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SERIES 'UPDATE ON PULMONARY HYPERTENSION'
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Medical management of primary pulmonary hypertension

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ABSTRACT: Primary pulmonary hypertension (PPH) is a poorly understood, progressive disease that is characterized by elevation of pulmonary artery pressure and vascular resistance, leading to right ventricular failure and death within 2–3 yrs after diagnosis.

Based upon the concept that vasoconstriction and thrombotic occlusion of resistance vessels precipitate this process, vasodilator therapy and anticoagulation have become the main strategies for improving survival in these patients. Whereas, a few years ago, medical therapy of primary pulmonary hypertension was perceived as a bridging therapy to lung or heart lung transplantation, modes of therapy are being clinically tested at this time to offer an alternative to the surgical treatment of this disease. However, no selective pulmonary vasodilator is yet available. Therefore, and because of the potential hazards of vasodilator treatment, standardized haemodynamic testing is performed prior to initiation of vasodilator treatment.

In this update, the currently available compounds both for haemodynamic testing and chronic therapy, their mode of action, method of administration and efficacy are reviewed.

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Primary pulmonary hypertension (PPH) is an uncommon disease characterized by increased pulmonary artery pressure (P_{pa}) and pulmonary vascular resistance (PVR), without an obvious cause [1–5]. A careful diagnostic evaluation, based on the exclusion of all other causes of pulmonary hypertension (table 1), is a requirement for appropriate management of this disease and alteration of its otherwise progressive course, which ends with right ventricular failure (RVF) and death of the patient [4].

Table 1. – Diagnostic entities resulting in pulmonary hypertension

Primary (1% of autopsy and catheter cases) including special forms such as:

Atrial septal defect (10%)
AIDS (0.5%) [6, 7]
Exogenous substance and drug-induced (*e.g.* toxic oil, aminorex fumarate, fenfluramine) [8–11]
Pulmonary capillary haemangiomatosis [12]
Veno-occlusive disease [13]
Platelet delta storage disease [14]
Familial PPH (7–10% of PPH, autosomal dominant with incomplete penetrance) [15]

Secondary:

to heart disease with elevated left atrial and end-diastolic left ventricular pressures (valvular, congenital [16, 17])
to systemic connective tissue diseases (*e.g.* CREST syndrome [18, 19])
to persistent foetal circulation [20]
to parenchymal lung disease (*e.g.* interstitial, obstructive, parasitic, granulomatous, kyphoscoliotic [21])
to pulmonary artery abnormalities (*e.g.* vasculitis, stenoses)
to alveolar hypoventilation syndromes (*e.g.* sleep apnoea syndrome [22])
to haemoglobinopathias [23] (*e.g.* sickle cell disease)
to chronic liver disease [24]
to pulmonary thromboemboli (CTEPH, ~0.1% of survived pulmonary emboli) [25]

AIDS: acquired immune deficiency syndrome; CREST: calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia; CTEPH: chronic thromboembolic pulmonary hypertension.

Haemodynamic testing

Based on the concept that vasoconstriction contributes to the pulmonary hypertension of most patients with PPH at some stage in the course of their disease, vasodilators offer a logical approach to therapy. Although little is known about the pathogeny of PPH and data now exist indicating that the elevation of P_{pa} is a common endpoint of a variety of disorders, it appears from a number of studies that the acute response to vasodilators gives an indication of the underlying pulmonary vascular morphology, and, thus, a clue to severity and prognosis of the disease.

