

# Inhaled iloprost for the control of pulmonary hypertension

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**Abstract:** Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by an elevated pulmonary arterial pressure and vascular resistance with a poor prognosis. Various pulmonary and extrapulmonary causes are now recognized to exist separately from the idiopathic form of pulmonary hypertension. An imbalance in the presence of vasoconstrictors and vasodilators plays an important role in the pathophysiology of the disease, one example being the lack of prostacyclin. Prostacyclin and its analogues are potent vasodilators with antithrombotic, antiproliferative and anti-inflammatory qualities, all of which are important factors in the pathogenesis of precapillary pulmonary hypertension. Iloprost is a stable prostacyclin analogue available for intravenous and aerosolized application. Due to the severe side effects of intravenous administration, the use of inhaled iloprost has become a mainstay in PAH therapy. However, owing to the necessity for 6 to 9 inhalations a day, oral treatment is often preferred as a first-line therapy. Numerous studies proving the efficacy and safety of inhaled iloprost have been performed. It is therefore available for a first-line therapy for PAH. The combination with endothelin-receptor antagonists or sildenafil has shown encouraging effects. Further studies with larger patient populations will have to demonstrate the use of combination therapy for long-term treatment of pulmonary hypertension.

**Keywords:** pulmonary arterial hypertension, prostacyclin, iloprost, inhaled

## Pulmonary hypertension

Pulmonary hypertension (PH) is an uncommon disease with a progressive course and poor prognosis. It is characterized by an elevated pulmonary arterial pressure exceeding 25 mmHg at rest.<sup>1</sup> The increase of pulmonary vascular resistance by different causes induces a right heart overload finally leading to right heart failure and death.

Vasoconstriction, in situ thrombosis in small arteries, and vascular remodeling by proliferation of smooth muscle cells with intimal fibrosis, medial hypertrophy, and adventitial thickening are major histopathological structural features of pulmonary vasculopathy.<sup>2</sup>

Underlying causes of PH have recently been summarized in the Venice classification (see Table 1).<sup>3</sup> Without treatment the median survival of patients with idiopathic pulmonary hypertension (IPAH) from the time of diagnosis is 2.8 years.<sup>4</sup>

This review highlights the role of prostacyclin in the pathophysiology of pulmonary arterial hypertension (PAH) and focuses on inhaled iloprost as a treatment for the various entities of PH. In addition, the role of iloprost for the control of acute PAH during surgery will be discussed.

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For the purpose of this review, we will refer to the Venice classification only, as further variations discussed recently have not yet been published officially. The term “primary pulmonary hypertension” used in previous classifications has been renamed and defined more precisely in the Venice classification of 2003<sup>3</sup> and includes IPAH and familial PAH since that time.

## Pathophysiology

In healthy subjects a balance of dilators and constrictors of the pulmonary vasculature results in a normal vascular tone in pulmonary arteries. The vessel's smooth muscle layer maintains a state of predominant relaxation.

Prostacyclin (PGI<sub>2</sub>) – a metabolite of arachidonic acid – is endogenously produced by PGI<sub>2</sub> synthase and released from pulmonary endothelial cells. It mediates vasodilatory effects on pulmonary arteries and systemic circulation by relaxation of smooth muscles and prevention of platelet aggregation due to an increasing intracellular concentration of cyclic adenosin monophosphate (cAMP).<sup>5</sup> In contrast, thromboxane<sup>6</sup> – produced by thromboxane synthase from arachidonic acid in platelets – mediates vasoconstriction and platelet aggregation.

