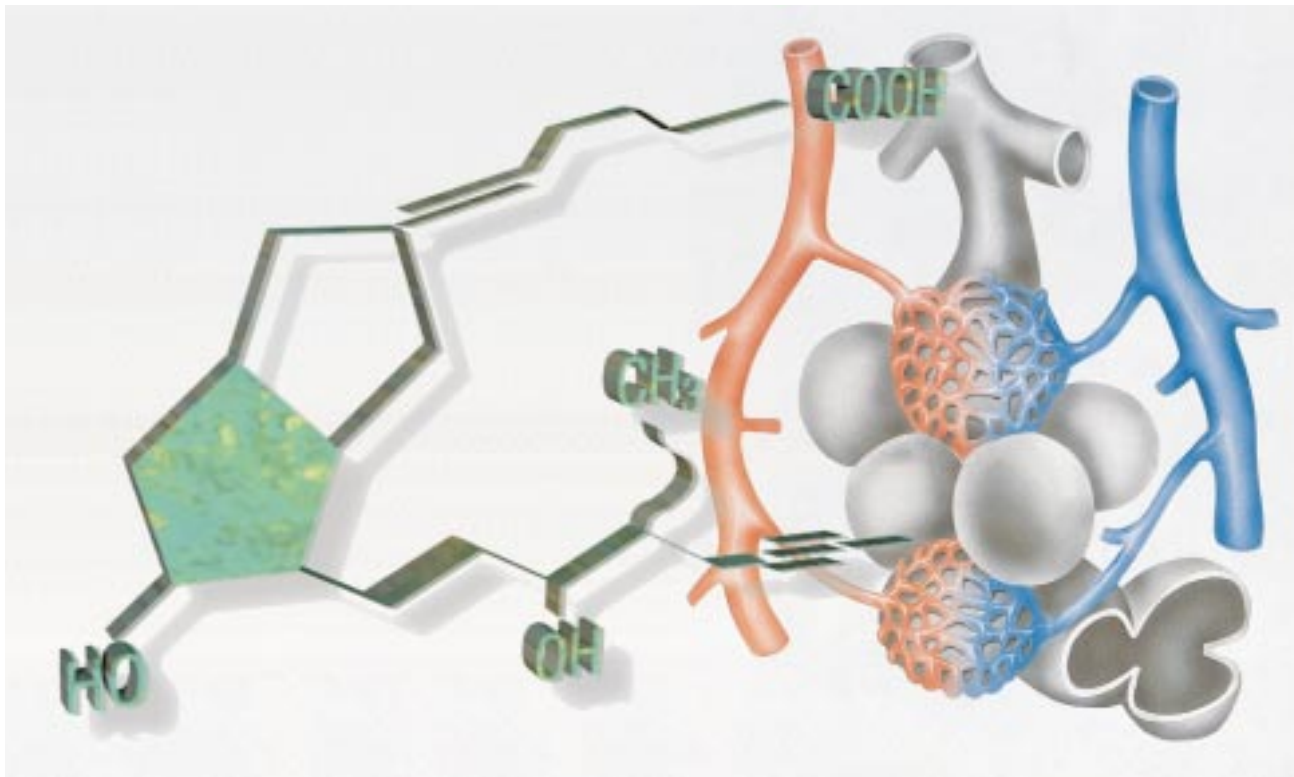


ILOPROST

CURRENT CASE REPORT



Aerosolized Iloprost: Application in children with pulmonary hypertension

*Dr. med. Peter Ahrens
Prof. Dr. med. Jens C. Möller*

- ▶ Fume inhalation trauma after explosion of gas bottle
- ▶ premature baby with a severe broncho-pulmonary dysplasia

**Pulmonary hypertension
- a therapeutic challenge**

Our report concerns two childhood clinical pictures, in which pulmonary hypertension has developed as a result of acute respiratory distress syndrome (ARDS). ARDS can develop as a secondary disease following inflammatory processes (pneumonia, aspiration) and various states of shock. It is a diffuse auto-destructive inflammation of the entire lung. Stimuli for pulmonary hypertension in its early stage are serotonin, thromboxane and leukotriene. In due course, endothelial edema and microthrombi develop in the capillary region. Finally, irreversible pulmonary hypertension can develop due to a proliferation of the vessel walls.

