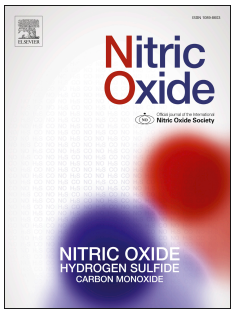

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Modulation of Pulmonary Blood Flow in Patients with Acute Respiratory Failure

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ABSTRACT

Background. Impairment of ventilation and perfusion (V/Q) matching is a common mechanism leading to hypoxemia in patients with acute respiratory failure requiring intensive care unit (ICU) admission. While ventilation has been thoroughly investigated, little progress has been made to monitor pulmonary perfusion at the bedside and treat impaired blood distribution. The study aimed to assess real-time changes in regional pulmonary perfusion in response to a therapeutic intervention.

Methods. Single-center prospective study that enrolled adult patients with ARDS caused by SARS-Cov-2 who were sedated, paralyzed, and mechanically ventilated. The distribution of pulmonary perfusion was assessed through electrical impedance tomography (EIT) after the injection of a 10-ml bolus of hypertonic saline. The therapeutic intervention consisted in the administration of inhaled nitric oxide (iNO), as rescue therapy for refractory hypoxemia. Each patient underwent two 15-minute steps at 0 and 20 ppm iNO, respectively. At each step, respiratory, gas exchange, and hemodynamic parameters were recorded, and V/Q distribution was measured, with unchanged ventilatory settings.

Results. Ten 65 [56-75] years old patients with moderate (40%) and severe (60%) ARDS were studied 10 [4-20] days after intubation. Gas exchange improved at 20 ppm iNO (PaO_2/FiO_2 from 86±16 to 110±30 mmHg, p=0.001; venous admixture from 51±8 to 45±7%, p=0.0045; dead space from 29±8 to 25±6%, p=0.008). The respiratory system's elastic properties and ventilation distribution were unaltered by iNO. Hemodynamics did not change after gas initiation (cardiac output 7.6±1.9 *vs.* 7.7±1.9 L/min, p=0.66). The EIT pixel perfusion maps showed a variety of patterns of changes in pulmonary blood flow, whose increase positively correlated with PaO_2/FiO_2 increase (R^2=0.50, p=0.049).

Conclusions. The assessment of lung perfusion is feasible at the bedside and blood distribution can be modulated with effects that are visualized *in vivo*. These findings might lay the foundations for testing new therapies aimed at optimizing the regional perfusion in the lungs.

KEYWORDS: Inhaled nitric oxide; lung perfusion; ARDS; Electrical Impedance Tomography;

INTRODUCTION

Hypoxemia due to impairment of pulmonary ventilation and perfusion (V/Q) matching is one of the most common causes of respiratory failure requiring intensive care unit (ICU) admission [1]. Over the past decades, the safety of mechanical ventilation increased significantly, leading to increased survival of ventilated ICU patients [2,3]. On the contrary, little progress has been made to monitor pulmonary perfusion and treat impaired pulmonary blood flow [4,5].

The first attempts to describe vascular deformation, microembolism, capillary leakage, and impaired vasoreactivity in patients with respiratory failure date back to the early 1970s' [4,6]. Thereafter, also the use of high positive end-expiratory pressure (PEEP) and the consequent regional alveolar overdistension, have been shown to cause a "stress failure of pulmonary capillaries", a condition well described by the physiologist John West [7,8]. Of note, most of those studies were based on lung biopsy samples and post-mortem analysis.

Subsequently, in 1981 Dr. Reginal Green and Dr. Warren Zapol studied pulmonary artery filling defects in patients admitted to the ICU with acute respiratory failure by using balloon occlusion pulmonary angiography (BOPA) *at the bedside* [9]. The Authors concluded with a question that still, after forty years, remains unanswered: "Could reduced lung damage and improved survival be achieved by using bedside angiographic findings to select patients in ARF for early anticoagulant or antithrombotic treatment of vaso-occlusive disease?" [9]. Such findings were based on vascular occlusion and contrast media injection, and blood flow distribution in the lungs was difficult to assess at a regional level [10].