In PAH, vascular remodeling and vasoconstriction are determined by an imbalance of the intracellularly synthesized factors.<sup>7</sup> Experiments in rats exposed to monocrotaline and in hypoxic mice developing PAH have shown increased PGI<sub>2</sub> synthase expression in the lung, partially antagonizing the rise in pulmonary arterial pressure.<sup>8,9</sup> A deficiency of PGI<sub>2</sub> synthase in remodeled pulmonary vasculature has been reported in patients suffering from severe PAH.<sup>10</sup> Accordingly, exogenous PGI<sub>2</sub> benefits patients with PAH by antagonizing the effects of vasoconstrictors such as thromboxane A<sub>2</sub> and serotonin,

which are increased in endothelial cells<sup>11</sup> causing platelet activation and thrombosis.<sup>12</sup> Prostacyclin also possesses positive inotropic effects resulting in an acutely increased cardiac output.<sup>13</sup> Long-term improvements of cardiac output may in contrast be caused by anti-remodeling effects of PGI<sub>2</sub>.<sup>14</sup>

Since the decrease of endogenous PGI<sub>2</sub> plays an important role in the pathogenesis of pulmonary arterial hypertension, the administration of exogenous PGI<sub>2</sub> and derivatives has become an area of intense investigation for more efficient therapies for patients with PAH.

## Prostacyclin and analogues

During the past two decades several PGI<sub>2</sub> derivatives have been synthesized and their effects on pulmonary arterial hypertension have been studied. Chronically intravenously administered epoprostenol<sup>14</sup> is characterized by a very short half-life (<6 min) but has a significant beneficial effect on patients with IPAH and scleroderma-associated PAH. The obligatory iv line, however, is prone to cause severe complications such as exit-site infections, deep venous thrombosis, catheter displacement, and pneumothorax.<sup>15,16</sup> Therefore, PGI<sub>2</sub> analogues with different physical conditions and half-lives delivered by alternative routes have been developed. Iloprost is a more stable analogue of PGI<sub>2</sub> with a longer half-life approaching 30 minutes and similar effects on hemodynamics compared to epoprostenol but still burdened with complications of its way of delivery.<sup>17</sup> Subcutaneously infused treprostinil with a half-life of 3 hours has led to improved exercise capacity and improved hemodynamics in patients with IPAH and PAH associated with collagen vascular disease.<sup>18</sup> However, side effects such as pain and induration at the infusion-site, headache, nausea, rash, and jaw pain are complications that are not rare. The first orally

**Table I** Venice classification of pulmonary arterial hypertension<sup>3</sup>

Group 1: Pulmonary arterial hypertension (PAH)	Idiopathic pulmonary hypertension (IPAH), familial PAH, associated with other diseases (eg, collagen vascular diseases, portal hypertension, congenital shunts, HIV infection, drugs and toxins), persisting PAH of the newborn, pulmonary venoocclusive disease, capillary hemangiomatosis
Group 2: Pulmonary venous hypertension	Left-sided atrial/ventricular heart disease, left-sided valvular heart disease
Group 3: PAH associated with hypoxemia/COPD	For example, interstitial lung diseases, chronic obstructive pulmonary diseases, sleep-disordered breathing, alveolar hypoventilation disorders
Group 4: PAH due to chronic thrombotic or embolic disease	Pulmonary embolism, thromboembolic obstruction of proximal or distal pulmonary arteries (eg, by foreign bodies, parasites, tumors, and so on)
Group 5: Miscellaneous underlying diseases	For example, sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels

active PGI<sub>2</sub> analogue, beraprost, had no significant effect on hemodynamics in patients with PAH in long-term studies<sup>19,20</sup> but has been shown to prolong survival in PAH patients, and to improve exercise capacity.<sup>21</sup> However, its use is limited by prostanoid typical side effects and diarrhea.

## Inhaled iloprost

For years, continuously administered PGI<sub>2</sub> and analogues have been used successfully to improve pulmonary hemodynamics and long-term prognosis in PAH patients. However, the development of tolerance and serious side effects of this treatment demonstrated the need for another route of application.