Previous methods of treatment have been the systemic application of prostacyclin (PGI₂) or the inhalation of nitric oxide (NO).

One of the main side-effects of systemic PGI₂ therapy is arterial hypotension, which is caused by a generalized vascular relaxation and which can, in isolated cases complicate this treatment and require the maintenance of sufficient arterial blood pressure by the addition of catecholamines.

Inhaled NO is diffused through the pulmonary interstice in the vessel walls and binds to cGMP in the muscle cells of the pulmonary vessel wall. The result is a relaxation of the vascular musculature. NO's half-life in vivo only amounts to approx. 0.1 to 5.0 seconds, necessitating continuous inhalation. Expensive and complicated measuring equipment is essential for obtaining an exact dosage and it can only be used on intubated or tracheotomized patients. The inhalation of nitric oxide leads to the emission of nitrogen dioxide as toxic waste and to the formation of methemoglobin.

Additional measures in the treatment of pulmonary hypertension are hyperventilation and alkalosis as well as an increase in the magnesium supply.

In recent years a new approach to the treatment of adult patients [3] has been tested, including treatment using the stable prostacyclin analog iloprost as an inhalant, which to our knowledge has not previously been used in the treatment of children. [4]

Patient 1

An 11 and a half year old girl suffered fume inhalation trauma and second to third degree surface burns of approx. 45 % when a gas bottle exploded. The burns were mostly in the facial area and on the shoulders, arms and thighs. ARDS developed due to inhalation trauma necessitating a high amount of assisted respiration (figure 1). The patient was tracheotomized in good time. Initially, we undertook to treat the child with the option of extracorporeal membrane oxygenation (ECMO). We treated the well developed pulmonary hypertension within the framework of ARDS, with inhalative NO and consistent application of analgesics, relaxation, and intravenous PGI₂ (Flolan,). Furthermore, treatment with catecholamines was necessary due to a circulatory insufficiency. By taking these measures it was possible to stabilize the respiratory situation to the extent that ECMO treatment was no longer necessary. During the artificial respiration the patient developed multiple pneumothoraces, which had to be drained alternately. The histological examination of an open lung biopsy showed diffuse alveolar damage with depictable alveole of max. 5 %. The width of the vessel walls was 10 times larger and the ventilatory lung parenchyma reduced to at least 80 % (figures 2 and 3).

Within an interval of 4 weeks NO inhalation could be slowly phased out when combined with a continuous dosage of intravenous PGI₂. Further attempts to reduce or discontinue the Flolan® treatment proved unsuccessful. A CAT of the thorax



Figure 1:
X-ray of the thorax in the initial phase of ARDS. The patient is tracheotomized.



Figure 2:
Histological survey of the lung parenchyma. There are no intact alveoli to be seen.



Figure 3:
Histological representation of a pulmonary vessel with the hypertrophic vascular wall clearly recognisable.

after 3 months of treatment (figure 4) shows the extent of damage to the lungs with bullae in the ventral thorax region and large atelectatic zones in the dorsal area. A slow reduction in the analgesics continually led to manifest pulmonary hypertension. Over the next months it was possible to attain complete auto-respiration with intermittent CPAP so that the only obstacle to a further increase in mobility and the continuation of pulmonary treatment was the long-term prostacyclin infusion. We began with overlapping iloprost inhalation therapy (Ilomedin® 5 x 10 µg per day, in every 1ml of isotonic sodium chloride solution/compressed air nebulizer) – a long-acting PGI₂-analog – and could finally end the systemic treatment.

Inhalation with iloprost was continued until the patient was discharged. When the tracheostoma had sealed up it was possible to continue the treatment by means of a compression nebulizer with a mouth-piece attachment.

The patient was able go home after 10 months. She was fully mobile, inhaled 5 times a day and underwent further treatment with CPAP by means of a mask and portable respirator. She required a continuous oxygen supply of up to max. 2 l/min, which was administered by means of a liquid oxygen tank. The iloprost treatment is being reduced further at this time (figures 5 and 6).

Patient 2

A premature baby born in the 28th week of pregnancy with severe bronchopulmonary dysplasia (BPD) was treated by us on repeated occasions

(figure 7). BPD is a chronic obstructive lung disease affecting premature babies, which entails prolonged treatment with oxygen. BPD intrinsically produces a chronic inflammation of the lung. Children with BPD may suffer recurrent obstructive bouts and cyanotic attacks. Secondary developments are a strain on the right ventricle and therefore cor pulmonale.

