Research article

Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension

Carmine D Vizza*, Giorgio Della Rocca†, Angelo Di Roma*, Carlo Iacoboni*, Federico Pierconti‡, Federico Venuta‡, Erino Rendina‡, Giovanni Schmid*, Paolo Pietropaoli† and Francesco Fedele*

*Department of Cardiovascular and Respiratory Sciences, University of Rome 'La Sapienza', Rome, Italy
†Department of Anesthesiology, University of Rome 'La Sapienza', Rome, Italy
‡Department of Thoracic Surgery, University of Rome 'La Sapienza', Rome, Italy

Correspondence: Giorgio Della Rocca, giorgio.dellarocca@uniroma1.it

Abstract

Introduction The use of low-dose dobutamine to maintain hemodynamic stability in pulmonary hypertension may have a detrimental effect on gas exchange. The aim of this study was to investigate whether inhaled nitric oxide (INO), dobutamine and a combination of the two have beneficial effects in patients with end-stage airway lung disease and pulmonary hypertension.

Method Hemodynamic evaluation was assessed 10 min after the administration of each drug and of their combination, in 28 candidates for lung transplantation.

Results Administration of INO caused a reduction in mean pulmonary arterial pressure (MPAP), an increase in PaO2 with a significant reduction in venous admixture effect (Qs/Qt). Dobutamine administration caused an increase in cardiac index and MPAP, with a decrease in PaO2 as a result of a higher Qs/Qt. Administration of a combination of the two drugs caused an increase in the cardiac index without MPAP modification and an increase in PaO2 and Qs/Qt.

Conclusion Dobutamine and INO have complementary effects on pulmonary circulation. Their association may be beneficial in the treatment of patients with mild to moderate pulmonary hypertension.

Keywords dobutamine, hemodynamic, lung transplantation, nitric oxide

Introduction

Pulmonary hypertension is a common complication of pulmonary parenchymal diseases. Its presence is associated with a poor prognosis in patients with severe chronic obstructive pulmonary disease (COPD) [1,2] and cystic fibrosis [3,4]. Pulmonary hypertension is not uncommon among patients awaiting lung transplantation, so this situation is frequently dealt with during surgical or diagnostic procedures. In these situations, vasodilator and inotropic drugs, mainly low-dose dobutamine, are usually used in order to maintain hemodynamic stability. However this approach may have a detrimental effect on gas exchange [5].

Recently, inhaled nitric oxide (INO) in combination with oxygen has been used successfully to improve oxygenation and pulmonary hemodynamics in patients with COPD and acute respiratory distress syndrome [6]. However, the hemodynamic effects of a combination therapy with nitric oxide...
In order to establish the preliminary bases for this therapeutic approach we investigated the acute hemodynamic effects of INO, dobutamine, and the combination of the two in a group of patients with mild to moderate pulmonary hypertension secondary to severe airway disease.

Materials and methods

Subjects

The study population was selected from among patients with end-stage pulmonary disease secondary to airway disease and pulmonary hypertension with a mean pulmonary arterial pressure > 20 mmHg who were evaluated for lung transplantation at the University of Rome hospital ‘La Sapienza’. Eight patients suffered from cystic fibrosis, nine from bronchiectasis, and 11 from COPD. The demographic and clinical data are summarized in Table 1. All patients were in a stable hemodynamic condition and were included in the study protocol after informed consent. The protocol was approved by the institutional review board for human studies.

Table 1

Demographic and clinical characteristics of the study population (28 patients)

| Characteristic         | Mean (± SD) |
|------------------------|-------------|
| Age (years)            | 38 ± 18     |
| Sex (M/F)              | 10/11       |
| Height (cm)            | 161 ± 12    |
| Weight (kg)            | 56 ± 19     |
| FVC (% predicted)      | 44 ± 12     |
| FEV1 (% predicted)     | 28 ± 26     |
| TLC (% predicted)      | 99 ± 31     |
| RV (% predicted)       | 208 ± 67    |

FVC, forced vital capacity; FEV1, forced exhaled volume in 1 s; RV, residual volume; TLC, total lung capacity.