An alternative way of administration of PGI<sub>2</sub> has therefore been developed with aerosolized iloprost through inhalation. This PGI<sub>2</sub> analogue possesses similar vasodilative potency and efficacy profile compared with epoprostenol leading to the same intracellular effects after binding to the prostaglandin receptor.<sup>22</sup> Iloprost remains stable at room temperature and in ambient light at pH 7.4 and offers a longer half-life (20–25 min<sup>23</sup>) compared to aerosolized PGI<sub>2</sub> or epoprostenol. Side effects, however, are very similar. The small aerosolized particles (median diameter 0.5–3 µm) are deposited in the lung parenchyma during tidal breathing.<sup>24,25</sup> Intra-acinar pulmonary arteries closely surrounded by alveolar surfaces are able to be dilated by alveolar PGI<sub>2</sub> deposition. However, 6.5 to 9.4 minutes post inhalation the effect of inhaled iloprost is terminated by β-oxidation resulting in an inactive metabolite.<sup>26,27</sup> It is therefore necessary to inhale iloprost with specialized nebulizers 6 to 12 times a day.<sup>28</sup> For practical purposes, the number of inhalations for long-term treatment is usually recommended with 6 to 9 times per day. However, powerful devices have made it possible to reduce the time used for inhalation from 15 by jet ventilators to 4 minutes by ultrasonic nebulizers.<sup>24</sup> A common dosage regimen starts with 2.5 µg per inhalation, and will be increased to 5 µg per inhalation if tolerated well.

Acting locally, inhaled iloprost selectively dilates pulmonary arteries. Systemic side effects are thus greatly reduced in comparison to intravenously or subcutaneously administered drugs.<sup>29</sup> Given the role of the PGI<sub>2</sub> receptor in the pathophysiology of PAH and the *in vivo* effects of PGI<sub>2</sub> and its derivatives inhaled iloprost has become a potent therapeutic option to treat patients with precapillary PH.

## Inhaled iloprost for PAH (group I)

The first study demonstrating a favorable effect of inhaled iloprost in patients with PAH was published as early as

1996 by Olschewski et al.<sup>22</sup> This group had demonstrated a vasodilative effect of inhaled PGI<sub>2</sub> in patients with ARDS before.<sup>30</sup> In addition, hemodynamic effects have also been reported in dogs with hypoxia-induced PH.<sup>31</sup> In 6 patients with idiopathic pulmonary arterial hypertension and PH associated with CREST syndrome 100 µg of PGI<sub>2</sub> (and iloprost in one patient) were aerosolized in 6 to 9 doses for 15 minutes each. Acute and long-term beneficial effects on hemodynamics were demonstrated. In 1999, 8 patients with PH accompanying lung fibrosis exhibited significant benefit to aerosolized PGI<sub>2</sub> suggesting a vasoconstrictive component in the pathophysiology of this clinical situation.<sup>32</sup> In both studies effects of the inhaled PGI<sub>2</sub> analogon iloprost lasted longer than effects after the aerosolized PGI<sub>2</sub>.

Short-term effects on exercise capacity and were studied by Wensel et al in 2000.<sup>33</sup> Exercise duration and ventilation (peak oxygen uptake, VE versus VCO<sub>2</sub> slope) improved significantly after the inhalation of iloprost in 11 patients with IPAH and PAH due to morbus Osler. In this study the strongest independent predictors of survival turned out to be VO<sub>2</sub>max and peak systolic blood pressure during exercise, highlighting the importance of performing cardiopulmonary exercise testing for future study assessment.

Hoeper et al compared acute effects of inhaled iloprost and nitric oxide.<sup>34</sup> The PGI<sub>2</sub> analogue iloprost resulted in a greater decrease in pulmonary artery pressure and a stronger increase in cardiac output. Vasodilatory effects of inhaled PGI<sub>2</sub> lasted for approximately 60 minutes. However, a maximum of 9 inhalations of iloprost per day were performed. Long-term beneficial effects on pulmonary artery pressure and exercise capacity had nevertheless been shown before. The authors therefore concluded that an inhibitory effect of PGI<sub>2</sub> on vasoproliferation existed. They also suggested that the number of daily inhalations could be reduced due to this additional lasting effect.

This persisting effect of inhaled iloprost in long-term treatment was also published by two groups in 2000. Olschewski et al examined 19 patients with PH in an open, uncontrolled, multicenter study. After inhaling iloprost for 3 months hemodynamic parameters and exercise capacity improved, whereas the acute response to iloprost did not change (results pre- versus post-inhalation were similar at 3 months).<sup>35</sup> In a prospective study Hoeper et al<sup>36</sup> investigated the effect of iloprost on exercise capacity and hemodynamics in 24 patients with IPAH of NYHA classes III and IV. Patients received 6 to 8 inhalations of 100 µg of iloprost per day. Six-minute walking distance (6MWD) increased significantly after

3 months of treatment. This effect was still maintained at 12 months. Improvements of hemodynamic parameters were also observed. It was suggested, that aerosolized iloprost be used for long-term therapy treatment of PH.