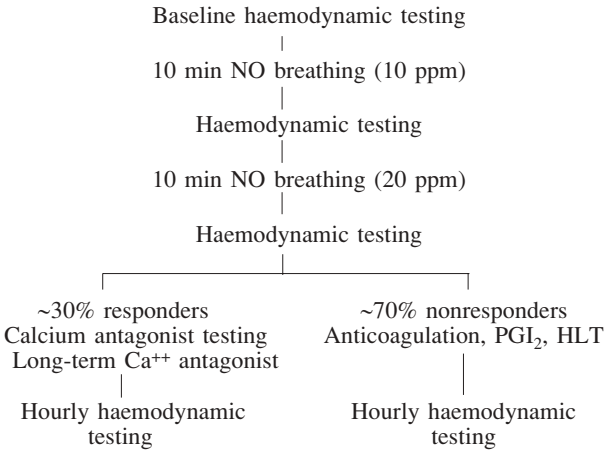
Morphometric studies have suggested that pulmonary vascular reactivity to vasodilators is lost as concentric medial hypertrophy gives way to intimal fibrosis and plexiform lesions. Therefore, various strategies have been developed for the evaluation of acute pulmonary vascular reactivity [26, 27]. A number of agents have

Table 2. – Haemodynamic testing

a) Current screening vasodilator agents to evaluate vasodilator reserve

Nitric oxide (NO) [28]
Epoprostenol sodium (prostacyclin (PGI_2)) [29–31]
Adenosine [32]
Acetylcholine [31, 33, 34]

b) Flow chart of haemodynamic testing



PGI_2: prostaglandin I_2 (prostacyclin); HLT: heart lung transplantation.

been successfully employed for acute testing (table 2a). At the present time, no selective intravenous or oral pulmonary vasodilator exists. The greatest and most reproducible vasodilator effect is achieved with inhaled nitric oxide (NO) and prostacyclin (table 2a), two agents that also offer the advantage of a very short plasma half-life. However, several groups have reported a higher incidence of adverse haemodynamic response in prostacyclin testing of patients with severe PPH compared with NO testing (personal communications).

Current practice of haemodynamic testing

The flow chart in table 2b depicts the practice of vasodilator testing. Pharmacological testing at our institution is carried out in the intensive care unit for a number of reasons:

1. Haemodynamic monitoring is carried out using a freshly implanted central venous line and involves measurement of cardiac output, pulmonary pressures, including capillary wedge pressure, central venous saturation and peripheral arterial saturation.
2. Prior to the measurements, the patient is rested for 2 h in a quiet environment.
3. Because of the lack of the normal gradient for myocardial perfusion between the aorta and the right ventricle, right ventricular coronary blood flow can be additionally compromised in the presence of a vasodilator, and result in acute right ventricular ischaemia. The occurrence of adverse side-effects, particularly when testing is carried out with prostacyclin, requires intensive care equipment.

Acute vasodilator testing should provide information about: 1) the presence or absence of vasoconstriction or "fixed" structural pulmonary vascular changes; 2) prognosis at the time of diagnosis; and 3) the haemodynamic safety of chronic vasodilator therapy.

Table 3. – Definition of response to pharmacological testing

Responders: reduction of PVR >20% and reduction of mean P_{pa} >20%
Nonresponders: no significant change of PVR
Unfavourable responders: symptomatic systemic hypotension with a reduction >20% of mean systemic blood pressure with no change or reduction of CI
Resistance responders: reduction of PVR >20% without significant reduction of mean P_{pa} (resistance responders are being evaluated and treated like responders)

PVR: pulmonary vascular resistance; P_{pa}: pulmonary artery pressure; CI: cardiac index.

Following baseline haemodynamic measurements, the patients breathe 10 parts per million (ppm) NO *via* a continuous positive airway mask (CPAP) mask, that they have already been wearing during the initial measurements. After 10 min, a complete haemodynamic measurement is performed. Another 10 min period of 20 ppm NO breathing follows, after which another complete haemodynamic measurement is performed. In "responders" (approximately 30% of adult and 60–70% of paediatric patients (table 3)) haemodynamic testing is continued with an oral dose of calcium antagonist (*e.g.* 10 mg of nifedipine), and measurements are taken every hour thereafter, with administration of another oral dose after each measurement, until the optimal response is reached in the absence of side-effects.

"Nonresponders" (table 3) are candidates for continuous intravenous prostacyclin therapy as a bridging therapy until transplantation, or as primary therapy. In instances when prostacyclin therapy cannot be administered for other reasons, standard therapy is initiated (see below).