Even banal respiratory infections aggravated the breathing difficulties of the patient to such an extent that the home oxygen therapy, administered by means of nasal tubes, was insufficient, and the oxygenation with a saturation of < 75 % deficit/wastes was considerably reduced. The above mentioned cyanotic crises re-occurred time after time due to the additional massive obstructive ventilation disorder, so that finally intubation and longer-term assisted respiration became necessary. Breathing difficulties similar to those connected with ARDS developed with pulmonary hypertension on top of the BPD. Previously existing serious lung impairment and reduced cardiac performance made treatment with catecholamines compulsory for the patient. Pronounced obstructive crises occurred again in the withdrawal phase, during which the patient had to be repeatedly sedated and relaxed, which was an obstacle to a complete discontinuation of the assisted respiration. In the meantime, the patient was tracheotomized to ensure spontaneous respiration and considerably reduce the respiratory resistance. We applied a long-term intravenous prostacyclin infusion to ensure continuous reduction of the vascular



Figure 4:
CT of the thorax after 3 months of treatment. There is a chest tube in the pneumothorax. Hypostatic discrepancy between cystic bullae in the ventral and atelectatic dorsal areas.

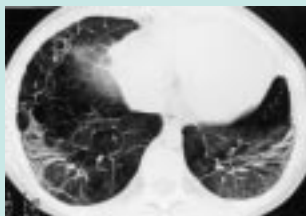


Figure 5:
CT of the thorax before the patient was discharged. There is considerable fibroid regeneration and an improvement in the distribution disorder in various regions of the lung.



Figure 6: Before the patient was discharged. The thorax shows a visible improvement with indications of retrograde fibrotic reconstruction.

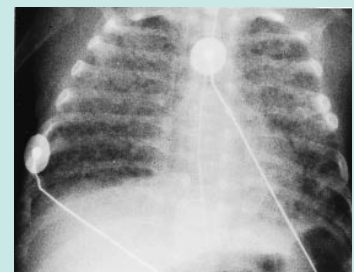


Figure 7: Breathing difficulties similar to those connected to ARDS in a premature baby with serious bronchopulmonary dysplasia.

pulmonary resistance. In due time the intravenous treatment was switched to an inhalant (Ilomedin® 4 x 25 µg per day). There were no further obstructive crises after the start of iloprost inhalation treatment accompanied by existing basic BPD therapy (diuretics, anti-obstructive inhalation). Gradual discontinuation of assisted respiration was now possible.

Discussion

In various tests, inhalative iloprost has already been proven to be an effective, selective vasodilator of the pulmonary circulation. Similar to nitric oxide inhalation, it is possible to apply safely without affecting the entire circulation [1,2,5]. In our cases the intermittent iloprost inhalation made it possible to take both children off the long-term assisted respiration and enable spontaneous self-respiration on the open tracheal cannula, at the same time abstaining from intravenous medication.

The blood pressure and heart rate of both children remained stable under the inhalation treatment. No comment can be made on the pulmonary pressure as neither patient had a pulmonary catheter, although doppler echo cardiographic tests confirmed a considerable effect on pulmonary hypertension.

Previous studies regarding selective vasodilation with prostacyclin inhalation and NO have concentrated on the treatment of adults. The inhalative NO treatment is a rescue process used com-

monly in pediatrics. Both our patients were also treated successfully with this method. Inhalative NO has an extremely short half-time of only 0.1 to 5.0 seconds, which means that continuous application with a closed system is necessary for long-term NO inhalation, to ensure, among other things, that the surrounding air is not polluted.

Inhalative iloprost is a practically side-effect free therapy that enables a gradual dosage reduction or can be used as a long-term prophylactic treatment of pulmonary hypertension. ■

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Dr. med. Peter Ahrens
Prof. Dr. Jens C. Möller
Lübeck University of Medicine, Clinic for Pediatrics
Ratzeburger Allee 160
23538 Lübeck

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Dr. Christine Leist (editorial responsibilities)
Doris Berger, Ulrike Hafner, Silvia Hasse,
Ursula Hilpert, Dr. Friederike Holthausen,
Sabine Jost

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