These encouraging findings in patients with precapillary PH stimulated the launch of a controlled study investigating the safety and efficacy of iloprost. The study was termed AIR for Aerosolized Iloprost Randomized study. It had been designed as a European, randomized, multicenter, placebo-controlled trial and was finally published by Olschewski et al.<sup>37</sup> Two hundred and three patients with IPAH, inoperable chronic thromboembolic PAH and PH associated with collagen vascular diseases or appetite suppressants in NYHA functional classes III and IV were included. The effects of 6 to 9 inhalations of 5 µg iloprost per day over a period of 12 weeks were evaluated regarding a combined end point of exercise capacity (increase of  $\geq 10\%$ ) and functional class. 16.8% of the patients in the verum group versus 4.9% of the placebo group achieved the combined endpoint of an increased 6MWD and NYHA class improvement without clinical deterioration ( $p = 0.007$ ). Of the iloprost group 23.8% improved by one NYHA class and 37.6% walked at least 10% further than at baseline. In contrast, 12.7% of the patients receiving placebo exhibited an improvement in NYHA classification, and the 6MWD increased in 25.5% by at least 10%. The increase of the 6MWD between the two groups did not reach statistical significance, but the improvement in functional class was significantly more frequent in the iloprost group ( $p = 0.03$ ). The 6MWD increased by 36.5 m at 12 weeks in all patients inhaling iloprost, and the increase was even greater in the subgroup of IPAH patients, at 58.8 m. Hemodynamic parameters following 12 weeks of inhalation of iloprost significantly improved in comparison with baseline values ( $p < 0.001$ ).

Common adverse effects were described as cough, headache, flushing and jaw pain. In this study serious side effects such as syncope, tachycardia, pneumonia and dyspnea occurred in 2% to 5% of the patients. Although in this study the impact of inhaled iloprost was not compared with the effects of alternative PGI<sub>2</sub> analogues, efficacy and safety of this form of application of iloprost were demonstrated.

Opitz et al studied the effects of inhaled iloprost with regards to the long-term tolerability and clinical efficacy in 76 patients still symptomatic with conventional treatment (IPAH, NYHA classes II and III).<sup>38</sup> At 12 months, 32 patients still remained on monotherapy with iloprost. The rate of event-free survival 3 months after starting therapy was 81%, 53% after 1 year and 13% at 5 years. Overall survival rates

showed moderate results, with 93% after 3 months, 79% at 1 year and 49% at 5 years.

Acute hemodynamic effects of inhaled iloprost were also analyzed by an in vivo investigation by Fruhwald et al. These authors implanted a hemodynamic monitoring device into 5 patients with PAH.<sup>39</sup> Its sensor was placed in the right ventricular outflow tract. Right ventricular pressures were recorded. As a result a significant decrease in pulmonary arterial pressure was seen following inhalation of iloprost. However, this effect lasted only 17 to 48 minutes. Thus, the duration of vasodilation caused by inhaled iloprost is significantly shorter than previously suggested. Nevertheless, rebound PH with hypoxemic periods at night during the interval without inhalation were not found by Mereles et al.<sup>40</sup> As a cause, the authors mentioned a different reaction to a lower heart rate and cardiac output at night due to a pre-dominant parasympathic tone. For patients who experience nightly rebounds, Domenighetti suggested a combination therapy with the vasodilating phosphodiesterase inhibitor sildenafil to cover the inhalation break.<sup>41</sup>

A comparison of the impact of aerosolized versus intravenous iloprost was done by Opitz et al<sup>42</sup> in patients with severe PAH. Similar hemodynamic changes were observed for both routes of application. In contrast, pulmonary vasoselectivity was greater using inhaled iloprost which is generally recognized to be of benefit. Few studies however, did not confirm the advantage of aerosolized iloprost over the intravenous application. In one study switch from epoprostenol to inhaled iloprost in 3 patients was unsuccessful due to development of right heart failure.<sup>43</sup> Another study reported improvement of exercise capacity with intravenous iloprost in 16 patients who deteriorated under therapy with inhaled iloprost.<sup>44</sup>