Selected vasodilators used for haemodynamic testing

Nitric oxide. NO has been identified as the powerful endothelium-derived relaxing factor (EDRF) [35]. Isolated pulmonary arteries of humans relax with NO, but investigation *in vitro* is difficult because the effects of NO, *e.g.* binding to haemoglobin, occur within fractions of a second. NO reacts with oxyhaemoglobin to form methaemoglobin, nitrites and nitrates. Because NO is inactivated by haemoglobin, its vasorelaxant effects are restricted to the abluminal surface of the endothelium. However, if NO is inhaled, this obstacle can be overcome. NO reaches the abluminal pulmonary arterioles, which are closely associated with bronchioli and alveoli and are involved in rapid transfer across the alveolocapillary barrier, in a similar way to carbon monoxide.

NO has recently been shown to selectively and acutely vasodilate pulmonary vessels in various hypertensive states of the pulmonary vascular bed, such as hypoxic pulmonary vasoconstriction [36, 37], PPH in the neonate [38, 39], congenital heart disease [40], pulmonary hypertension after cardiac surgery [41–43], the adult respiratory distress syndrome [44], and chronic obstructive pulmonary disease [34]. In a preliminary report Pepke-Zaba *et al.* [45] have shown, in a small group of eight

adult patients with severe PPH, that short-term inhalation of NO led to selective pulmonary vasodilatation. However, the individual haemodynamic response was not provided in this study, and the air-NO mixture was tested only at a single concentration. Recent data have indicated the safe use of NO as a screening vasodilator agent in PPH, allowing discrimination between responders and nonresponders [28].

Prostacyclin (PGI_2). PGI_2 or epoprostenol sodium is a potent vasodilator that, when given acutely and chronically, has been shown to produce substantial and sustained haemodynamic but also symptomatic responses in patients with pulmonary hypertension. Prostacyclin, a metabolite of arachidonic acid, is synthesized and released from vascular endothelium and smooth muscle cells.

Mechanism of action. Vasodilation is thought to be mediated by activation of specific membrane PGI_2 receptors that are coupled to the adenylate and guanylate cyclase systems. Other effects, also mediated by specific receptors, include inhibition of platelet activation and aggregation, as well as leucocyte adhesion to the endothelium [46].

NOOTENS *et al*. [46], studied the haemodynamic effects of prostacyclin in PPH and compared them with the effects of adenosine. Prostacyclin caused a fall in PVR from 13 to 10 Wood units (mean±SD 22±8%; $p<0.01$), and a significant increase in cardiac output ($p<0.01$), with no change in mean P_{pa}. There was a significant fall in systemic arterial pressure (P_{sys}) and in systemic vascular resistance (SVR) ($p<0.001$), with a trend towards increases in pulmonary capillary wedge pressure (PCWP) ($p=0.06$) and heart rate ($p<0.05$).

Side effects. Prostacyclin frequently causes adverse reactions, such as cutaneous flushing and headache, which usually resolve within a few minutes after discontinuation of the infusion. Sometimes bradycardia and severe systemic hypotension occur. Gastrointestinal symptoms are rarely reported.

Comparison between NO and prostacyclin in the assessment of pulmonary vasodilator response. In a recently published study, SITBON *et al*. [28] examined the short-term haemodynamic effects of incremental concentrations of an inhaled air-NO mixture compared with intravenous prostacyclin in 35 consecutive patients with PPH (25 females and 10 males). According to the definition of a significant response, *i.e*. reduction of PVR by at least 20%, 13 patients were responders to NO and PGI_2, whereas 22 patients did not respond to either drug. An additional interesting finding was that the level of mean right arterial pressure was lower in responders than in nonresponders (mean±SD 7±3 *vs* 10±4 mmHg; $p<0.03$).

