety of conditions, evidence of a related illness should be considered. Orthopnoea and paroxysmal nocturnal dyspnoea are suggestive of pulmonary congestion due to left-sided heart disease. Raynaud's phenomenon, arthralgias and non-specific systemic symptoms should raise the possibility of an underlying connective tissue disorder. A history of snoring or apnoea warrants evaluation for sleep-disordered breathing. The appearance of peripheral oedema and abdominal distension indicate advanced disease with the development of right ventricular dysfunction and tricuspid regurgitation. Classical physical signs of PAH include a loud pulmonary component of the second heart sound and the presence of a left parasternal heave suggestive of right ventricular hypertrophy. The murmurs of pulmonary and tricuspid regurgitation and signs of right ventricular failure indicate advanced disease. Other physical signs-for example, finger clubbing in the case of cyanotic congenital heart disease-may provide insights into the underlying aetiology.

□ The modification of the New York Heart Association (NYHA) classification of functional status by the WHO sponsored expert group for patients with PAH has provided a very useful framework for describing symptom



severity both in clinical trials and clinical practice. The function classes are defined as follows:

1. NYHA/WHO class I: patients with PHT in whom there is no limitation of usual physical activity; ordinary activity does not cause increased dyspnoea, fatigue, chest pain or presyncope.
2. NYHA/WHO class II: patients with PHT who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or presyncope.
3. NYHA/WHO class III: patients with PHT who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or presyncope.
4. NYHA/WHO class IV: patients with PHT who are unable to carry out any physical activity at rest and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Diagnostic Evaluation

Figure 2 summarises the diagnostic algorithm for PAH. Electrocardiographic (ECG) signs of the right heart compromise include right axis deviation, right ventricular hypertrophy and peaked p waves. However, the ECG lacks sufficient diagnostic accuracy to serve as a screening tool for the detection of PAH. Although the chest x ray may disclose abnormal anatomic features due to PAH and its potential causes, it is usually normal in those without symptoms. The most useful and accessible imaging modality for diagnostic purposes is echocardiography, providing a quantitative estimate of pulmonary arterial pressure and assessment of associated anatomical abnormalities such as right ventricular enlargement. Once the presence of PAH is confirmed, investigations should be aimed at identifying an underlying cause. Echocardiography provides the benefit of being able to exclude considerable left heart disease and congenital heart disease and guiding the need and timing of cardiac catheterisation. Chronic thromboembolic pulmonary disease is a potentially curable condition that should be considered in all patients with unexplained PAH. Ventilation perfusion scanning should be performed to rule out the condition, as a normal scan effectively excludes the diagnosis. Pulmonary function testing and arterial blood gas sampling should be carried out to check for underlying chronic airway or parenchymal lung disease. However, it should be borne in mind that even about 20% of patients with idiopathic PAH or chronic pulmonary thromboembolic disease have a restrictive defect (lung volumes, 80% of predicted). If PAH remains unexplained, serological testing for connective tissue disease and HIV infection should be carried out. Although PAH has been described in all of the connective tissue disorders, it occurs most commonly in systemic sclerosis and mixed connective tissue disease, affecting 15-20% of cases. HIV infection is associated with an increased prevalence of PAH of up to 1 in 200 cases. Notably, PAH also occurs in other diseases such as

sickle-cell disease, and chronic liver and renal disease. Ingestion of appetite suppressants, tryptophan and contaminated rapeseed oil have all been associated with the development of PAH. Because of its inherent risks, lung biopsy is not recommended unless diagnosis can be made by only histological examination. Right heart catheterisation remains the gold standard for assessment of pulmonary haemodynamics by providing direct and accurate measurements of pulmonary arterial pressure, pulmonary vascular resistance and cardiac output. The absence of identifiable secondary causes of PAH should prompt the need for genetic testing. Mutations in the bone morphogenetic protein receptor II gene have been identified in approximately 50% of patients with a familial history of PAH and 25% of patients thought to have sporadic idiopathic PAH. Familial PAH is inherited in an autosomal dominant manner with incomplete penetrance of 10-20%. The age of onset of familial PAH is broad, ranging from 1 to 74 years. Genetic testing is usually performed in families with PAH in whom a specific bone morphogenetic protein receptor II mutation has previously been identified. A subject who possesses this mutation has a 10-20% risk of developing familial PAH, whereas in case of absence of the mutation, the risk is no different from the general population. Patients with idiopathic PAH should be advised about the availability of genetic testing and counselling for their relatives.