Recently our group implemented the use of electrical impedance tomography (EIT) a non-invasive, radiation-free tool, that has been used to assess, through saline injection, blood perfusion distribution in the lungs at the bedside [11–13]. In this study, we hypothesized that changes in regional pulmonary blood flow distribution can be quantified as a result of a therapeutic intervention in critically ill patients with acute respiratory distress syndrome (ARDS). We used inhaled nitric oxide (iNO) as a therapeutic intervention to induce a redistribution of blood perfusion in the lungs [14]. Inhaled nitric oxide is a potent, fast-acting, selective pulmonary vasodilator that can improve oxygenation by releasing pulmonary vasoconstriction and thus increasing perfusion in

ventilated regions [15]. The role of iNO in the treatment of acute respiratory failure has been limited so far as a "rescue" therapy in patients with pulmonary hypertension, right ventricular dysfunction, and/or refractory hypoxemia [16].

To date, the clinical response to iNO is generally evaluated by measuring gas exchange after the initiation of iNO administration. In the current study performed in critically ill patients with ARDS, we assessed changes in regional pulmonary perfusion in response to iNO and, simultaneously, assessed oxygenation, systemic and pulmonary hemodynamics, venous admixture, and dead space.

MATERIALS AND METHODS

This is a single-center prospective study that enrolled patients admitted to the ICU of the ASST Grande Ospedale Metropolitano Niguarda (Milan, Italy) with ARDS caused by SARS-Cov-2 between March and May 2021. The study was approved by the institutional review board of Milano Area 3 (approval number 56-11022021) and informed consent was obtained according to local regulations. The inclusion criteria were age ≥18 years old, bilateral pneumonia and ARDS defined according to Berlin criteria,[17] and the clinical decision to administer iNO as rescue therapy in the presence of refractory hypoxemia (defined as an arterial partial pressure of oxygen [PaO_2] of less than 60 mmHg, and FiO_2 of 0.8-1.0, and a positive end-expiratory pressure [PEEP] of greater than 10 cmH_2O for more than 6 hours) [18,19]. Patients were excluded in the presence of a cardiac pacemaker and/or implantable defibrillator, and with major skin lesions on the chest wall.

Study procedures

Patients were sedated, paralyzed, and mechanically ventilated in volume-controlled mode (Draeger Evita V800, Draeger Medical, Lübeck, Germany). Patients were in the supine position and trunk inclination was not modified during the study [20]. Ventilatory parameters were set by the clinical team and kept constant throughout the study period. Study data were retrieved before and 15 minutes after initiation of iNO at the dose of 20 ppm (NOxBOX, Ltd, UK). Responsiveness to iNO was defined as a >20% increase of PaO_2/FiO_2 after 15 minutes of gas administration. Hemodynamic parameters were assessed in real-time by means of thermodilution through the Pulse Contour Continuous Cardiac Output (PiCCO®, Pulsion Medical System SE, Feldkirchen, Germany). The images obtained by chest computed tomography (CT) scan performed in the closest timeframe, before or after the study day, were collected.

The distribution of ventilation and perfusion in the lungs was assessed using electrical impedance tomography (EIT, Enlight 1800, Timpel, Sao Paulo, Brazil). Lung perfusion was

recorded after injection of a 10 ml bolus of 7.5% hypertonic saline through a central venous catheter. At each study step (*i.e.*, 0 and 20 ppm iNO), we recorded the followings:

1. Respiratory parameters: tidal volume, PEEP, peak inspiratory pressure, plateau pressure, driving pressure, and compliance of the respiratory system (C_{rs}).
2. Gas exchange parameters through central venous and arterial blood gas: PaO_2/FiO_2, venous admixture (Qva/Qt), and dead space (Vd/Vt, computed as the difference between arterial and end-tidal CO_2 divided by the arterial pCO_2).
3. Vital signes: blood pressure, heart rate (HR), central venous pressure (CVP), peripheral oxygen saturation (SpO_2), and end-tidal CO_2 ($etCO_2$).
4. Hemodynamics (PiCCO®): cardiac index (CI), stroke volume index (SVI), global end-diastolic volume index (GEDVI), extra-vascular lung water index (EVLWI), intrathoracic blood volume index (ITBVI), and systemic vascular resistance index (SVRI).
5. Recording of ventilation and perfusion distribution in the lungs through EIT reported as the ratio between anterior and posterior percentage distribution.