Nitric oxide at 10 ppm produced maximal pulmonary vasodilatation within the first 2 min of inhalation, with no additional decrease both in mean P_{pa} and (total) PVR in responders when NO was administered at higher doses of 20 and 40 ppm. There was a close correlation between the percentage change in mean P_{pa} and PVR observed during NO inhalation and prostacyclin infusion. During the air-NO inhalation at the maximal concentration (40 ppm), the mean decrease in mean P_{pa} and PVR was 36±12% (range 15–52%) and 40±13% (range 30–65%), respectively. The mean decrease in P_{pa} and PVR achieved with a mean prostacyclin dose of 9.8±1.9 $ng \cdot kg^{-1} \cdot min^{-1}$ was 33±11% (range 17–50%) and 50±11% (range 31–67%), respectively.

Cardiac output did not change during NO inhalation, but rose significantly with prostacyclin infusion. Heart rate significantly decreased in responders to NO, whereas there was a slight but not significant rise in heart rate during prostacyclin infusion. Stroke volume increased significantly during both NO inhalation and prostacyclin infusion. SVR was lowered by prostacyclin, but did not change at any concentration of NO. Inhalation of NO did not produce clinical evidence of systemic vasodilation. The venous methaemoglobin level increased significantly after NO inhalation, while, at face mask level, NO_2 remained below 0.4 ppm. Inhaled NO in air at low concentrations seems to be as effective as prostacyclin for the acute assessment of pulmonary vasodilator response.

Compared with prostacyclin, NO may offer several advantages, such as a shorter delay before a peak effect is reached, easier administration, better safety and lower cost. At the present time, NO may be considered the gold standard screening agent in patients with severe PPH to be tested for vasodilator responsiveness and long-term vasodilator therapy. However, its safety and mode of administration for long-term use in PPH patients remains to be further evaluated.

Adenosine. Adenosine, an intermediate product in the metabolism of adenosine triphosphate, has been shown to be a potent vasodilator agent in addition to other pharmacological effects, such as modulation of platelet function. Vasodilation is thought to be mediated by action on specific vascular receptors. The mechanism that produces these effects is considered to be secondary to stimulation of endothelial cell and vascular smooth muscle receptors of the A2-type, which induce vascular smooth muscle relaxation by increasing intracellular cyclic adenosine monophosphate (cAMP). Adenosine causes coronary vasodilatation, decreases SVR and causes relaxation of smooth muscle *in vitro*, including pulmonary arteries and arterioles. Continuous intravenous infusion of adenosine in normal subjects decreases SVR and increases pulmonary blood flow, without significant changes in SAP.

Adenosine is a stable compound with a favourable safety profile and a very short serum half-life, which makes it a useful and desirable agent for testing vasodilator reserve of the pulmonary vascular bed in patients with pulmonary hypertension. In the study by SCHRADER *et al*. [32], patients were given an initial 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dose of adenosine. The dose was increased by 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 2 min intervals to a maximum dose of 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or until the development of side-effects. The data showed that the administration of maximal doses of adenosine (mean±SD 256±46 $\mu g \cdot kg^{-1} \cdot min^{-1}$) produced a 2.4% reduction in P_{pa}, which was statistically nonsignificant. However, adenosine caused a 37% decrease in PVR ($p<0.001$), and a 57% increase in cardiac index ($p<0.001$).

Side-effects. Chest pain (pressure or heaviness), dyspnoea, tingling, numbness of the extremities and nausea and/or a reduction in mean systemic blood pressure to

70 mmHg and an increase or decrease in heart rate of more than 50 beats·min^{-1} were noted as side-effects during adenosine infusion.

Comparison between adenosine and prostacyclin. The overall effect of the two drugs on PVR is similar, as well as a substantial increase in cardiac output. Both compounds decrease SVR. Prostacyclin induces a significant fall in P_{sys}, an effect not seen with adenosine. The longer half-life of prostacyclin may possibly account for this difference, with the effect of higher plasma concentrations in the systemic circulation.