Precapillary PH of classification group I other than IPAH has rarely been treated with inhaled PGI<sub>2</sub> analogues. Launay et al published a study in 5 patients with PH associated to CREST syndrome in 2001, demonstrating improvements in NYHA functional class and exercise capacity.<sup>45</sup> The 6MWD increased from  $352 \pm 48$  to  $437 \pm 56$  m ( $p = 0.06$ ) at 6 months. Along these lines Hallioglu et al<sup>46</sup> also observed an advantage of aerosolized iloprost over intravenous infusion in children with PH secondary to congenital heart disease. In this study the decrease in pulmonary-to-systemic vascular resistance ratio was found to be significantly greater with inhaled iloprost.

## Inhaled iloprost for pulmonary hypertension of other Venice classification groups

Chronic thromboembolic pulmonary hypertension (CTEPH) develops within the first 2 years<sup>47,48</sup> in approximately 4%

of all patients diagnosed with acute pulmonary embolism. There have been only scarce reports using aerosolized iloprost for the treatment of CTEPH patients. In the AIR study<sup>37</sup> a subgroup receiving iloprost comprised 33 patients with CTEPH representing 67% of the patients in the “nonprimary pulmonary hypertension” group. Iloprost inhalation in this group resulted in beneficial effects on exercise capacity and improvement of NYHA class. However, in this study separate data for CTEPH patients were not mentioned. Kramm et al reported successful treatment of residual postoperative PH after pulmonary thrombendarterectomy.<sup>49</sup> In addition to these studies, several case reports on inhaled iloprost in CTEPH have been published.<sup>50,51</sup>

Ulrich et al showed similar pulmonary artery compliance in 35 patients with IPAH and 22 with CTEPH performing acute vasoreactivity testing with inhalative nitric oxide and iloprost.<sup>52</sup> The existence of a reversible vasoconstrictive component in CTEPH was also suggested in a study observing significant acute hemodynamic improvement after inhalation of iloprost.<sup>53</sup>

For patients with PAH classified other than groups I and IV (Venice classification) only a few cases have been published. A patient with systemic sclerosis and lung fibrosis

suffering from severe PAH who had contraindications for bosentan treatment received inhaled iloprost. Exercise capacity and hemodynamics improved<sup>54</sup> shortly after treatment had been started.

Long-term experiences with novel treatments for portopulmonary hypertension have been rare so far. Hoeper et al recently observed improved survival rates and greater improvements in hemodynamics as well as exercise capacity in patients with portopulmonary hypertension on bosentan therapy compared to patients with portopulmonary hypertension on inhaled iloprost.<sup>55</sup>

## Combination therapies

Owing to the repeated and still somewhat tedious application of inhaled iloprost, orally available pharmaceuticals have recently been preferred as initial therapy of PH. None of the new drugs approved for PH appears to be able to completely prevent progress in all cases. For this reason the combination of compounds acting via different pathways has been investigated by several authors. Inhaled iloprost has been combined with either an endothelin-receptor antagonist or with a phosphodiesterase (PDE) inhibitor – both specific pulmonary vasodilators. Iloprost has also been used in combination with dual oral therapy.

**Table 2** Selection of studies examining the effect of aerosolized prostacyclin and iloprost in patients with pulmonary arterial hypertension