EIT data analysis

We measured the lung impedance variation related to ventilation (ΔZ_V) and perfusion (ΔZ_Q) before and 15 minutes after iNO. Lung perfusion was assessed by the first-pass kinetic method after injecting 10mL of 7.5% hypertonic saline solution.[21] The perfusion distribution at the pixel level was corrected by cardiac output (CO) according to the formula:

$$\mathrm{Q(pixel)} = \frac{\Delta \mathrm{ZQ(pixel)}}{\mathrm{DZQ(total)}} * CO$$

The EIT analysis was performed: 1) by splitting the lung image into two gravitational regions with similar height, defined as anterior and posterior (*e.g.*, the anterior lung region is the non-dependent region in the supine position), and 2) at the pixel level (from the EIT matrix containing with 32x32 pixels). We excluded pixels corresponding to the heart area detected by the first-pass kinetic method and pixels with changes < 5% of the pixel with maximum ΔZ_V or ΔZ_Q.

The ventilation/perfusion mismatch was estimated by summing the percentage of ventilated and non-perfused pixels (suggesting dead space) and perfused, but non-ventilated pixels

(suggesting shunt). We mapped the positive changes in perfusion distribution at the pixel level, considering pixels with changes bigger than 20% after iNO. The cutoff of 20% was established similarly to the criteria of iNO responsiveness.

Statistical analysis

The normality of data distribution was tested using the Shapiro–Wilk test. Normally distributed data are expressed as means ± SD, whereas nonnormally distributed data are expressed as median and interquartile range. Categorical variables are expressed as count (n) and percentage (%). The presence of outliers was assessed during the evaluation of the distribution of data; however, no action was foreseen. The offline processing of perfusion distribution was performed after blinding data about gas exchange. Continuous variables were compared before and 15 minutes after iNO administration through paired t-test if normally distributed or through Wilcoxon signed-rank if not normally distributed. A linear regression model was implemented, with either the increase in perfusion or V/Q mismatch changes as continuous predictors and PaO_2/FiO_2 changes, as continuous outcome. R-squared was computed. A $p<0.05$ was deemed statistically significant. Statistical analysis was performed using GraphPad Prism (version 8.4, GraphPad Software, San Diego, California, USA) and STATA (version 13.0, StataCorp, Texas, USA).

RESULTS

Study population

Ten patients were enrolled, of whom four were female. The results about EIT data refer to eight patients out of ten, as the offline analysis revealed motion artifacts in two patients, thus precluding data validity. Mean age and body mass index were 65 [56-75] years and 32 [28-41] kg/m^2, respectively. The median SAPS II at ICU admission was 46 [40-53] and the SOFA score was 7 [6-9]. The severity of ARDS was moderate in four (40%) and severe in six (60%) patients. Patients were studied 10 [4-20] days after intubation. On the study day, tidal volume was 5.9 [5.7-6.6] ml/kg predicted body weight, PEEP was 13 [10-16] cmH_2O, C_{rs} was 26 [25-37] ml/ cmH_2O, and PaO_2/FiO_2 was 86 [76-101] mmHg. Five patients out of ten were on vasopressors, the dose of which was unchanged throughout the study (*i.e.*, before and after iNO therapy). ICU mortality was 40%. All patients' characteristics and ventilatory settings on the study day are summarized in Table 1.