Hemodynamic study

All patients underwent a complete hemodynamic evaluation such as that required for routine screening prior to lung transplantation at the University of Rome hospital. Under local anesthesia a 7 F Swan-Ganz triple lumen thermodilution catheter was inserted through the femoral vein and was positioned in the pulmonary artery. A polyethylene catheter was introduced into the radial artery. Transducers were referenced 5 cm below the sternal angle in the supine position. Right atrial pressure (central venous pressure, CVP), mean pulmonary arterial pressure (MPAP), mean pulmonary artery occluded pressure (PAOP), and mean systemic arterial pressure (MAP), were measured as the average of four respiratory cycles. Transpulmonary gradient (TPG) was defined as MAP–PAOP. Cardiac output was measured in triplicate by thermodilution. Cardiac index, systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were calculated using standard formulae.

Samples of arterial and mixed venous blood were analyzed for oxygen pressure, carbon dioxide pressure, and pH using a blood gas analyzer (Instrumentation Laboratory Model 1300; Milan, Italy), which was calibrated with a proper gas mix with oxygen concentration of 90%.

Anatomic shunt/venous admixture effect (Qs/Qt) was calculated according to Cotes [9], using the mass balance equation:

\[ \frac{Q_s}{Q_t} = \frac{C_{cO_2} - C_{aO_2}}{C_{cO_2} - C_{vO_2}} \]

where \( C_{cO_2} \) is capillary content of \( O_2 \), \( C_{aO_2} \) is arterial content of \( O_2 \), and \( C_{vO_2} \) is mixed venous content of \( O_2 \). Arterial, capillary, and mixed venous oxygen content were calculated as follows:

\[ \text{content} = (Hb \times 1.39 \times \% \text{ saturation}) + (P_{O_2} \times 0.003). \]

Arterial and venous mixed \( P_{O_2} \) and saturation were measured on blood samples, capillary saturation was assumed to be 100%, while alveolar \( P_{O_2} \) was calculated as \( (P_{bar} - 47) \times F_{I_{O_2}} - P_{aCO_2}/R \), where \( R = 0.8 \).

Study protocol

The protocol was single blinded: the patient breathed through a face mask (oxygen or oxygen + INO) and received an infusion (saline or dobutamine) throughout the study.
Measurements were started after 20 min of quiet rest in order to reach hemodynamic stability. A complete hemodynamic profile was taken before each drug administration (baseline 1, baseline 2, baseline 3), during inhalation of nitric oxide (40 ppm for 10 min), dobutamine (10 µg/kg/min for 10 min), and a combination of all the above. All tests were performed while patients were breathing 100% O₂ via a face mask, in order to measure shunt.

Nitric oxide was obtained from a stock tank containing 500 ppm of nitric oxide in N₂ and its administration was controlled using two electrochemical cell monitors Politron NO and NO₂ (Drager; Lubeck, Germany) for INO and NO₂ produced. Inspired O₂ concentration was measured through a connection to a gas-analyzer (Capnomac-Datex; Helsinki, Finland). The sequence of drug challenge (INO, INO + dobutamine, dobutamine; or dobutamine, INO + dobutamine, INO) was chosen randomly and each treatment started after hemodynamic values returned to the baseline level (± 5%).

Statistical analysis
Data are reported as means ± standard deviation (SD). For the sake of clarity the baseline column in the tables reflects the mean of the three baselines prior to each drug challenge.

Comparison between each baseline and drug challenge was made by a paired t-test. The effects of the various treatments were compared by using one-way analysis of variance with multiple dependent measures. If a significant difference was found, a Duncan’s multiple range test was used to determine the statistical significance among treatments. A level of $P < 0.05$ was considered significant.

Results
Inhaled nitric oxide challenge
Taking the whole population into consideration, INO caused a slight decrease in MPAP, PVRI, and TPG without significant modifications in the other hemodynamic parameters (Table 2). These modifications were accompanied by a striking increase in PaO₂ and a significant reduction in venous admixture effect.

The same trend was also observed when each disease group was analyzed separately (Tables 3–5).

Dobutamine challenge
Dobutamine infusion caused an increase in cardiac index, heart rate, systemic vascular index (SVI), and MPAP with no change in CVP, PAOP, and MAP. PVRI and SVRI decreased significantly (Table 2). There was also a decrease in PaO₂ and a significant increase in $Q_s/Q_t$, with no change in PaCO₂.