Natural History

Symptomatic status and the 6-min walk test are predictive of survival. An absence of symptoms or mild symptoms with normal activity is associated with a mean survival of 5 years, whereas moderate symptoms preventing normal activity or symptoms at rest are associated with a mean survival of 2.5 years and 6 months, respectively. If left untreated, PAH is characterised by a progressive increase in pulmonary vascular resistance leading to worsening right ventricular function and death.

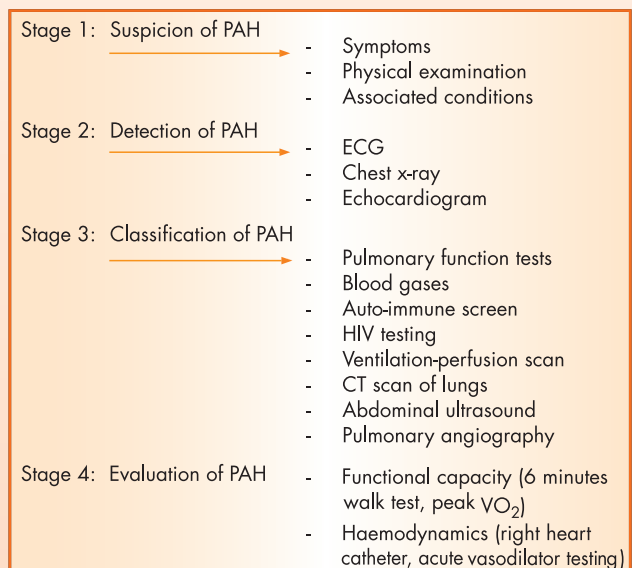


Figure 2: Diagnostic evaluation of pulmonary arterial hypertension (PAH).



General Treatment Measures

General treatment measures for PAH should be considered after the identification of any underlying associated disorders or contributing factors (fig-3). Although these treatments (calcium channel blockers, warfarin, supplemental oxygen, diuretics and digoxin) are not supported by randomised controlled trials, they are widely used in the management of PAH and are generally accepted as being important and efficacious.

Intense vasodilator testing is central to formulating the treatment strategies for idiopathic PAH, the primary objective being to delineate those who show considerable reductions in pulmonary arterial pressure (defined as a fall in mean pulmonary arterial pressure of at least 10 to ≤ 40 mm Hg, with an increased or unchanged cardiac output) and might effectively be treated with oral vasodilating drugs. The principle of intense vasodilator testing and treatment was established by an early report which showed that oral diazoxide improved clinical symptoms and cardiopulmonary haemodynamics when given to those with a positive response to injections of diazoxide directed into the main pulmonary trunk. After a number of clinical studies since then, shortacting vasodilators in the form of either intravenous epoprostenol or inhaled nitric oxide are now the preferred agents for vasodilator testing. In addition, based on therapeutic studies in PAH over the past two decades, patients who show a remarkable response to vasodilator testing are given oral calcium channel blockers as first-choice vasodilating drugs. In a prospective non-randomised study, Rich et al showed that 17 patients with a favourable good vasodilator response had a 94% 5-year survival rate when treated with high-dose calcium channel blockers compared with a 38% 5-year survival rate in 47 patients classified as non-

responders to intense vasodilator testing. Nifedipine, amlodipine or diltiazem may be given, and the choice could be based on the baseline heart rate. Verapamil should be avoided because of its negative inotropic effect. In general, the use of calcium channel blockers should be monitored closely to determine both the safety and efficacy of treatment. Calcium channel blockers should not be used empirically to treat PAH in the absence of proved vasoreactivity, and should be avoided in unstable patients or those with severe right heart failure.

