



UNRAVELLING THE MODE OF ACTION OF PULSED INHALED NITRIC OXIDE IN SEVERE IPF USING FUNCTIONAL RESPIRATORY IMAGING (FRI)



B. Hajian¹, B. Shivalkar¹, F. Ferreira², C. Van Holsbeke², W. Vos², J. De Backer², D. Quinn³, A. Hufkens¹, P.M. Parizel¹, J. Clukers¹, W. De Backer¹
¹Antwerp University Hospital, Antwerp, Belgium; ²FLUIDDA NV, Kontich, Belgium; ³Bellerophon Therapeutics, Warren, NJ, USA

Introduction

Earlier studies have indicated a possible beneficial effect of inhaled nitric oxide (iNO) in patients diagnosed with idiopathic pulmonary fibrosis (IPF) by lowering pulmonary arterial pressure (PAP) without significant alterations in PaO₂ (J Appl Physiol. 2011;110(3):638–45). However, the regional effects of iNO on lung vessels have so far never been elucidated. Further, the chronic effect of pulsed iNO in this population has not been studied. In this study, we analyzed the effects of pulsed iNO in four IPF patients with severe pulmonary hypertension (PH) using functional respiratory imaging (FRI) as well as hemodynamics and exercise tolerance.

Methods

Pulsed iNO, provided by the INOpulse® delivery system, along with oxygen was administered to 4 patients diagnosed with World Health Organization Group 3 PH associated with IPF (Table 1). Patients 1 and 2 received 75 µg/kg IBW/hr iNO and patients 3 and 4 received 30 µg/kg IBW/hr iNO. All underwent 2 low dose high resolution CT scans using contrast before and during 20min (acute) iNO administration. Two of the four patients also underwent chronic treatment on iNO for four weeks. Acute changes in regional flow distribution and changes in vessel caliber at the lobar level were analyzed. In addition, acute changes in hemodynamics and chronic changes in exercise tolerance were also assessed.

Table 1: Summary Results

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	71	67	66	75
Gender	Female	Female	Male	Male
iNO Dose (µg/kg IBW/hr)	75	75	30	30
TLC (% predicted)	76	57	59	73
Acute Change Blood Vessel Volume (%)	14.0 ± 4.7	34.2 ± 7.6	2.8 ± 3.0	10.1 ± 3.4
Acute Change sPAP (%)	-9.3	-9.7	-14.3	-23.3
Chronic Change 6MWD (meter)	99	-	50	-
Chronic Change DSP* (meter%)	81.1	-	75.1	-
Chronic Change IDSP** (meter%)	82.9	-	82.8	-

Results

Results indicate an average increase in blood vessel volume of 15.3% during acute inhalation of pulsed iNO (p<0.001, see Figure 1). This increase was observed across all lobes in patients 1, 2 and 4. Patient 3 showed a reduced response acutely (average increase in blood vessel volume 2.8%) but after 4 weeks of treatment the average increase improved to 6.0%. A significant association (p=0.009) was also found between ventilation and vasodilation during iNO therapy, suggesting that regions with better ventilation experience more vasodilation (Figure 2). Additionally, patients did not show signs of oxygen desaturation on iNO. Potential signs of rebound were noted for the iNO 75 dose; the lower dose of iNO 30 was administered without signs of rebound. All patients demonstrated a reduction in sPAP with acute administration of iNO (-14.15±6.5%). The two patients who were treated with iNO for four weeks demonstrated an average increase in 6MWD of 75 meters. In addition, both patients showed increases in composite endpoints of oxygen saturation and 6MWD (DSP* and IDSP**).