The same trend was also observed when each disease group was analyzed separately (Tables 3–5).

Inhaled nitric oxide plus dobutamine challenge
The combination of INO and dobutamine caused a significant increase in cardiac index, heart rate and SVI, without modifying either MPAP or MAP, as a result of a significant
fall in pulmonary and systemic vascular resistance. CVP and PAOP had no significant change. There was a significant increase in PaO₂ and slight but not significant increase in \( Q_s/Q_t \) with no change in PaCO₂. The same trend was also observed when each disease group was analyzed separately (Tables 3–5).

### Table 3

Hemodynamic and gas exchange response to inhaled nitric oxide (INO), dobutamine, and INO plus dobutamine in bronchiectasis (9 patients)

|                              | Baseline 1 | INO       | Dobutamine | INO+Dobutamine |
|------------------------------|------------|-----------|------------|----------------|
| Cardiac index (l/min/m²)     | 3.9 ± 1.9  | 3.8 ± 1.5 | 5.6 ± 1.4  | 4.5 ± 0.3      |
| Heart rate (beats/min)       | 87 ± 17    | 85 ± 12   | 115 ± 25   | 114 ± 23*      |
| SVI (ml/m²)                  | 43 ± 15    | 43 ± 13   | 53 ± 27    | 42 ± 12        |
| CVP (mmHg)                   | 3.2 ± 2.8  | 4 ± 3     | 3.2 ± 2.7  | 3.2 ± 3.9      |
| MPAP (mmHg)                  | 33 ± 16    | 28 ± 14   | 37 ± 17    | 36 ± 17        |
| PAOP (mmHg)                  | 9.4 ± 2    | 7.8 ± 1   | 12.5 ± 5   | 9.2 ± 3.3      |
| MPAP–PAOP (mmHg)             | 24 ± 15    | 20 ± 14   | 24 ± 17    | 27 ± 18        |
| PVRI (dyne/s/cm²/m²)         | 781 ± 424  | 662 ± 355 | 569 ± 321  | 641 ± 335*     |
| MAP (mmHg)                   | 86 ± 10    | 88 ± 9    | 90 ± 14    | 79 ± 11        |
| SVRI (dyne/s/cm²/m²)         | 1919 ± 684 | 1974 ± 712| 1272 ± 256 | 1391 ± 237*    |
| \( Q_s/Q_t \) (%)           | 19 ± 5     | 11 ± 4*   | 24 ± 7     | 15 ± 12        |
| \( PaO_2/FiO_2 \) (mmHg)     | 366 ± 113  | 448 ± 92  | 344 ± 95   | 435 ± 115      |
| \( PaCO_2 \) (mmHg)          | 51 ± 20    | 52 ± 23   | 53 ± 24    | 56 ± 23        |

* \( P < 0.05; **P < 0.01. CVP, cardiovenous pressure; INO, inhaled nitric oxide; MAP, mean systemic arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occluded pressure; PVRI, pulmonary vascular resistance index; SVI, systemic vascular index; SVRI, systemic vascular resistance index.

### Table 4

Hemodynamic and gas exchange response to inhaled nitric oxide (INO), dobutamine, and INO plus dobutamine in cystic fibrosis (8 patients)

|                              | Baseline | INO       | Dobutamine | INO+Dobutamine |
|------------------------------|----------|-----------|------------|----------------|
| Cardiac index (l/min/m²)     | 3.6 ± 0.6| 3.6 ± 0.5 | 5.1±0.6    | 4.7±0.5**      |
| Heart rate (beats/min)       | 90 ± 26  | 90 ± 25   | 102±22     | 104 ± 18       |
| SVI (ml/m²)                  | 43 ± 12  | 43 ± 10   | 52 ± 10    | 47 ± 7         |
| CVP (mmHg)                   | 1.4 ± 1.9| 1.6 ± 2.1 | 1.9 ± 2.4  | 1.4 ± 2        |
| MPAP (mmHg)                  | 24 ± 4   | 22 ± 3    | 26 ± 5     | 24 ± 3         |
| PAOP (mmHg)                  | 5.7 ± 2.7| 6.5 ± 3.5 | 6.2 ± 3.3  | 5.6 ± 2.6      |
| MPAP–PAOP (mmHg)             | 18 ± 2   | 16 ± 2*   | 20 ± 2     | 18 ± 3         |
| PVRI (dyne/s/cm²/m²)         | 591 ± 148| 548 ± 140 | 448 ± 96*  | 460 ± 98*      |
| MAP (mmHg)                   | 83 ± 15  | 83 ± 11   | 87 ± 13    | 89 ± 13        |
| SVRI (dyne/s/cm²/m²)         | 1826 ± 261| 1825 ± 230| 1371 ± 193 | 1495 ± 197**   |
| \( Q_s/Q_t \) (%)           | 20 ± 7   | 17 ± 4    | 30 ± 6*    | 22 ± 5         |
| \( PaO_2/FiO_2 \) (mmHg)     | 276 ± 56 | 350 ± 48* | 260 ± 56   | 319 ± 65       |
| \( PaCO_2 \) (mmHg)          | 54 ± 11  | 55 ± 11   | 54 ± 12    | 53 ± 12        |