Calcium-channel blockers. In 1987, RICH and BRUNDAGE [47] conducted a study to investigate the use of high doses of calcium channel blockers in patients with PPH. They found that when the drugs were titrated to produce maximal physiological effects and the patients were able to tolerate this high-dose therapy, reductions in P_{pa} and PVR appeared to last for a longer period of time. Patients, who had favourable responses showed improved symptoms as well as regression in right ventricular hypertrophy, documented by electrocardiography and echocardiography.

These, at the time sensational, results have served as the basis for a prospective study with nifedipine and/or diltiazem for patients with severe pulmonary hypertension of unknown aetiology. Of 64 patients, 17 responded to drug testing with a 39% reduction in mean P_{pa} ($p<0.001$) and a 53% reduction in the PVR index ($p<0.001$). Of the 17 patients who responded to treatment, 13 received a mean (±SD) daily dose of 172±41 mg of nifedipine and 4 received a mean daily dose of 720±208 mg diltiazem. Thirteen of the 17 patients who responded agreed to return for annual follow-up. Clinical improvement was noted in all patients. Functional exercise capacity and serial haemodynamic studies also documented the effectiveness of nifedipine and diltiazem; the mean P_{pa} and PVR at follow-up were similar to values obtained after the initial drug challenge in nearly all patients. The patients who were acute responders to either nifedipine or diltiazem had markedly better survival during the 5 year follow-up and thereafter, compared to the patients who showed no response. In a more recent study, RICH and co-workers [48] reported an improvement of 94 *versus* 55% 5 year survival in patients who responded to chronic high-dose oral calcium channel blockade.

In conclusion, of all adult patients with PPH, about 30% show a positive response to drug testing with either NO or prostacyclin. However, only about a third of these responders show acute vasoreactivity to administration of calcium channel blockers. Consequently, the overall response rate to either nifedipine or diltiazem is not greater than 5–10% of all patients with PPH who are eligible for testing.

The evaluation of the acute haemodynamic testing follows the definitions outlined in table 3.

Long-term medical therapy

General considerations

At the present time, pulmonary vasodilator therapy and oral anticoagulation are the main tools of long-term medical therapy. In addition, while a few years ago medical therapy in severe cases of PPH was designed as a bridging therapy to allow survival of patients until lung/heart-lung transplantation, medical therapy appears to have become an alternative to transplantation therapy in selected patients [30]. A wide variety of drugs are available today, with prostacyclin, and calcium channel blockers being the most widely-used and best studied (table 4).

Table 4. – Compounds used in the treatment of primary pulmonary hypertension

Parasympathomimetic agents
Acetylcholine [31, 33, 34]
Alpha-adrenergic antagonists
Tolazoline [49, 50]
Prazosine [51]
Phentolamine [52]
Urapidil [53]
Direct-acting vasodilators
Hydralazine [54–59]
Diazoxide [60–64]
Nitrates [59]
Nitroprusside [59, 65]
Angiotensin-converting enzyme inhibitors
Captopril [66–68]
Bipyridine derivatives
Amrinone [55]
Calcium channel blocker
Nifedipine [32, 55, 69–78]
Diltiazem [79, 80]
Verapamil [81, 82]
Prostaglandins
PGI_2 (prostacyclin, epoprostenol) [17, 30, 49, 83–90]
PGE_1 [91, 92]
Iloprost [93]
Anticoagulation
Coumadine [47, 94]

PG: prostaglandin.

Based upon the result of the initial testing, responders are continued on calcium channel blockers at a dose that permits maximal haemodynamic response in the pulmonary vascular bed in the absence of adverse side-effects. According to the dosing regimen of acute vasodilator testing (table 2b), the long-term dose would be one or two steps below the maximal dose that was tolerated without adverse symptoms, *e.g.* 20–40 mg nifedipine or 60–120 mg diltiazem below the maximal dose. Nonresponders to calcium channel blockers are placed on continuous prostacyclin, after obtaining informed consent, and a careful evaluation is made of the suitability for continuous intravenous therapy utilizing an ambulatory infusion pump (see below).

