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Review

Inhaled nitric oxide in cardiac surgery: Evidence or tradition?

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ABSTRACT

Inhaled nitric oxide (iNO) therapy as a selective pulmonary vasodilator in cardiac surgery has been one of the most significant pharmacological advances in managing pulmonary hemodynamics and life threatening right ventricular dysfunction and failure. However, this remarkable story has experienced a roller-coaster ride with high hopes and nearly universal demonstration of physiological benefits but disappointing translation of these benefits to harder clinical outcomes. Most of our understanding on the iNO field in cardiac surgery stems from small observational or single centre randomised trials and even the very few multicentre trials fail to ascertain strong evidence base. As a consequence, there are only weak clinical practice guidelines on the field and only European expert opinion for the use of iNO in routine and more specialised cardiac surgery such as heart and lung transplantation and left ventricular assist device (LVAD) insertion. In this review the authors from a specialised cardiac centre in the UK with a very high volume of iNO usage provide detailed information on the early observations leading to the European expert recommendations and reflect on the nature and background of these recommendations. We also provide a summary of the progress in each of the cardiac subspecialties for the last decade and initial survey data on the views of senior anaesthetic and intensive care colleagues on these recommendations. We conclude that the combination of high price tag associated with iNO therapy and lack of substantial clinical evidence is not sustainable on the current field and we are risking loosing this promising therapy from our daily practice. Overcoming the status quo will not be easy as there is not much room for controlled trials in heart transplantation or in the current atmosphere of LVAD implantation. However, we call for international cooperation to conduct definite studies to determine the place of iNO therapy in lung transplantation and high risk mitral surgery. This will require new collaboration between the pharmaceutical companies, national grant agencies and the clinical community. Until these trials are realized we should gather multi-institutional experience from large retrospective studies and prospective data from a new international registry. We must step up international efforts if we wish to maintain the iNO modality in the armamentarium of hemodynamic tools for the perioperative management of our high risk cardiac surgical patients.

> "If I go out into nature, into the unknown, to the fringes of knowledge, everything seems mixed up and contradictory, illogical, and incoherent. This is what research does; it smooths out contradictions and makes things simple, logical, and coherent."
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> **Albert Szent-Gyorgyi**
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> In 'Dionysians and Apollonians', *Science* (2 Jun 1972), **176**, 966. Reprinted in Mary Ritchie Key, *The Relationship of Verbal and Nonverbal Communication* (1980), 318.

1. Introduction

When we read the quotation of the most famous Hungarian

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Nobel prized scientist on direction of science, one wonders if basic and clinical research on the medical use of nitric oxide (NO) is going the wrong way. Two decades ago, at the height of the celebration of unprecedented basic science discoveries leading to the shared Nobel Prize to pioneers of NO research, there was high expectations for clinical applications and successes of this remarkable molecule. The mindful discoveries of Pepke Zaba [1] and Frostell et al. [2] showing selective pulmonary vasodilation by inhalation of NO (iNO) and reversing the phenomenon of hypoxic pulmonary vasoconstriction opened exciting opportunities to apply such novel gaseous therapy to various conditions associated with pulmonary hypertension (PH) or hypoxic states. Shortly, such promise was translated into critical care medicine by showing that breathing NO caused a reproducible decrease in pulmonary artery pressure (PAP) without affecting the systemic circulation including systolic arterial pressure and cardiac output, but augmenting arterial oxygenation in patients with ARDS, due to selective vasodilation in ventilated lung regions [3,4]. This potential was further explored by paediatric lung injury and PH teams showing consistent physiological benefit of inhaled NO in reducing the PAP and right-to-left shunting of venous blood and also clinical advantages in the need for invasive mechanical support and increased survival rates [5,6]. Such progress led to FDA approval of inhaled NO for treating hypoxemia in term neonates [7]. Thus, the link between the exiting NO molecule, as “wonder drug of the decade” [8], the “magic bullet” [9]and clinical progress seemed simple, logical, and coherent.

This picture has become more complicated especially following the relative failures of the multicentre clinical trials in ARDS, and inhaled NO was labelled as only “cosmetic therapy” and the “wrong bullet for the wrong target” [10–13]. The logical translation of multiple physiological benefits of NO to the clinical settings of ischemia reperfusion injury or increased permeability occurred only with limited success in perioperative medicine. Furthermore, the coherence between clinical benefits of iNO in term infants and those of preterm has not been realised and controlled trials appear to contradict the initial enthusiasm of pilot observational studies in both the medical and surgical fields. While there is approved licence and marketing authorisation for the use of inhaled NO in cardiac surgery, the evidence for this application remains debated. Thus, the promise of iNO has not been fulfilled and recent progress is far from simple, and neither logical nor coherent.