Microscopic thrombosis has been shown in some patients with idiopathic PAH. In addition, patients with right ventricular failure and venous stasis are at an increased risk for pulmonary thromboembolism. Consequently, improved survival has been reported with oral anticoagulation in patients with idiopathic PAH. When considering long-term anticoagulation in patients with PAH, the risk:benefit ratio should be carefully taken into account. In general, patients with PAH receiving treatment with long-term intravenous epoprostenol (discussed below) should be anticoagulated in the absence of contraindications, partly because of the risk of catheter-related thrombosis.

As hypoxaemia is a potent pulmonary vasoconstrictor, supplemental oxygen should be used as necessary in patients with idiopathic PAH to maintain oxygen saturations at . 90% at all times. Diuretics and digoxin may be given in patients with right heart failure, and respiratory tract infections should be treated aggressively.

Newer Drug Therapies

Patients with moderate to severe limitation of physical activity unresponsive to calcium channel blockers should be considered for long-term treatment with more specialised treatments such as prostacyclin analogues or endothelin receptor antagonists (fig-3). In contrast with the treatments described in the previous section, the efficacy of these more specific treatments is supported by a limited number of randomised controlled trials.

Prostacyclin analogues

There is evidence to suggest that a relative deficiency of prostacyclin, a potent vasodilator with antiplatelet effects, may contribute to the pathogenesis of PAH. Consequently, recent studies have investigated the possibility that prostacyclin analogues might be of long-term benefit to patients with moderate or severe PAH. Randomised, controlled, open label trials of the intravenously administered prostacyclin analogue, epoprostenol, have shown a beneficial effect on exercise capacity, haemodynamics and quality of life in patients with moderate to severe PAH. In addition, a recent report of long-term epoprostenol therapy in 162 consecutive patients with idiopathic PAH followed up for an average of 3 years observed a 3-year survival rate of 63% compared with the expected survival of 35% based on historical data. However, the use of epoprostenol is complicated by the need for continuous intravenous infusion, causing inconvenience to the patient and increasing the risk of systemic infection and venous thrombosis. The drug is unstable at room temperature and has a very short half life of 6 min in the bloodstream. Common side effects include

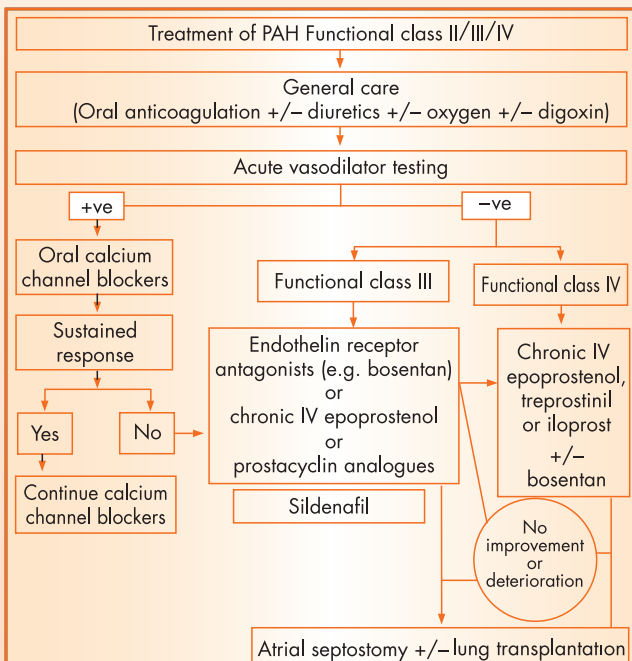


Figure 3 : Algorithm for the treatment of pulmonary arterial hypertension (PAH).



headache, flushing, jaw pain, nausea and rash; because of its short half life, abrupt cessation of treatment can also cause a rebound worsening of PAH in some patients.