Apart from vasodilator therapy, oral anticoagulation, medication with glycosides and diuretics, and physical rest remain important additions to medical therapy in PPH. The rationale for glycosides is the prevention of the potentially devastating effect of atrial arrhythmias in this disorder, where atrial systole is an important contributor to ventricular filling in the presence of elevated end-diastolic ventricular pressure. A potential positive inotropic effect on the right ventricle has not been proved.

The rationale for oral anticoagulants is the frequent histopathological finding of extensive thrombosis in small pulmonary resistance vessels, but also in the main pulmonary arteries, resulting in confusing clinical

presentation and misinterpretation of similar cases as chronic thromboembolic pulmonary hypertension [95]. Our own experience, derived from transoesophageal echocardiography and nuclear magnetic resonance studies, has been the frequent observation of slow flow phenomena, sludging and microcavitations in the dilated main pulmonary arteries in patients with PVR above 1,000 dynes·sec·cm^{-5}, and poor right ventricular function with cardiac indices below 2 L·m^{-2}. Oral anticoagulation appears to prevent major thrombotic and thromboembolic complications in these settings.

Diuretics are used for the treatment of right ventricular failure. Potassium-saving diuretics, *e.g.* spironolactones are preferred, especially early on in the course of the disease, because of their milder mode of action, their aldosterone-antagonistic effect, which is desirable in the presence of liver congestion, and the possibility of using them on a daily basis.

Despite all pharmacological measures to reduce PVR, patients need to be advised to avoid physical activity, which causes dramatic increases of PVR. Furthermore, pregnancy and, more specifically, the postpartal period, are associated with serious aggravation of pulmonary hypertension [96]. Efficient birth control, avoiding oestrogen-progesterone formulations, is a very important measure in young female PPH patients.

Long-term continuous intravenous infusion of epoprostenol

Epoprostenol (prostacyclin or prostaglandin I_2 (PGI_2)) is a potent, endogenous, short-acting vasodilator and inhibitor of platelet aggregation, that is produced by the vascular endothelium. Epoprostenol decreases PVR and increases cardiac output and systemic oxygen delivery, when acutely administered to patients with PPH [97]. It has been widely-used in these patients on a short-term basis to determine the potential and magnitude of their vasoreactivity, and whether long-term oral vasodilator therapy is warranted [30, 49, 72, 88–90, 97]. As early as 1984, HIGENBOTTAM and co-workers [88] reported the case of a single patient with severe PPH, in whom long-term continuous infusion of epoprostenol lessened disability and bought time for heart-lung transplantation. Subsequently, in an uncontrolled study, JONES *et al*. [89] reported sustained improvement in exercise tolerance in 10 patients with PPH treated with continuous epoprostenol. Thus, this procedure appeared at an early stage to be particularly useful as a "bridge" to lung transplantation in seriously ill patients with PPH, in whom oral vasodilator therapy was either contraindicated or of no demonstrable benefit. In 1990, RUBIN and co-workers [90], following an 8 week randomized prospective trial including 24 patients with severe PPH, reported that treatment with continuous intravenous epoprostenol produced haemodynamic improvement, as well as increased exercise capacity.

Long-term administration of epoprostenol is a complex procedure, and requires profound commitment from patients, as well as physicians. It should be used only by clinicians thoroughly experienced in the diagnosis and management of patients with PPH [98]. The current indication for such therapy is represented by patients in New York Heart Association (NYHA) functional class III or IV, who fail to respond to conventional therapy, either at presentation or over time. The drug is delivered on an ambulatory basis through a portable, lightweight, positive pressure driven infusion pump (fig. 1), which is connected to a permanent central venous catheter inserted into a subclavian or jugular vein, and tunnelized subcutaneously.

Fig. 1. – Ambulatory infusion pump system using a percutaneous central venous catheter. A variety of different pump models is currently available, permitting the patient to carry an infusion pack in a special shoulder bag, including ice packs for cooling the drug.