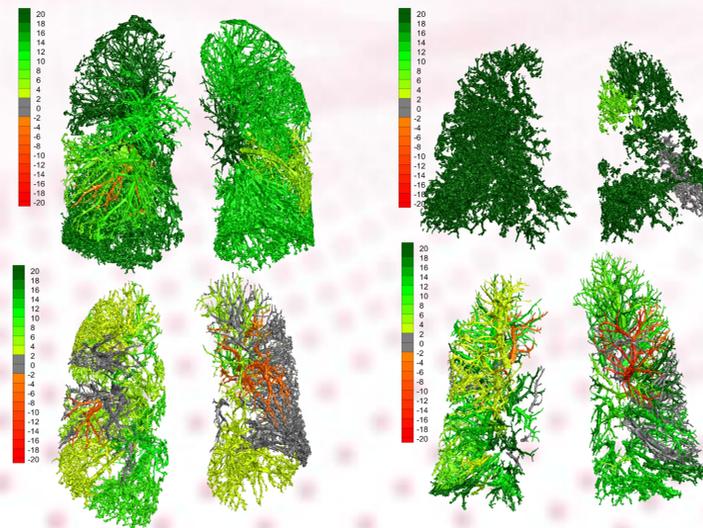


Figure 1: Change in Blood Vessel Volume Compared to Baseline During Acute iNO Administration for patients 1 - 4

*Distance Saturation Product (DSP) is the product of the distance walked and the lowest oxygen saturation (SpO₂ nadir) during the 6MWT

**Integral Distance Saturation Product (IDSP) is the product of the distance walked and the integral average of the oxygen saturation during the 6MWT

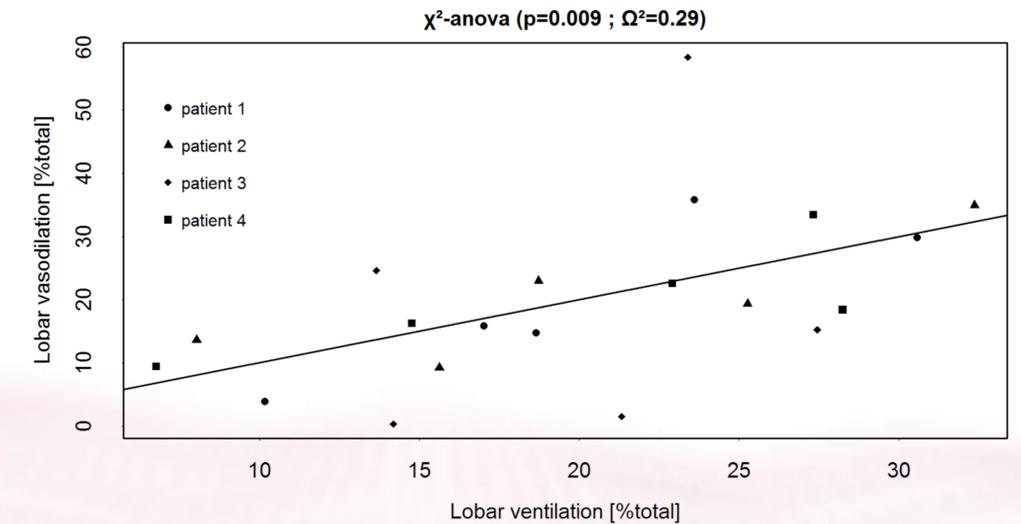


Figure 2: Correlation between Lobar Ventilation and Lobar Vasodilation

Conclusions

- This FRI analysis demonstrates that iNO results in regional dilatation of blood vessels in the lung in the well-ventilated areas.
- Ventilation/perfusion (V/Q) mismatch is thus prevented by targeted vasodilation by administration of pulsed iNO.
- Pulsed iNO showed improved hemodynamics in all subjects for both 30 µg/kg IBW/hr and 75 µg/kg IBW/hr dose.
- Pulsed iNO shows increase in exercise capability as determined via 6MWD and composite endpoints of oxygen saturation and 6MWD (DSP* and IDSP**).

This study is supported by Bellerophon Therapeutics
 B. Hajian and W. De Backer have no relevant financial interests