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Atrial and brain natriuretic peptide concentrations and the response to inhaled nitric oxide in patients with acute respiratory distress syndrome ☆

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Abstract

Purpose: The response to inhaled nitric oxide (iNO) is inconsistent in patients with acute respiratory distress syndrome (ARDS). We sought to determine whether the response to iNO, defined as 20% Pao_2/Fio_2 increase from baseline, depends on the level of cardiac natriuretic peptides.

Materials and methods: This is a prospective cohort study including 11 consecutive patients with ARDS who were eligible to receive iNO. Measurements of plasma concentrations of atrial natriuretic peptide (ANP), N-Terminal-Pro-B-Type Natriuretic Peptide (NT-pro-BNP) and 3′,5′-cyclic guanosine monophosphate were obtained before initiating iNO and 30 minutes later during iNO. Baseline cardiac peptides, oxygenation, and hemodynamic variables and their change during iNO were compared among responders and nonreponders to iNO.

Results: Baseline ANP and NT-pro-BNP concentrations were higher in patients that responded to iNO and tended to decrease during iNO in responders only. 3′,5′-Cyclic guanosine monophosphate concentrations were not different among responders and nonresponders and were unchanged during iNO. Baseline ANP was strongly correlated with change in intrapulmonary shunt, and baseline NT-pro-BNP and its change were correlated with the change in cardiac output.

Conclusions: High ANP and NT-pro-BNP concentrations are associated with the response to iNO. These data suggest that cardiac peptides have the potential to identify a subgroup of patients with ARDS who might derive clinical benefit from iNO.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is characterized by hypoxemia, pulmonary hypertension, and an impaired ventilation/perfusion ratio [1]. Inhaled nitric oxide (iNO) has been administered as a rescue therapy to improve oxygenation in patients with refractory hypoxemia [2-7]. It has been hypothesized that iNO-induced selective vasodilatation, occurring predominantly in ventilated regions, optimizes the ventilation/perfusion ratio in patients with ARDS [8]. However, a number of patients do not respond to iNO with an expected improvement in oxygenation or with a reduction in mean pulmonary artery pressure (MPAP) [9-11]. The reasons for the inconsistent response to iNO administration are not fully understood; various mechanisms have been proposed including the distribution of pulmonary blood flow before iNO [12], a decreased production of 3′,5′-cyclic guanosine monophosphate (cGMP) [13], and the presence of potential antagonists such as endothelin [14].

Nitric oxide has been shown to play a role on cardiac natriuretic hormone secretion [15]. Cardiac natriuretic peptide hormones, atrial and brain natriuretic peptides, are synthesized in response to atrial/ventricular stretch or pressure overload states and are important regulators of cardiovascular homeostasis through their action, among others, on vascular tone [16,17]. The effects of these hormones are mediated via cGMP as intracellular second messenger, as already demonstrated in patients with severe chronic heart failure [18]. Likewise, in patients with ARDS, there is some evidence that natriuretic peptide levels are elevated, even in the presence of normal left ventricular function, and normalize with the improvement of respiratory function, suggesting a role of right ventricular overload due to increased pulmonary resistances [19]. Plasma concentrations of natriuretic peptides and their associations with the response to iNO have not been investigated in patients with ARDS. We postulated that the response to iNO could be related to the interplay of humoral processes implicated in the common pathway mediated via the generation of cGMP. The present study was designed to prospectively investigate if the early response to iNO can be explained by differences in the plasma concentrations of atrial and brain natriuretic peptides in patients with ARDS and to investigate the effect of iNO on the plasma concentrations of these peptides. Levels of cGMP were measured to evaluate the overall effect on its production both from iNO and from changes in natriuretic peptides activity from baseline and during iNO.

2. Materials and methods

The study protocol was approved by the institutional ethical committee of the Geneva University Hospitals. Informed consent for study participation was obtained from the patient's next of kin. Patients admitted to the surgical intensive care unit and meeting the criteria of ARDS were prospectively identified. Acute respiratory distress syndrome was defined according to the American European Consensus Conference [1]. When iNO was prescribed as a rescue treatment in patients with ARDS with severe refractory acute hypoxemic pulmonary failure despite an adequate treatment strategy [20], the patient was eligible to enter in the study.

2.1. Study protocol

All patients were equipped with an indwelling arterial catheter and a pulmonary artery catheter. Inhaled NO, at an initial concentration of 10 ppm, was administered by continuous flow through a catheter directly connected to inspiratory limb of the ventilatory circuit and titrated to the lowest concentration generating the same amount of improvement from baseline in Pa_{O_2}/F_{IO_2} ratio and/or MPAP [9]. For study purposes, patients were defined as 'responders' if at least a 20% improvement in Pa_{O_2}/F_{IO_2} ratio was observed during iNO. Arterial blood samples were drawn for measurement of atrial natriuretic peptide (ANP), and the inactive N-terminal fragment of Brain (B-Type) Natriuretic Peptide (NT-pro-BNP), and cGMP at baseline before starting iNO and 30 minutes after initiating iNO. Arterial and mixed-venous blood gas analyses were obtained at the same time points. Hemodynamic measures including systemic and pulmonary arterial pressures, heart rate, and cardiac output were collected simultaneously with the blood gas draws. The intrapulmonary shunt fraction (Qs/Qt) was calculated according to the following formula: $Qs/Qt = (Cc_{O_2} - Ca_{O_2}) / (Cc_{O_2} - Cv_{O_2})$, where Qs represents shunt flow, Qt cardiac output, Cc_{O_2} capillary oxygen content ($Cc_{O_2} = 1.36 \times Hb + 0.03 \times Pa_{O_2}$, where Pa_{O_2} is the alveolar oxygen content), Ca_{O_2} arterial oxygen content, Cv_{O_2} mixed venous oxygen content.

No changes in patient body position, ventilatory settings, medication doses, and fluid infusion were allowed during the study protocol. Patients were ventilated with lung protective ventilation strategy, with target tidal volume of 6 mL/kg of ideal body weight (mean ± SD, 6.3 ± 1.5 mL/kg) adjusted to maintain plateau pressures less than 30 cm H_2O and inspiratory to expiratory ratio of 1:1.

2.2. Laboratory techniques

Three milliliters of arterial blood was collected in tubes containing 7.5 mmol/L EDTA and immediately centrifuged at 3000 rpm at 4°C. The plasma aliquots were immediately separated and frozen at −70°C and batched for the assays. Atrial natriuretic peptide was measured by radioimmune assay (^{125}I-ANP, Peninsula Laboratories Europe LTD, Merseyside, UK) using rabbit anti-α-atrial natriuretic polypetide 1-28 (human, canine) serum (Phoenix Pharmaceuticals, Inc, Mountain View, CA). The

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