	Patients	PH form	NYHA	Outcome	Remarks
Wensel et al <sup>33</sup>	11	IPAH, PAH due to morbus Osler	III	Acute hemodynamic improvement: mPAP –5.7 mmHg PVR –333.2 dyn*s/cm <sup>5</sup> CO + 1.1 L/min VO <sub>2</sub> max + 1.4 L/min*kg	
Olschewski et al <sup>35</sup>	19	IPAH, secondary PH, PAH associated with connective tissue disease		Improvement of hemodynamics and exercise capacity after 3 months: 6MWD + 148 m mPAP –7.5 mmHg PVR –295 dyn*s/cm <sup>5</sup>	Open, multicenter, uncontrolled
Hoeper et al <sup>36</sup>	24	IPAH	III, IV	Improvement of hemodynamics and exercise capacity after 12 months: 6MWD + 85 m, mPAP –7 mmHg PVR –280 dyn*s/cm <sup>5</sup>	
Olschewski et al <sup>37</sup>	203	IPAH, CTEPH, PAH associated to other diseases	III, IV	After 3 months: 6MWD + 36.5 m postinhalation mPAP –4.6 mmHg PVR –239 dyn*s/cm <sup>5</sup>	Multicenter, placebo-controlled
Opitz et al <sup>38</sup>	76	IPAH	II, III	Overall survival 79% at 1 year of therapy	

**Abbreviations:** CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; 6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; VO<sub>2</sub>max, maximum oxygen consumption.



In 2001 Schermuly et al described an additive vasodilative effect of PGI<sub>2</sub> simultaneously applied with PDE inhibitors while maintaining lung selectivity in rabbits.<sup>56</sup> Wilkens et al proposed prolonged and increased vasodilation following inhaled iloprost when the PDE-5 inhibitor sildenafil was added in 5 patients with IPAH. Combining the two therapeutic strategies resulted in a significantly lower mean pulmonary artery pressure compared to that reached by application of each of the single compounds.<sup>57</sup> In a group of 73 patients with PH, 14 deteriorated while on iloprost applied by inhalation. Adding sildenafil to the existing iloprost therapy improved exercise capacity from  $256 \pm 30$  m to  $349 \pm 32$  m ( $p = 0.002$ ) at 12 months. Pulmonary vascular resistance decreased from  $2494 \pm 256$  to  $1950 \pm 128$  dyn\*s/cm<sup>5</sup> as early as 3 months after installation of combination therapy.<sup>58</sup>

Improvements in exercise capacity (6MWD increased by  $58 \pm 43$  m) and maximal oxygen consumption (from  $11 \pm 2.3$  to  $13.8 \pm 3.6$  mL  $\times$  min<sup>-1</sup>  $\times$  kg<sup>-1</sup>) were also reported in a series of 20 patients (9 patients on aerosolized iloprost, 11 patients on oral beraprost) after 3 months of treatment by Hoeper et al 2003<sup>59</sup> adding the endothelin-receptor antagonist bosentan.

Seyfarth et al<sup>60</sup> observed an increase in exercise capacity and a decline of the Tei index, indicating improvements in right heart function 6 months after adding inhaled iloprost to existing bosentan therapy in 10 patients with IPAH, CTEPH and PAH associated with interstitial lung disease. Nine patients also improved in NYHA functional class.

The STEP trial included 67 PAH patients of functional class NYHA III, receiving either inhaled iloprost or placebo in addition to bosentan therapy for a minimum of 4 months.<sup>61</sup> An increase in the postinhalation, 6MWD of 30 m ( $p = 0.001$ ) was reported in the verum group and of 4 m ( $p = 0.69$ ) in the placebo group compared to baseline values. However, the group-adjusted difference of 26 m was achieved with only a marginal significance of  $p = 0.051$ . 34% of the patients in the iloprost group improved in functional class versus 6% on placebo ( $p = 0.002$ ). A significant prolongation of the time to clinical worsening was demonstrated using combined instead of mono therapy. In this study the authors suggested, that inhaled iloprost is an option for expanding monotherapy when necessary, whereas Hoeper et al<sup>62</sup> presented a multi-center study (COMBI trial) in 2006, in which adding inhaled iloprost to bosentan failed to show positive effects on hemodynamics in 40 IPAH patients. The authors discussed the smaller sample size and higher disease severity in the COMBI trial as reasons for the difference in outcome

of these two similarly designed studies. However, the median changes in the 6MWD revealed a significant advantage for the iloprost group (+25 m) in comparison to the placebo group (+5 m).

Unfortunately, all studies investigating the effect of a combination therapy have been performed with small populations and relatively great heterogeneity in terms of forms of PH.