* \( P < 0.05; **P < 0.01. CVP, cardiovenous pressure; INO, inhaled nitric oxide; MAP, mean systemic arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occluded pressure; PVRI, pulmonary vascular resistance index; SVI, systemic vascular index; SVRI, systemic vascular resistance index.
Comparison of treatments

Only INO caused a light but statistically significant reduction of MPAP and TPG without changes in cardiac index or SVRI. On the other hand, only dobutamine and the combination of the two drugs elicited an increase in cardiac index with a reduction in SVRI.

In order to analyze pulmonary hemodynamic response, we plotted the modification of TPG in function of pulmonary flow on a pressure-flow chart with isoresistance lines passing through the origin of the axis. Three different patterns were observed: INO caused a downward shift through lower isoresistance lines; dobutamine caused a shift right and upwards, almost parallel to the isoresistance line representing the flow–pressure relationship for a vascular resistance equal to 300 dynes/s/cm^5; and the combined treatment showed an intermediate reaction with a rightward shift (Figure 1).

Arterial blood gases analysis showed no change in arterial CO2 tension during the administration of the three regimens. On the other hand, PaO2 increased with INO therapy and the combined therapy with dobutamine and INO, while it decreased when dobutamine was used by itself.

This behavior was congruent with the reduction in Qs/Qt during treatment with INO and the increase in Qs/Qt during treatment with dobutamine alone. During therapy with the combination of the two drugs (INO + dobutamine) Qs/Qt increased slightly, thus the increase in PaO2 is mainly a result of an increase in mixed venous oxygen saturation.

Discussion

Inhaled nitric oxide challenge

As was expected, our study confirms that INO has a selective vasodilator effect on pulmonary circulation in patients with severe airway disease. Treatment with INO slightly reduced MPAP, PVRi, and TPG, with no changes in cardiac index, MAP and SVRI. Its actual vasodilator effect is documented by
the reduction in TPG, and a downward shift of pulmonary pressure–flow relationship. The magnitude of MPAP reduction in our study population was smaller than that reported in other studies [10,11]. These differences can be reconciled considering that in our study patients were on 100% oxygen and, possibly, with a complete abolition of hypoxic vasoconstriction. Moreover, the severity of lung disease and the variability in vascular responsiveness can explain this difference.

The relevant finding was that the vasodilator effect of INO was accompanied by an improvement in arterial oxygenation. Previous studies demonstrated that INO may improve or worsen arterial oxygenation in patients with COPD. In severe COPD, Barbera et al. [11] demonstrated that INO, when administered in room air, impairs pulmonary alveolar ventilation/capillary flow ratio \(V_A/Q_C\) and slightly reduces arterial oxygenation, while Moinard et al. [12] observed no change in PaO2.

On the other hand, Yoshida et al. [13] and Germann et al. [14] observed an increase in PaO2 and a reduction of pulmonary venous admixture using low-dose nitric oxide (5–20 ppm) in combination with oxygen.

Our data are in agreement with those two studies. By combining INO with oxygen, it is conceivable that, in alveolar units with low \(V_A/Q_C\), the increase in alveolar PO2, resulting from the high FiO2, matched the improved alveolar perfusion, minimizing the worsening of pulmonary \(V_A/Q_C\) seen during the administration of INO alone [13].

