

Endothelium Derived factors and Pulmonary Hypertension

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Introduction

Two contrasting factors derived from endothelium, both previously unidentified, one a vasoconstrictor, the other a vasodilator, play a major role in the pathophysiology of pulmonary hypertension (PHT).¹

After a cursory glance at the pulmonary vasculature, I will make a few comments about Nitric Oxide (NO) and Endothelin, previously known as endothelium derived relaxant factor and endothelium derived contracting factor.

Pulmonary vessels

Macroscopically the pulmonary vessels are large and relatively thin walled. As much as 20% of right ventricular stroke volume can be accommodated in the main and branch pulmonary arteries.

Muscularisation is incomplete with muscle fibres running more longitudinally than circumferentially when compared to the systemic circulation.

Recruitment and distensibility are properties of the pulmonary vessels which allow pulmonary artery pressures to remain low despite 5-fold fluxes in CO, even in the presence of atelectasis, infection, and resection of large amounts of lung tissue.

Recruitment of vessels begins as CO increases. Occurring with recruitment and extended after recruitment is maximal, distension of these vessels accommodates the increased blood flow. This is demonstrated in children with congenital heart disease where distensibility of pulmonary vessels measured with echocardiography correlates with pulmonary-to-systemic vascular resistance ratios.²

The endothelium is a metabolically active tissue able to regulate blood flow, coagulation and inflammation as well as serving its purpose as part of a vascular conduit.

Pulmonary hypertension is a heterogenous group of disorders with widely differing aetiologies, grossly divided into primary and secondary causes.

Despite this, the histological changes in all types of PHT are very similar. At a meeting in Evian in France the World Health Organisation recognised this and adopted a new classification of the disease.³

In examining histological specimens of patients with irreversible pulmonary hypertension, Tudor comments that the law of the endothelial cell monolayer has been broken. This is characterised by endothelial and smooth muscle proliferation with occlusion of the vascular lumen.¹

He further proposes that the endothelium and vascular smooth muscle form a syncytium, with the endothelial cell functioning as pressure sensor and a regulator of smooth muscle tone.

It is also interesting to note that the same factors which promote vasodilation and constriction at an endothelial level, are mediators for growth promotion or growth suppression at a smooth muscle cell

level.

Several genetic factors clearly play a role in this disease. It has recently been discovered that primary pulmonary hypertensives lack a receptor for Transforming Growth Factor- β which may allow clonal expansion of endothelial cells.⁴

Nitric Oxide

Previously known as Endothelin Derived Relaxant Factor, Nitric Oxide (NO) is a potent vasodilator of pulmonary and systemic blood vessels. Pulmonary selectivity relies on inhaled NO being delivered directly to ventilated pulmonary vasculature with rapid plasma inactivation before reaching the systemic circulation.

Inhaled NO has been used for persistent pulmonary hypertension of the newborn, in adults with ARDS, pulmonary thrombo-emboli, and many others. For the sake of brevity, I will have to single out a few applications.

To address surgery for congenital heart disease, inhaled NO is a known and proven pulmonary vasodilator. The question remains how effective is it, and how does it compare to other interventions. Hyperventilation with induced alkalosis and high FiO₂ has been used for years to decrease pulmonary vascular resistance and has been shown by Morris et al to be as effective as inhaled NO.⁵ The NO group however had higher cardiac indices with less systemic hypertension because of the absence of systemic effects.

In a longer term study, Mc Crindle ventilated post-operative congenital heart disease cases with pulmonary hypertension (PAP>25mmHg), with either NO at 10ppm or nitrogen until they were ready for extubation. In the NO group there were significantly fewer episodes of pulmonary hypertension, defined as Rp/Rs ratio of greater than 0.75.⁶

In adult cardiac surgery, numerous studies have shown that inhaled NO is a selective pulmonary vasodilator.

The ability of inhaled nitric oxide to cause reductions in pulmonary hypertension may be predicted by pre-operative pulmonary vascular resistance.⁷

Interestingly, the dose-response curve for inhaled NO has not and perhaps cannot be defined.