Respiratory mechanics, gas exchange, and EIT ventilation distribution

The elastic properties of the respiratory system and distribution of ventilation were unaltered by the initiation of iNO at 20 ppm. Specifically, driving pressure did not change significantly after iNO administration (13±3 *vs.* 14±3 cmH_2O, p=0.09) and EIT showed similar regional ventilation distribution before and after gas administration (1.02±0.41 and 1.10±0.50, anterior/posterior %, p=0.39). Figure S1 (Supplemental Digital Content 1) shows EIT ventilation distribution maps along with a chest CT scan performed, in median, two days before the study day.

Systemic oxygenation improved upon starting iNO therapy. Specifically, SpO_2 increased from 90±3% to 95±3% (p<0.001) and PaO_2/FiO_2 from 86±16 to 110±30 mmHg (p=0.001). The PaO_2/FiO_2 increase was >20% in six patients (60%). $PaCO_2$ did not change significantly after iNO initiation (53±6 vs 51±6 mmHg, p=0.09), while both venous admixture and dead space decreased, 51±8% to 45±7% (p=0.0045), and 29±8% to 25±6% (p=0.008), respectively. Respiratory parameters are summarized in Table 2. Changes in venous admixture, dead space, and

PaO_2/FiO_2 are reported in Table 3, with respect to V/Q mismatch and positive perfusion changes for each patient.

Hemodynamics and EIT perfusion distribution

No significant variations in common hemodynamic parameters were observed after iNO administration, as HR, MAP, and CVP were unaffected by gas therapy (Table 2). Cardiac output and SVI did not change significantly (7.6±1.9 vs. 7.7±1.9 l/min, p=0.66, and 43±9 vs. 45±7 ml/m^2/beat, p=0.15, respectively). Inhaled NO had no impact on both preload and afterload indexes such as GEDVI and SVRI, 730±126 vs. 699±106 ml/m^2 (p=0.28), and 1445±622 vs. 1486±594 $dyn*s*cm^{-5}*m^2$ (p=0.67), respectively.

Taken together the respiratory and hemodynamic results confirm prior findings suggesting that iNO breathing increases oxygenation by improving overall ventilation/perfusion matching. EIT pixel perfusion maps showed a variety of patterns of changes in pulmonary blood flow after starting iNO, unveiling, at the bedside, the heterogeneity of vasculature responses in ARDS patients. The modifications in perfusion distribution induced by iNO are shown in the EIT pixel perfusion maps reported in Figure 1. Figure S1 displays the diversity of CT-morphological presentation, the EIT ventilation, and EIT pixel perfusion maps. Quantification of V/Q mismatch and positive perfusion changes are reported in Table 3, with respect to venous admixture, dead space, and PaO_2/FiO_2 for each patient. Finally, to assess the clinical relevance of the EIT perfusion maps, the pixel increase of regional pulmonary flow was compared to systemic oxygenation response measured as change in PaO_2/FiO_2 and, despite the few observations, a modest positive correlation was found (R^2=0.50, p=0.049) (Figure 2).

DISCUSSION

This study assessed the distribution of blood perfusion in the lungs utilizing a radiation-free and non-invasive tool in a cohort of patients with ARDS admitted to the ICU. The administration of a selective pulmonary vasodilator led to a redistribution of blood perfusion in the lungs, without affecting the main hemodynamic parameters. Such modulatory effect was assessed at the bedside and visualized *in vivo*.

This proof-of-concept study shows that pulmonary blood perfusion can be modulated at the bedside in patients with respiratory failure admitted to the ICU. Of note, blood redistribution occurred in the lungs in every patient enrolled after starting iNO, regardless of the clinical response (oxygenation). This finding suggests that iNO is able to modulate pulmonary perfusion at the *regional* (pixel) level. However, such an effect does not necessarily translate into an improvement in gas exchange, which in fact reflects the overall lung function. The possibility to investigate at the bedside blood distribution in the lungs will hopefully provide more insights to understand how iNO and other vasoactive therapies work in patients with respiratory failure, not only due to ARDS.

