Editorial

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Perioperative Care in Patients with Pulmonary Hypertension after Cardiac Surgery: Clinical Management, Outcome and Future Clinical Research

Results from an Expert Meeting

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Pulmonary hypertension (PH) is defined as a haemodynamic and pathophysiological condition, characterized by an increase in mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest, as assessed by right heart catheterization. PH encompasses multiple disease subtypes. The 5 major groups, according to the updated WHO classification, are: (1) pulmonary arterial hypertension (PAH); (2) PH owing to left heart disease; (3) PH owing to lung diseases and/or hypoxaemia; (4) chronic thromboembolic PH, and (5) PH with unclear multifactorial mechanisms [1].

PH increases morbidity and mortality in adult patients undergoing heart surgery. It is an independent risk factor for the development of acute right ventricular failure. Cardiopulmonary bypass exacerbates PH in patients undergoing cardiac surgery.

In children with congenital heart disease, pre-operative dynamic PH may be superimposed and aggravated by acute post-operative PH or persist as chronic PH, especially in children who are not operated on early enough. Persistent PH of the newborn is classified as a subcategory of group 1 PAH.

The stable prostacyclin analogue iloprost is available as a formulation for inhalation and for intravenous administration (Ventavis® and Ilomedin®) and acts as a specific vasodilator in patients with PAH [2]. It is well known that inhaled iloprost improves right ventricular function and decreases right ventricular afterload in these patients.

The use of the inhaled formulation has been approved in Europe since 2003 for the treatment of primary PH in patients with NYHA (New York Heart Association) functional class III to improve physical exercise capacity and symptoms. Approval was subsequently granted in Australia and the USA, in 2004 and 2005, respectively, for a broader range of indications, including NYHA functional class IV and additional forms of PH. The intravenous preparation has been approved in Germany for the treatment of advanced thrombangiitis obliterans, in New Zealand for PH and in several countries worldwide for peripheral arterial occlusive disease and Raynaud syndrome.

In the context of post-operative critical care medicine, iloprost is currently used on a case-by-case basis. However, various small-scale trials have provided clear evidence of its clinical effects in different surgical settings.

In adult heart and thoracic surgery, inhaled iloprost has been successfully used in heart and/or lung transplant recipients, in patients who have undergone mitral valve surgery during weaning from the cardiopulmonary

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bypass, in the immediate postoperative period after pulmonary thrombendarterectomy, as well as for severe acute right heart failure after left ventricular assist device implantation. In the case of persistent pulmonary hypertension after weaning from a cardiopulmonary bypass, iloprost has also been found to be effective.

In a direct comparison, inhaled iloprost produced a significantly stronger reduction in mean pulmonary arterial pressure and pulmonary vascular resistance than inhaled nitric oxide did.

In children with congenital heart disease (CHD), the efficacies of inhaled nitric oxide and inhaled iloprost administered directly after corrective surgery were compared in a prospective open-label proof-of-concept study. Neither substance on its own prevented pulmonary hypertensive crises in high-risk infants, so a combination of both substances should be tested in future trials.

Very interesting data are coming from China, where there are more than 4 million untreated CHD patients. The role of aerosolized iloprost in the treatment of PH after CHD repair was investigated in a placebo-controlled pilot study. Inhaled iloprost significantly improved haemodynamics in a dose-dependent manner and prevented reactive PH and pulmonary hypertensive crises in most of these mechanically ventilated children.

PH encompasses multiple disease subtypes. However, all existing treatments are indicated only for PAH, even though PAH accounts for only 6% of PH cases. Intensive research is therefore necessary to better understand the pathophysiology of PH and to detect new signalling pathways that allow the development of new compounds in order to improve the prognosis of PAH and non-PAH PH patients. Animal experiments, although unpopular, are needed, because there is no ethical justification for drug testing in humans without prior tests of safety and toxicology. However, the rat model has its limitations in performing studies of human PH. This is why pig and sheep models have been developed that are suitable to simulate congenital heart disease and other forms of PH.

Promising new substances that are already being tested in phase II and phase III clinical trials in patients with various forms of PH and in acute decompensated heart failure, are, among others, riociguat, a stimulator of the soluble guanylate cyclase (sGC), and cinaciguat, a sGC activator.

At an international expert meeting that was initiated by the University Hospital Leuven, Belgium, and took place on 27 November 2009 in Athens, Greece, the abovementioned study results and experiences in various countries concerning the clinical use of iloprost in intensive care medicine for adults and for children were presented and discussed in a plenary session. Furthermore, recent findings from animal models of PH and new clinical trials were introduced.

I wish you an informative and exciting reading.

Matthias Gorenflo

References

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