**Dobutamine challenge**

The effect of dobutamine on pulmonary circulation has not been extensively assessed in patients with mild to moderate pulmonary hypertension. In two small studies, dobutamine increased cardiac output and improved oxygen transport and oxygenation in patients with massive pulmonary embolism [15,16]. Experimental studies in dogs with pulmonary hypertension secondary to embolization of the pulmonary vascular bed demonstrated that dobutamine increases the cardiac index and decreases calculated PVRI. However, pulmonary pressure–flow plots suggest that these findings are not a result of vasodilation [17].

In the study reported here, dobutamine infusion showed similar hemodynamic effects. Dobutamine caused a significant increase in the cardiac index, with a concomitant reduction in SVRI and PVRI. The reduction in PVRI was not proportional to the increase in the cardiac index, leading to an increase in MPAP. This behavior could be explained mainly as a recruitment of vessels rather than as a real vasodilator effect. It is noteworthy that the pressure–flow plot showed a slope very close to that of the isoresistance line equal to 300 dynes/s/cm5. If we accept the viscoelastic model of the pulmonary circulation, this is the case in which the vascular closing pressure is higher than PAOP and should be considered as the effective outflow pressure for the pulmonary vascular bed. Considering PAOP as outflow pressure, the transpulmonary gradient is overestimated by the calculation of pulmonary vascular resistance, and it becomes flow-dependent even if no vasodilation has occurred [18]. The prevalent role of vascular recruitment as a mechanism in pulmonary vascular resistance reduction during dobutamine therapy is supported by the concomitant reduction in arterial oxygenation and the increase in pulmonary \(Q_A/Q_i\). This strongly suggests a worsening of regional \(V_A/Q_C\) as a result of an increased perfusion of poorly or unventilated areas of the lung.

**Inhaled nitric oxide plus dobutamine challenge**

To our knowledge, the interaction of INO and dobutamine on the pulmonary circulation has not been previously reported. Our results indicate that the combined use of both drugs produces a complementary effect which improves circulation and gas exchange. The combination of both drugs causes an increase in cardiac index but no change in MPAP. This suggests that the increase in the cardiac index induced by dobutamine is counterbalanced by the concomitant actual pulmonary vasodilation induced by NO. This interpretation is supported further by analysis of the pulmonary pressure–flow relationship: during administration of the combination of the two drugs the line has a slope intermediate between that of dobutamine and INO when each is given alone.

The other relevant finding is that the favorable hemodynamic effects are not associated with a deterioration in gas exchange, probably because of the vasodilatory effect of INO, which is evident in well-ventilated areas of the lung.

In accordance with the results of the present study, the algorithm reported in Figure 2 may be suggested as a guide in the management of patients with mild to moderate secondary pulmonary hypertension in cases of acute cardiorespiratory decompensation.

Inhaled nitric oxide and dobutamine have significant hemodynamic effects in mild to moderate pulmonary hypertension. Nitric oxide has a real, selective pulmonary vasodilating effect accompanied by an improvement in arterial oxygenation, but no change in cardiac output. Dobutamine, on the other hand, increases pulmonary blood flow in the face of increasing mean pulmonary pressure and a decrease in PaO2. The combination of the two drugs shows more favorable effects. In fact, the increase in cardiac index is associated with no modification in MPAP, and an increase in PaO2. These data show that INO and dobutamine have a complementary beneficial action; further studies are warranted to examine their use as a therapeutic option in right ventricular failure during exacerbations of chronic pulmonary disease.

**Study limitation**

Patients with different diseases but who shared a common physiopathology (severe airways disease) were included in this study. Although the small number of patients in each
Figure 2

Decisional algorithm according to the different values of cardiac index and the different values of MPAP and PAOP (MPAP–PAOP) in cases of acute cardiac decompensation. \( ^{=} \) low TPG; \( ^{\uparrow} \) moderate TPG; \( ^{\uparrow\uparrow} \) high TPG. INO, inhaled nitric oxide; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occluded pressure; TPG, transpulmonary gradient.

Dobutamine INO+Dobutamine INO

\( \downarrow \) PaO\(_2\)

INO+Dobutamine

| Cardiac index | \( \uparrow \) MPAP–PAOP | \( \uparrow \) MPAP–PAOP | \( \uparrow\uparrow \) MPAP–PAOP |

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Competing interests

None declared.

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