The requirement for constant intravenous infusion of epoprostenol has led to the development of prostacyclin analogues with alternative routes of delivery. Treprostinil is a prostacyclin analogue which is stable at room temperature, has a half life of 3 h and can be given subcutaneously. The use of treprostinil has shown improvements in exercise capacity and haemodynamics similar to intravenous epoprostenol. However, a significant problem associated with treprostinil is pain and erythema at the infusion site, making administration of the target dose of the drug difficult to achieve.

▣ The use of the inhaled prostacyclin analogue, iloprost, is an attractive alternative option that has been applied to clinical practice and, based on available data, appears to be a safe, effective and well-tolerated treatment for severe PAH. A 3-month, randomised, double-blind, placebo-controlled trial in 203 patients with PAH showed significant beneficial effects on symptoms status, exercise capacity and haemodynamics. Inhaled iloprost is generally well tolerated, but its main drawback is the relatively short duration of action requiring the use of 6-9 inhalations/day. Beraprost is the latest in the line of prostacyclin analogues and the first orally acting agent. It is an approved therapy for PAH in Japan and is currently under evaluation in Europe.

Endothelin receptor antagonists

Endothelin receptor antagonism is a promising therapeutic approach supported by increasing evidence of the pathogenic role of endothelin-1 in PAH. Endothelin-1 is a potent vasoconstrictor that might contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH. Plasma levels of endothelin-1 are correlated with exercise capacity, haemodynamics and disease severity. The endothelin receptor antagonists, bosentan and sitaxsentan, have undergone randomised, double-blind, placebo-controlled clinical trials in moderately to severely symptomatic patients with PAH. Both drugs have shown improvements in exercise capacity and haemodynamics after 3-4 months of treatment. Both drugs also have the advantage of oral administration with sitaxsentan owing to superior oral bioavailability and a longer duration of action. However, side-effects, including syncope and flushing, are common; in addition, the drugs should be administered cautiously because of a dose dependent increased risk of hepatotoxicity and important drug interactions.

Phosphodiesterase inhibitors

Several phosphodiesterase inhibitors, including dipyridamole, cause potent pulmonary vasodilatation in animal models of acute and chronic PAH. Early clinical studies showed that dipyridamole could reduce PAH. However, in practice, its use has been limited by the lack of potency and selectivity and systemic side effects. Several reports of non-randomised single-centre studies using the phosphodiesterase inhibitor sildenafil for the treatment of PAH suggest this agent to be promising, with

relatively few side effects. Sildenafil has been shown to block acute hypoxic pulmonary vasoconstriction in healthy volunteers and improve exercise capacity and pulmonary artery pressure in patients with PAH. However, randomised controlled trials are needed to compare the efficacy of sildenafil with those of other agents and evaluate its role in combination therapy. The use of combination therapies with different mechanisms of action has not been formally evaluated in clinical trials.

Surgical Treatment

The advances in medical therapies have overshadowed the role of surgical interventions. The rationale for surgical therapies in PAH is based on the identification of subsets of patients in whom a specific procedure is indicated. The three main forms of surgical treatment are atrial septostomy, pulmonary thromboendarterectomy and lung transplantation. The aim of atrial septostomy is to create a right to left shunt to decompress the right ventricle and increase systemic blood flow. This procedure was introduced following the observation that patients with PAH and a patent foramen ovale awaiting transplantation had a survival advantage over those without a patent foramen ovale. However, the procedure carries significant periprocedural morbidity and mortality, limiting its use to patients with severe PAH unresponsive to medical treatment, and requiring palliation or a bridge to transplantation. Pulmonary thromboendarterectomy may be indicated in patients with chronic pulmonary thromboembolism with moderate to severe symptoms, raised pulmonary vascular resistance, surgically accessible thrombus and no major comorbidities. However, great care must be taken in the appropriate selection of candidates for this technique as procedural mortality can be high. The use of prostacyclin analogues has reduced the need for lung transplantation. In the current era, transplant surgery should not be considered until after the failure of medical therapy.