These controversies are reflected in the daily decision making of the practicing clinicians. As an example, coinciding with the writing of this review, we were responsible for the perioperative care of 4 urgent patients over the last two days: two with insertion of left ventricular assist device (LVAD), one lung transplant and one aortic dissection. All of them received iNO at various stages for variable reasons and the patients had mixed outcomes.

These cases highlight the fact that decision making, by clinicians, regarding the use of iNO remains heterogenic and they also emphasize the burning questions of iNO therapy in the highly specialised field of cardiac surgery: What is the evidence for the routine indications to institute iNO therapy in the setting of cardiothoracic transplantation and LVAD insertion? What information do we have regarding clinical outcomes with this unique therapy? What are the optimal timings to institute iNO, should it be prophylactic or only treat manifest RV failure? If there is little evidence from existing trials, should we still utilise iNO as a last resort such as in the case of our aortic dissection patient? Furthermore, we needed at least 4 delivery systems practically ready in the hospital and use them simultaneously in these patients. How much NO should be available in a specialised centre and how many delivery systems are needed for the safe management of the patients? Finally, these therapies have been costly, and helped the survival of only two patients out of the four treated during these two days. Therefore, we should consider the cost implications and financial burden of this therapy to the hospital.

2. Perceived indications for iNO in cardiothoracic surgery

The most recognised principal characteristics of iNO is the cGMP and soluble guanylate cyclase activation mediated vascular relaxation. In addition, various biochemical effects modulate multiple aspects of oxidative stress, inflammation, permeability and coagulation which may involve cGMP – dependent and – independent mechanisms [14–17]. While the former is a straightforward nearly universal hemodynamic event decreasing the resistance of the vascular bed in question, the latter mechanisms are greatly affected by tissue specificity, exhibit species difference and determined by the nature and quantity of simultaneously present oxygen free radicals and therefore much less predictable. Nevertheless, these biochemical properties have raised the attractive clinical potential that iNO could modulate the pulmonary and systemic inflammatory response associated with cardiac surgery and the cardiopulmonary bypass system. In addition, iNO may directly or indirectly influence the inherent pulmonary and myocardial ischemia-reperfusion phenomena during surgery [18–20].

However, the most widely used indication in cardiac surgery has been the effect of iNO in reducing pulmonary vascular resistance and pulmonary pressures, especially in the setting of pulmonary hypertension, which is the most critical determinant of right ventricular afterload, during impending right ventricular failure [21–24]. In theory, this particular effect could be achieved by any broad intravenous vasodilator including the NO donor nitroglycerin or sodium nitroprusside or phospodiesterase inhibitors or calcium antagonists. However, these agents would also produce systemic vasodilation potentially reducing RV perfusion pressure. This could be disastrous in the setting of distending RV, where elevated intraventricular pressure is already compromising myocardial perfusion leading to myocardial ischemia, further reduction in contractility and diastolic function, triggering a one way downward spiral that can only lead to hemodynamic collapse [25,26]. Moreover, all these intravenous vasodilators would dilate all perfused microvessels in the lung even in non-ventilated regions and thus may cause ventilation-perfusion mismatch in the lung increasing pulmonary shunt circulation with resultant effects of arterial hypoxemia.

What is truly attractive of iNO is the selectivity of its action on pulmonary vasodilation as its systemic effects are inhibited as a result of binding to hemoglobin, which prevents NO mediated vasorelaxation in the systemic circulation. Thus, iNO predictably reduces pulmonary vascular resistance (PVR), providing better afterload conditions for RV ejection while maintaining perfusion pressure and contractility of the RV to facilitate offloading the systemic venous return through the pulmonary vasculature to the left ventricle. In addition, and in contrast to intravenous vasodilators, iNO improves ventilation-perfusion matching and oxygenation as an inhalation agent reaching only ventilated regions of the lung, selectively dilating capillaries only in ventilated areas [27,28].

It is important to recognise that the interaction between iNO and haemoglobin in the pulmonary circulation may also lead to conservation of NO with unique transport mechanism of NO to systemic vascular beds and intricate release mechanisms especially in tissue compartments with low oxygen tension. This may occur through variety of nitrogen species but overall could provide an important mechanism for documented endocrine functions of iNO in specific conditions [29,30]. Such pathway could complement the complex bioactivation mechanisms providing NO release from inorganic nitrate and nitrite in acidic environments and/or via the action of deoxyhaemoglobin [31].