Temporary peripheral intravenous infusions may be used until central access is established. The initial chronic infusion rate of epoprostenol can be determined by acute dose-ranging procedures during right heart catheterization, with the infusion rate initiated at 2 ng·kg^{-1}·min^{-1}, and increased in increments of 2 ng·kg^{-1}·min^{-1} every ≥15 min, until side-effects, such as nausea, vomiting, headache or hypotension, occur [30, 84, 90]. During acute dose-ranging in clinical trials, the mean (±SD) maximum dose which did not elicit dose-limiting pharmacological effects was 8.6±0.3 ng·kg^{-1}·min^{-1}. Chronic infusions are then initiated at a dose of 4 ng·kg^{-1}·min^{-1} below the maximal tolerated dose determined during dose-ranging. However, the long-term infusion dose may be adjusted according to clinical needs and tolerance of the patients, and without the results of an acute dose-ranging during catheterization, particularly when the latter is thought to be hazardous in unstable and critically ill patients. Epoprostenol is, thus, infused continuously at an initial dose of 1–2 ng·kg^{-1}·min^{-1}, which is increased in a stepwise fashion by 1–2 ng·kg^{-1}·min^{-1} every 6–8 h over a 4–6 day time-period. Before hospital discharge, patients are trained in sterile technique, catheter care, drug preparation and administration of reconstituted solutions to be used for no longer than 8–12 h at room temperature.

The adequacy of treatment is assessed, based on clinical symptoms, and by means of serial 6 min walk-tests (with encouragement) carried out before and during the course of therapy. Based on persistence, recurrence, or worsening of symptoms, or because of deterioration of exercise capacity over time, increases in the chronic infusion rates can be expected in many patients [30, 84, 86, 88]. This is not necessarily due to a disease progression, as patients needing dose increase usually recover clinical stability with only small increases of 1–2 ng·kg^{-1}·min^{-1}. Furthermore, many of these patients who may initially have been sensitive to small doses of

epoprostenol do subsequently tolerate much higher doses, suggesting tachyphylaxis [30, 84, 86, 88, 89].

Several adverse events clearly attributable to the drug are common, usually short-lasting and reversible, and are regarded as minor complications. These include flushing and warmth, loose stools, headaches, photosensitivity, abdominal and jaw pain, nausea and vomiting, flu-like symptoms, anxiety and nervousness. Serious complications are most often attributable to the delivery system. Catheter-related sepsis has been reported in 10–14% of patients [30, 84, 86], is usually not fatal, but requires catheter replacement and prolonged hospital stay. Furthermore, clotting of the venous line has been reported, despite long-term anticoagulant therapy [86]. Mechanical problems in the drug delivery system, including occlusions, perforations, dislodgements of the catheter, and pump malfunction may result in underdosing or interruption of the infusion. While therapy is interrupted, patients can experience an exacerbation of symptoms, such as presyncope or syncope [83], which have been fatal [84]. Finally, most deaths that have occurred in patients while receiving continuous epoprostenol were attributable to disease progression [84, 86, 88].

There is now sufficient evidence that treatment with continuous epoprostenol not only improves exercise endurance and restores a good quality of life in most patients [30, 86], but also improve survival. In a nonrandomized study, HIGENBOTTAM and co-workers [88] reported that long-term treatment with epoprostenol could effectively improve survival of patients entered into the lung transplantation waiting list, and that it could double their chances of successful transplantation, compared with those patients who did not receive epoprostenol. BARST *et al*. [84] drew similar conclusions from the results of an open, multicentre, uncontrolled trial involving 18 patients with severe PPH treated with epoprostenol, who were compared with 31 PPH patients from the National Institute of Health (NIH) Registry who received standard therapy. It is interesting that in this study, some patients were treated with epoprostenol for periods greater than 5 yrs.

The beneficial effects of long-term epoprostenol infusion on survival have recently been confirmed by the results of a prospective, randomized, multicentre open trial, comparing the effects of epoprostenol plus conventional therapy with those of standard therapy alone in 81 PPH patients belonging to NYHA functional class III or IV [30]. As early as the 12th week of therapy, 8 patients had died, all of whom had been randomly assigned to receive conventional therapy. This study is the first randomized, controlled study undertaken to evaluate the influence of treatment of PPH on survival.