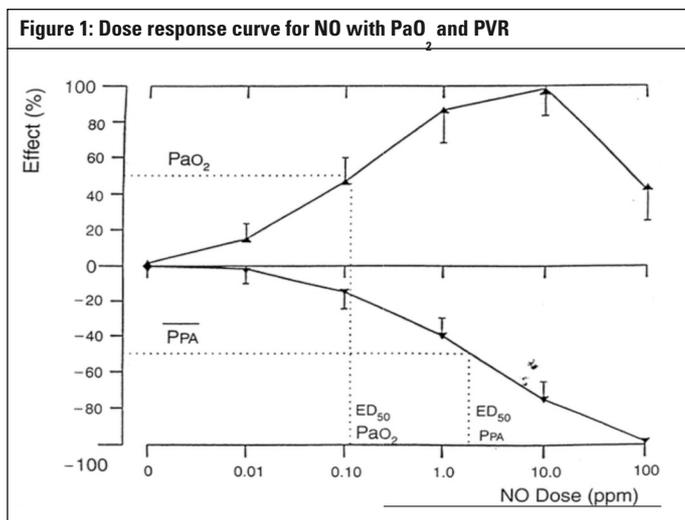
Lindberg and co-workers found that inhaled NO was effective in reducing pulmonary vascular resistances across a dosage range of 2ppm to 25ppm. Their conclusion is that doses of less than 2ppm need to be studied.⁸

Solina and co-workers claimed a ceiling effect of 10ppm for inhaled NO in patients assigned to receive doses between 10ppm and 40ppm. No differences were found between groups. Significantly, doses below 10ppm were not studied.⁹

A different picture appears to be the case in ARDS where inhaled

NO has two response curves for its effect on PaO₂ and pulmonary artery pressures.

Up to a dose of 10ppm, improvements in PaO₂ are the result of improved V/Q matching as inhaled NO improves blood flow to alveoli which are being ventilated. Above 10ppm it appears that NO loses its specificity for ventilated alveoli, perhaps because these higher doses cannot be eliminated by haemoglobin as quickly. At these higher doses, pulmonary arterial pressures continue to drop, but at the expense of an increasing V/Q mismatch.¹⁰ (Figure 1)



Confounding all such studies is that the use of inhaled NO is often associated with the use of other vasodilators or inodilators.

The potential toxicity if inhaled NO and resultant oxidant damage remains worrisome.

In the setting of high FiO₂, NO may react with superoxide radicals to form peroxynitrite, a highly reactive oxygen species which directly causes oxidation, peroxidation, and nitration of biologically important molecules such as lipids, proteins and DNA.¹¹

Addressing pulmonary toxicity, a study of one day old piglets ventilated with 100% oxygen and 40ppm NO for 76 hours showed greater lung protein leakage from endothelial structures than did their NO deprived controls.¹² Encouragingly, this was not associated with alterations in lung mechanics or gas exchange

Inhaled NO is inactivated by circulating haemoglobin, a reaction whose swiftness allows for pulmonary selectivity. In doing so the haemoglobin moiety is reduced forming methaemoglobin.¹¹

Endothelin

Endothelin is a family of polypeptide hormones liberated from endothelium.

As with NO, endothelins have been implicated in several disease states such as hypertension, type 2 diabetes, hypercholesterolaemia and cardiac failure.

Endothelin-1 is the most extensively studied of the more than 20 endothelins and is a potent vasoconstrictor and bronchconstrictor.

Endothelin has been implicated in several disease states including primary pulmonary hypertension, polycystic ovarian syndrome, Parkinson's disease and migraine.¹

In the shocked state, Reinhardt and coworkers found that endothelin-1 levels are a marker for endothelial dysfunction as reflected by peripheral oedema. This same study also found a trend towards increased organ dysfunction with elevated endothelin levels.¹³

In sepsis and septic shock reductions in left ventricular stroke work index are accompanied by increases in plasma endothelin concentrations.¹⁴

In primary pulmonary hypertensives, Rubens and co-workers measured PAP and PVR and found that both measurements correlated with endothelin-1 levels sampled from pulmonary artery catheters.¹⁵

High endothelin-1 levels are also found in patients with central apnoea syndrome.¹⁶

In patients with mitral stenosis requiring valve replacement, regression of pulmonary hypertension at 6 months can be predicted by measuring pulmonary capillary endothelin levels at the time of surgery.¹⁷

In 7 children with intractable cardiac shunting associated with pulmonary hypertension despite NO therapy, Schulze-Niek and colleagues showed a reduction in PVR from 7.7 Wood units to 4.7 Wood units with an infusion of BQ-123, an endothelin receptor antagonist. Predictably, the patients with the highest endothelin-1 concentrations responded best to the treatment.¹⁸

Animal models of prolonged CPB suggest that endothelin receptor antagonists may be coronary vasodilators and may improve spasm in these patients. These outcomes were achieved with better myocardial ATP stores.¹⁹

This animal data is borne out in humans following percutaneous transluminal coronary angioplasty and stenting, where vasospasm can be reduced radiographically with endothelin-1 antagonists.²⁰

Finally, in paediatric ARDS patients, severity of respiratory illness correlated with endothelin levels in plasma.²¹

Summary

PHT is a complex clinical entity, whose causes, risk factors and natural history we are beginning to understand. Clearly, the endothelium and its factor will be at the centre of this understanding and will hopefully be accompanied by new treatments for the disease, and better insight into current therapies.

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