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Hemodynamic effects of inhaled nitric oxide and phosphodiesterase inhibitor (dipyridamole) on secondary pulmonary hypertension following heart valve surgery in adults

Francesco Santini*, Gianluca Casali, Gianluigi Franchi, Stefano Auriemma, Mario Lusini, Luca Barozzi, Alessandro Favaro, Antonio Messina, Alessandro Mazzucco

Division of Cardiac Surgery and Anesthesiology, University of Verona, OCM Borgo Trento, Piazzale Stefani 1, 37126, Verona, Italy

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Abstract

Background: Inhaled nitric oxide (iNO) is proposed in the management of pulmonary hypertension (PH) in patients undergoing cardiac surgery. Secondary PH related to a long-standing heart valve disease however may be refractory to iNO. Aim of this prospective study was to determine whether the combination of iNO plus dipyridamole (DP), a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor (PDE5), may enhance and/or prolong the response to iNO in adult patients with secondary valve-related PH undergoing cardiac surgery, and attenuate rebound events related to its discontinuation.
Methods: Responses in 27 patients, 11 male, mean age 72±11 years, with PH due to mitral and/or aortic valve disease, were studied in the Intensive Care Unit after cardiac surgery, during sedation and stable hemodynamic conditions. The effect of isolated iNO administration (40 ppm), iNO combined with DP (0.2 mg/kg i.v.), and DP alone (1 mg/kg/24 h) on pulmonary vascular resistance, mean pulmonary artery pressure, cardiac index, mixed venous O2Sat%, and mean arterial pressure were determined.
Results: All patients showed at least a 10% decrease in pulmonary vascular resistance vs. baseline after administration of iNO [responders]. Inhaled NO and the combination of iNO/DP produced a reduction of pulmonary vascular resistance and mean pulmonary artery pressure ($p<0.05$). Cardiac index improved with a significant difference between iNO and the association iNO/DP versus baseline ($p<0.05$). This significant hemodynamic improvement versus baseline was maintained during isolated DP administration ($p<0.05$), but not during isolated iNO discontinuation. Mixed venous oxygen saturation showed an overall improvement of 17% ($p<0.05$).
Conclusions: Inhaled NO and DP infusion might represent a valuable association in the management of PH secondary to a heart valve disease in patients undergoing cardiac surgery. Their beneficial hemodynamic effects might be particularly valuable in the management of patients with associated right ventricular dysfunction.

Keywords: Nitric oxide; Pulmonary hypertension; Dipyridamole; Cardiac surgery

1. Introduction

Increased pulmonary artery pressure (PAP) and vascular resistance (PVR) may worse operative mortality after cardiac surgery by determining right ventricular dysfunction thus compromising cardiac output [1].

Nitric oxide (NO) is an endothelial-derived relaxing factor which modulates basal tone and influences vasoreactivity in the pulmonary vascular bed. NO lowers PVR by stimulating soluble guanylate cyclase in pulmonary vascular smooth muscle to produce 3′,5′-cyclic guanosine monophosphate (cGMP), which in turn produces vascular smooth muscle relaxation. Pulmonary vascular tone depends greatly on cGMP concentration which is determined by the balance of its production by guanylate cyclase and degradation by cGMP-specific phosphodiesterase (PDE5) (Fig. 1).

* Corresponding author. Tel.: +39 45 8072476; fax: +39 45 8073308.
E-mail address: fsant@yahoo.com (F. Santini).