In keeping with the results of a study reported by RUBIN *et al*. [9] in the early 1990s, all subsequent studies evaluating haemodynamics in patients on long-term epoprostenol have reported an overall improvement in pulmonary haemodynamics during the first months of therapy, which is maintained over time [30, 85, 86, 88, 99]. Epoprostenol-treated patients have significant reductions in mean P_{pa} and PVR, and significant increases in cardiac output. However, this overall improvement in pulmonary haemodynamics is usually moderate, and does not seem to correlate with the long-term effects of therapy.

In the few studies in which patients were randomized, patients were treated independently of the short-term responses to epoprostenol during dose-ranging [30, 86, 90]. However, long-term beneficial effects, particularly on survival, were commonly seen in patients in whom no short- or long-term haemodynamic changes were manifested with epoprostenol [86, 90]. Thus, the long-term effects of epoprostenol in PPH may be only partially related to its vasodilator properties, and may be due, at least in part, to increased systemic oxygen transport [90], or to other as yet unknown effects on vascular growth and remodelling, *e.g*. the formation of new plexiform lesions, or platelet-endothelium interaction [83, 85, 100].

Anticoagulation

It has not yet been proved that thrombosis in small pulmonary vessels plays a role in the pathogenesis of PPH. WAGENVOORT and WAGENVOORT [101] analysed postmortem lungs from 156 patients with PPH. They found that in 31 of the 156 patients organized thrombi were located within small pulmonary arteries. It was concluded from these findings that thrombosis may be an important mechanism in the pathogenesis of PPH. In agreement with this concept is the clinical observation that anticoagulation appears to be effective in patients with PPH. A number of studies [48, 94] have meanwhile provided evidence that anticoagulation prolongs life in this patient group (for example, RICH *et al*. [48] reported 47 *versus* 31% 5 year survival).

Practice of oral anticoagulation. Oral anticoagulation with coumadines is the therapy of choice. Because of the frequent occurrence of chronic RVF and liver congestion, with subsequent fall in the plasma levels of circulating coagulation factors, the desired International Normalized Ratios are arbitrarily set low at 2.0–3.0 in our institution. Oral anticoagulation is also continued in parallel to long-term intravenous prostacyclin. In special circumstances, anticoagulation is performed with subcutaneous low molecular weight heparins, but data concerning the "safety" of such regimens are lacking. The question of whether long-term "platelet antagonists", such as the glycoprotein receptor IIb/IIIa antagonists or ticlopidine, will be as effective as coumadine, needs to be answered as our knowledge concerning the role of platelets in PPH increases and randomized studies are performed.

Future directions of therapy

Therapy in the future will depend on new insights into the pathogenesis of pulmonary hypertension (*e.g*. the understanding of molecular mechanisms underlying familial PPH) and the delineation of pathologically distinct entities within the clinical appearance of severe pressure elevation in the pulmonary vascular bed. Among the currently available drugs, the vasodilator prostacyclin has been outstanding in its capacity: 1) to lower PVR acutely; and 2) to improve exercise capacity and outcome in chronically treated patients, despite the lack of an acute haemodynamic response to the drug. However,

continuous delivery of the drug requires an ambulatory infusion pump over a central venous line, with a number of serious complications arising from infections, mechanical failure and human error.

Iloprost, a prostacyclin derivative with a plasma half-life of 1–3 h depending on the method of application, permits sufficient vasodilation without the need for continuous infusion. However, intravenous infusion is still required once daily, while the inhalation of the resuspended compound requires three hourly inhalative therapy [93]. The current need for an oral vasodilator is clear, since the majority of PPH patients are under 40 yrs of age and considerably handicapped by permanent intravenous infusion systems.

Another recently discovered vasodilator with very favourable properties is nitric oxide. Chronic ambulatory application [102], both continuous or in "spikes" is possible *via* portable containers in a similar fashion to long-term oxygen therapy, but this is still at an early stage of clinical evaluation [103, 104].

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