Inhaled iloprost is currently approved for IPAH functional class III in Europe by the European Medicine Agency (EMA), whereas it may be used for patients with PAH in functional classes III and IV in countries under the law of the Food and Drug Administration (FDA) and for PAH as well as CTEPH (NYHA III, IV) in Australia.

## Anesthesiologic management of patients with pulmonary hypertension and the role of inhaled iloprost

PH represents a major risk factor for an increased perioperative mortality regardless of which anesthetic technique is used: stress, pain, mechanical ventilation and systemic inflammation may lead to a further increase of pulmonary pressure with the consequence of acute right heart insufficiency and failure. Ramakrishna and coworkers identified several independent predictors for short-term morbidity and mortality: a history of pulmonary embolism, NYHA functional class  $\geq$  II, high-risk surgery, and duration of anesthesia  $>3$  hours.<sup>63</sup> In his patient cohort 42% developed one or more short-term morbid events. In this study, the intraoperative use of vasopressors and the non-use of nitric oxide were associated with an increased postoperative mortality. Depending on the underlying disease and the kind of surgical intervention, mortality ranges between 7% and 24%, especially in cases of emergency interventions.<sup>64-66</sup>

The perioperative management of patients with severe PH should start preoperatively with a multidisciplinary approach to optimize the clinical conditions (anesthesiologist, cardiologist, pulmonologist, and surgeon). Preoperative evaluation includes echocardiography with special attention to the level of right ventricular dysfunction. In selected cases, right heart catheterization should be done preoperatively to test for responsiveness of the pulmonary vasculature to intravenous or inhaled vasodilators. All options to treat PH (oxygen, endothelin-antagonists, PDE-inhibitors, intravenous or inhaled prostanoids) should be exploited prior to surgery. If PH is newly diagnosed, Fox and coworkers recommend preoperative therapy with oral sildenafil (50–100 mg).<sup>67</sup>

Preoperative sedation (midazolam) should be reduced to a minimum or substituted by psychological care to avoid respiratory insufficiency and acidosis.

Both general and regional anesthesia may be used in patients with severe PH, none of them has been proven superior to the other, but both are risky. In principle, 100% oxygen should be used, and acidosis, hypothermia, and hypercarbia should strictly be avoided due to their pulmonary vasoconstrictive effects.

Epidural anesthesia has been used safely in patients with PH for non-cardiac surgery, vaginal delivery, and cesarean section.<sup>68</sup> Owing to the better hemodynamic stability, spinal catheter technique should be preferred over spinal single shot anesthesia.

## Intraoperative monitoring and treatment of pulmonary hypertension

An intra-arterial line for beat-to-beat measurement of arterial blood pressure is essential to ensure sufficient myocardial perfusion pressure and for frequent blood gas analysis. A pulmonary artery catheter is essential for the continuous monitoring of mean pulmonary arterial pressure and, if necessary, for measurement of pulmonary capillary wedge pressure. Using specialized pulmonary arterial catheters, continuous monitoring of right ventricular ejection fraction is possible (Vigilance;<sup>®</sup> Edwards Lifesciences). A central venous catheter is helpful for monitoring of right ventricular preload and necessary for central administration of vasoactive drugs. Whenever possible, transesophageal echocardiography is an excellent method for visualization of right ventricular filling and function.

The challenge for the anesthesiologist is to prevent patients from intraoperative PH crisis by optimization of oxygenation, analgesia, intravascular volume, ventilation, and acid-base status. Nevertheless, an increase of pulmonary pressure may occur and should be treated immediately to avoid right heart insufficiency and failure.

In all cases with systemic normo- or hypertension, intravenous administration of vasodilators is effective to reduce both systemic and pulmonary vascular resistance: milrinone or PGI<sub>2</sub> are established intravenous therapies for an effective treatment of PH. Right ventricular preload may be reduced by continuous infusion of nitroglycerin or sodium nitroprusside.<sup>67,69,70</sup> However, intravenous vasodilators should be used very carefully to avoid a drop of the mean arterial pressure. In case of hypotension, intravenous vasodilators may cause worsening of right ventricular perfusion and consecutive right ventricular failure.