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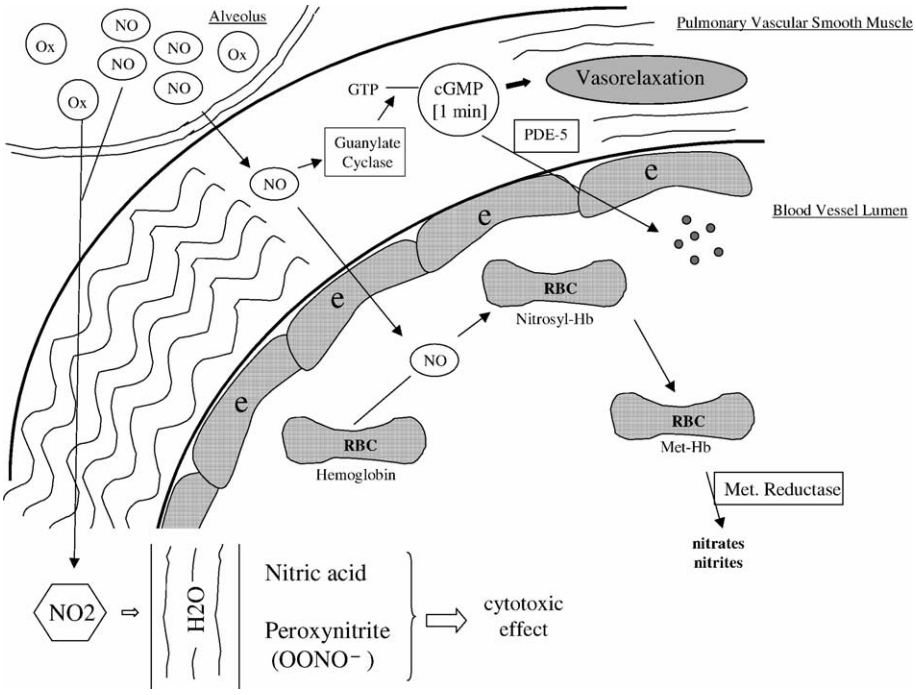

Fig. 1. Inhaled into the alveolus, NO diffuses across the alveolar-capillary membrane and activates guanylate cyclase to generate cyclic guanine 3′,5′ monophosphate (cGMP). Pulmonary vasorelaxation is mediated through cGMP which then undergoes degradation by the cGMP-specific phosphodiesterase enzymes (PDE5), thus showing a mean half-life of less than 1 min. Diffused into the blood vessel lumen, NO is bound to hemoglobin (Hb) and inactivated. Hemoglobin converts to nitrosyl-hemoglobin, to methemoglobin (Met-Hb), and then to nitrates and nitrites by methemoglobin reductase found in erythrocytes. With exposure to oxygen, NO is oxidized to NO2 which is very cytotoxic because it is rapidly converted by water in nitric acid and peroxynitrite which then rapidly promote cytotoxic effects.

Experimental work suggests that endogenous NO activity (and thus cGMP production) is attenuated in some models of PH and also in clinical pulmonary hypertension [2–4]. In addition, persistent or increased PDE5 activity contributes to increased pulmonary vascular tone in adult rats exposed to chronic hypoxia [5]. Thus, the high resting pulmonary vascular tone and altered vasoreactivity that characterize clinical pulmonary hypertension may reflect decreased endogenous NO production and/or increased or persistent PDE5 activity [6].

In clinical practice, inhaled nitric oxide (iNO) has been utilized as a *selective* pulmonary vasodilator in patients undergoing cardiac operation with evidence of *secondary* PH [1,7–9]. Responsiveness to iNO therapy however appeared to be quite variable, with some patients having limited or transient hemodynamic improvement.

The possibility to increase cGMP production by iNO and to reduce its breakdown by PDE5 inhibitors (zaprinast, dipyridamole) has been tested in animal and clinical trials in the past [1,6–11]. Data from clinical studies however showed often significant limitations in view of the small number of patients enrolled and of the definition of PH. Moreover, very few observations dealt with the issue of PH control by iNO after routine cardiac surgery in adults [1,12,13].

Aim of our study was to determine whether the combined use of iNO, associated and followed by the administration of the specific PDE5-inhibitor dipyridamole (DP), to prevent cGMP breakdown, had any clinical advantage compared to the use of iNO alone in adult patients with a heart valve disease and associated long-standing PH in the immediate post-operative course following cardiac surgery. The observation was also devoted to evaluate the potential of DP to mitigate the reported clinical effect related to iNO abrupt discontinuation (rebound PH).

Dipyridamole was chosen in view of its known PDE5 inhibitory activity, excellent safety profile in humans, and prompt commercial availability.

2. Materials and methods

The following study protocol was reviewed and approved by the Ethical Committee of the University of Verona on the 5th of April, 2000.

Between May 2000 and December 2002, 27 patients, 11 males and 16 females with a mean age of 72±11 years (range, 52–79 years) with pulmonary hypertension (defined as a mean pulmonary artery pressure >35 mm Hg, and/or a transpulmonary gradient >10 mm Hg) secondary to a mitral and/or aortic valvular disease were proposed for surgical repair and thus enrolled in this study after informed consent was obtained from each patient. Patients with reactive airways disease requiring chronic bronchodilator or anti-