Conclusions

The past decade has seen major advances in our understanding of the pathophysiological mechanisms underlying the development of PAH. The diagnosis is now more clearly defined according to a new clinical classification, and clear algorithms have been devised for the investigation of PAH. A number of controlled clinical trials have shown benefit of newer drug therapies such as prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors, and these advances in medical therapy have limited the role of surgical interventions. However, the complexity of the treatment options and the relatively rare occurrence of the disease necessitate referral to a specialist centre. Further research into the underlying mechanisms of disease and the evaluation of novel treatment modalities should lead to continued improvements in the management of this condition.

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Cardiology News

Outcome of Thrombolytic Treatment for Stroke Poor When Iron Stores High

Stroke patients with increased serum ferritin concentrations before thrombolytic treatment are more likely to have a poor clinical outcome, according to researchers in Spain. Iron overload has been associated with greater oxidative stress and brain injury in experimental cerebral ischemia and reperfusion. To see if iron levels affect stroke outcome, the researchers studied 134 consecutive patients with acute ischemic stroke treated with tissue plasminogen activator (t-PA) at four centers. They determined serum ferritin levels, as an index of cellular iron stores, at baseline and at 24 and 72 hours after treatment. Overall, 73 patients (54.5%) had poor outcome at 90 days. Ferritin concentrations at baseline were significantly higher in patients with poor outcome compared to those with good outcome, at a median of 165.1 ng/mL versus 17.5 ng/mL, respectively ($p < 0.001$). Serum ferritin levels higher than 79 ng/mL before tissue plasminogen activator treatment were independently associated with poor outcome. If these findings are confirmed iron chelators or free radical trapping agents should be used to reduce the neurotoxic effects of iron in patients with acute ischemic stroke who are treated with intravenous t-PA.

Stroke 2007;38:90-95.

Milk Blunts Benefits of Tea on Endothelium

German researchers have shown that adding milk to tea appears to blunt any protective effect that tea may have on endothelial cells. Tests on 16 volunteers showed that black tea significantly improves dilation in the brachial arteries, but that adding milk completely attenuated the effect. It is too early on the basis of this one study in just 16 people--to advocate that people not add milk to tea. It is also important to note that the milk is not in itself deleterious, rather, it blocks the benefits of the tea, which results from caseins in the milk binding to catechins in the tea. The latter are thought to mediate the effects on endothelial cells.

Eur Heart J 2007; DOI:10.1093/eurheartj/ehl442.

Iron Deficiency Accounts for Most Anemia in Heart Failure Patients

Most cases of anemia in patients with advanced heart failure derive from iron deficiency, according to a report from Greece. Iron deficiency is the most common anemia in patients with severe heart failure. When diagnosed, it must be aggressively treated. The team examined the etiology of anemia in 37 patients with end-stage congestive heart failure (CHF) that was refractory to standard medical therapy. Twenty-seven of the patients had iron deficiency anemia as confirmed by bone marrow aspirations. Tests for occult fecal blood were negative in 89% of patients with iron deficiency and in all patients without iron deficiency. The correction of anemia in patients with chronic heart failure is associated with clinical and probably survival improvement.

J Am Coll Cardiol 2006;48:2485-2489.

High Intake of Heme Iron Boosts Cardiovascular Risk in Diabetics

A diet rich in heme iron and in red meat may have adverse cardiovascular consequences in women with type 2 diabetes. It might be advisable that patients with type 2 diabetes may limit consumption of heme iron and red meat. Diabetes-related metabolic abnormalities may aggravate the adverse effects of excess iron stores on cardiovascular health. However, they say, little is known about whether iron consumption may also affect coronary heart disease risk. High intakes of both heme iron and red meat were associated with a significantly increased risk of fatal coronary heart disease, coronary revascularization, and total coronary heart disease. Specifically, total coronary heart disease risk was 50% greater in women with the highest intake of heme iron compared with those with the lowest intake. Diet-associated risks were greater in postmenopausal than in premenopausal women.

Diabetes Care 2007;30:101-106.

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Editorial Note

Dear Doctor,
We are happy to present the 8th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "**Pulmonary Arterial Hypertension**". We will appreciate your thoughtful comments to enrich the publication.
Thanks and regards.