In PH patients with intraoperative systemic hypotension, inhalation of vasodilators is an advantageous alternative to reduce pulmonary pressure without negative effects on mean arterial pressure and myocardial perfusion. Lung-selective vasodilation is possible using nitric oxide, milrinone, PGI<sub>2</sub>, or iloprost (Table 3).<sup>69–73</sup> Inhaled iloprost, however, is superior to the others in this list, because of its longer half-life, its lack of severe side effects and its ease of administration. Kurzyna et al<sup>74</sup> for instance, describe the use of inhaled iloprost as a rescue therapy in 4 patients with deteriorating hypoxemia after atrial septostomy probably caused by an oversized right-to-left shunt. In desperate cases, a combination therapy may augment the vasodilatory effects.<sup>75</sup>

## Postoperative care

For all patients with significant PH postoperative intensive care monitoring is obligatory for at least 12 hours. Attention should focus on adequate oxygenation and ventilation, monitoring of right heart function and mean pulmonary arterial pressure, avoidance of acidosis, and adequate treatment of pain.

## Conclusion

Years of investigation have led to the acceptance of inhaled iloprost as a major strategy to be used in precapillary PH. The majority of the studies have demonstrated significant beneficial effects of inhaled iloprost on hemodynamics, exercise capacity and survival. Recently, potent orally

**Table 3** Treatment of intraoperative pulmonary hypertension crisis<sup>69</sup>

- 1) General principles
  - a. Optimization of right ventricular preload
  - b. Reduction of right ventricular afterload
  - c. Stabilization of coronary blood flow
  - d. Avoidance of hypoxic vasoconstriction and acidosis
- 2) Intravenous vasodilators
  - a. Milrinone (25–50 µg/kg BW bolus, followed by 0.5–0.75 µg/kg BW per minute continuous infusion)
  - b. Sodium nitroprusside (0.2–0.5 µg/kg BW per minute continuous infusion)
  - c. Prostacyclin (4–10 ng/kg BW per minute continuous infusion)
  - d. Iloprost (1–3 ng/kg BW per minute continuous infusion)
- 3) Pulmonary selective vasodilation
  - a. Iloprost (5–10 µg diluted in 10 mL saline solution, nebulized over 10 min, repeated every 2–4 hours)
  - b. Prostacyclin (25–50 µg diluted in 50 mL saline solution, nebulized over 15 min, repeated every hour)
  - c. Nitric oxide (5–40 ppm continuously)

available drugs have been developed that work well as first-line PAH therapeutics. Due to its more complex application involving 6 to 9 inhalations a day inhaled iloprost is no longer the first choice in PAH therapy. However, it is clearly a very valuable option if oral treatment is impossible or for combination therapy if monotherapy does not suffice.

Aerosolized iloprost clearly has an advantage over intravenously or subcutaneously administered PGI<sub>2</sub> analogues with only limited side effects due to targeted delivery resulting in a selective pulmonary effect. Aerosolized iloprost may therefore be given to patients with acute hemodynamic instability. Improvements in the application mode may be hoped for such as the development of longer stable PGI<sub>2</sub> analogues and more potent and faster delivery units.

The wide use of aerosolized iloprost is also reflected in its use for vasoreactivity testing in patients with PH. In that respect, iloprost proved to be even more potent than NO.<sup>76</sup>

The combination with other vasodilators has resulted in encouraging effects on hemodynamics and tolerance. Further studies with higher numbers of patients will demonstrate if combined strategies including inhaled iloprost are in fact appropriate for long-term PAH treatment.

Beside the key study (AIR) to prove inhaled iloprost as a potent therapeutic for patients with precapillary PH with limited functional capacity (NYHA III, IV), all other studies were non-controlled, but suggested effectiveness, tolerability, and longer survival.

Patients with functional classes NYHA II and III exhibited more benefit on monotherapy with iloprost than classes IV and therefore these patients appear to be especially suited for inhaled iloprost. Further evaluation might focus on early combined treatment involving inhaled iloprost and oral treatment in NYHA class II patients but will also have to evaluate all combinations used for pulmonary arterial hypertension.

## Disclosures

The authors declare no conflicts of interest.

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