Since its first description in 1967 by Ashbaugh and colleagues, [22] ARDS has been extensively investigated over the last decades, being a leading cause of acute respiratory failure that requires ICU admission [1]. The main pathological features of ARDS are diffuse alveolar damage and high permeability pulmonary edema, leading to a disorder of both ventilation and perfusion [23]. However, while ventilation has been thoroughly studied and multiple approaches to tailor mechanical ventilation at the bedside have been proposed, perfusion derangement has been poorly assessed, especially with methods easily applicable and replicable in the ICU.

The earlier techniques to assess the regional distribution of blood in the lungs were based on radioactive tracers, such as low solubility elements like ^{133}Xe and ^{99}Tc, administered intravenously. The analysis of perfusion required a gamma camera to generate two-dimensional images of lung distribution during a breath-holding maneuver [24]. Such precursor methods have been largely replaced by scanning techniques [25]. Magnetic resonance imaging (MRI), dual-energy computed tomography scan, [26,27] positron emission tomography (PET), and single-

photon emission computed tomography (SPECT) are examples of techniques currently used, however, mainly for research purposes [28–30].

The multiple inert gas elimination technique (MIGET) is a different approach that explores the distribution of ventilation-perfusion ratios in patients with lung disease by infusing a mixture of dissolved inert gases with different solubilities into a peripheral vein and then measuring the concentrations of the gases in arterial blood and expired gas. Still, the MIGET is barely applicable outside of a research context, being cumbersome and technically challenging [31].

The first attempt to assess lung perfusion at the bedside relies on Dr. Green and Dr. Zapol's studies in the early 1980s. Being interested in the assessment of vascular lesions occurring during acute respiratory failure, the authors implemented a smart method to study the pulmonary vasculature directly at the bedside, *i.e.* balloon occlusion pulmonary angiography (BOPA) [9]. A pulmonary artery catheter, used for hemodynamic monitoring, was placed, a contrast agent was injected through the distal port, and pulmonary angiography was then performed through a mobile radiographic unit. For the first time, pulmonary artery filling defects were detected at the bedside and compared with post-mortem histologic studies. This landmark study initiated the quest for a therapy to improve lung perfusion in the setting of ARDS that could be monitored at the bedside. Different drugs have been proposed and tested, such as anticoagulant and antithrombotic agents, systemic vasodilators such as nitroprusside, prostaglandins and phosphodiesterase inhibitors, and selective pulmonary vasodilators such as iNO and inhaled prostacyclins [32].

In this study, we showed that it is possible to modulate blood perfusion in the lungs while visualizing the effects of such modulation *in vivo* at the bedside. We used EIT, as an easily applicable, non-invasive, bedside tool in patients admitted to the ICU, differently from other scanning techniques where patients need to be transferred to dedicated research labs. Among perfusion-modulating drugs, we chose iNO as it is relatively safe and commonly used in the ICU setting in patients with refractory hypoxemia. Moreover, iNO is a pulmonary *selective* vasodilating drug with no impact on systemic hemodynamics, whose effects are immediately evident once the gas is administered, and rapidly vanish once the gas is discontinued [14,33,34]. To the best of our

knowledge, only a recent case report explored the possibility to modulate and visualize pulmonary perfusion at the bedside [35]. However, no respiratory and hemodynamic data nor quantitative EIT measures were provided.

Some results of our study deserve to be discussed. We found 60% iNO responsiveness, defined in terms of PaO_2/FiO_2 ratio increase, which is consistent with other data reported in the literature [36]. However, the EIT perfusion maps shown in Figure 1, demonstrated that changes and redistribution of blood in the lungs occur in every patient, regardless of their clinical response. Therefore, it is reasonable to think that the classic clinical endpoints do not reflect what we found at the pixel level. Of note, the parameter that seemed to correlate the most with gas exchange improvement was the positive perfusion change (Figure 2), which is consistent with *regional* improvements in V/Q matching. Another important finding is that hemodynamics, specifically cardiac output, and the other thermodilution-derived parameters remained constant before and after iNO administration. The absence of effects at the macro-hemodynamic level corroborates the hypothesis that our intervention (*i.e.*, iNO administration) modulated regional lung perfusion, without interfering with right heart function [37].

The *in vivo* assessment of blood distribution in the lungs has a strong clinical implication as it might facilitate the development of therapies that impact on lung perfusion. In fact, while research efforts have been largely focused on ventilation, little progress has been done on the perfusion side, being the latter more difficult to measure and modify. The possibility of visualizing both lung ventilation and perfusion at the bedside might encourage the scientific community to find strategies to improve ventilation/perfusion matching, which is ultimately the main determinant of respiratory gas exchange [38].

This study has some strengths. The prospective design guarantees the robustness of both methods and data analysis, as the same study protocol was rigorously applied to all patients. The real-time hemodynamic measurement through transpulmonary thermodilution allowed a quantitative assessment of blood distribution in the lungs and the estimation of the possible effects of iNO on right heart function. Of note, ventilatory settings were unchanged throughout the study steps. Therefore, all modifications that we recorded should be ascribed only to perfusion changes

due to iNO, since no lung recruitment/derecruitment was possible. Finally, the study has novelty, as we focused on and manipulated regional perfusion in the lungs, which was quite difficult before, due to the many technicalities of the available imaging procedures.

We also acknowledge some limitations of the study. We enrolled a relatively small number of patients. However, as in other similar physiological studies, ten patients were enough to detect a signal to test our hypothesis. Most patients had class II obesity and were critically ill, as shown by the relatively high SAPS II and SOFA scores, which might hamper the generalizability of our results. However, the decision to administer iNO was clinical and related to the severity of each patient's condition. In our study, we did not use a pulmonary artery catheter, thus no values of pulmonary arterial pressure were retrieved. However, CVP and CO measurements suggest that right heart function was not significantly influenced by iNO in our cohort of patients. Also, differently from a previous report, [35] we did not find any significant change in perfusion between the anterior and the posterior lung regions. However, the redistribution of blood flow related to iNO is not dependent on the gravitational forces, and this is particularly true in ARDS where lung impairment is not homogeneous. We believe that the assessment of the redistribution of perfusion was only possible by mapping the chest at the pixel level, as we showed in Figure 1. All patients included in the study had ARDS caused by SARS-Cov-2 infection, which might limit the generalizability of our findings. However, several studies have investigated differences and similarities between SARS-Cov-2 and typical ARDS, which is *by definition* a very heterogeneous disorder [39–41]. Finally, we acknowledge that most patients were studied 10-15 days after intubation when ARDS might have progressed towards a higher degree of edema, inflammation, and fibrosis of the lung parenchyma, thus potentially impacting on perfusion distribution. Treatment with iNO was started as a *rescue* therapy after the failure of standard interventions, such as high PEEP levels, neuromuscular blockers, and prone positioning [42].

Demonstrating any clinical and biological benefits or improvement due to iNO is beyond the aims of the study. We believe that animal studies should test whether iNO improves pulmonary endothelial function, modulate inflammation, and prevent intrapulmonary thrombosis. Future studies should also test the hypothesis on whether iNO can reduce inflammation by diverting blood

flow from the most injured areas to less injured ones. The observations provided by the present study are limited to blood flow redistribution. However, we think that our results might lay the foundations to test novel hypotheses in future therapeutic studies.

CONCLUSIONS

Our results prove that the assessment of lung perfusion is feasible and relatively simple at the bedside and that in a cohort of patients admitted with ARDS, blood distribution in the lungs can be modulated with real-time effects that are visualized in vivo. Our findings lay the foundations for testing new therapies aimed at optimizing the regional perfusion in the lungs. Future studies are needed to test the clinical benefits of measuring and improving regional ventilation/perfusion matching at the bedside.

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Figure legends

Figure 1

Electrical impedance tomography (EIT) perfusion maps. Images were obtained with Enlight 1800 (Timpel SA, Sao Paulo, Brazil) using the first-pass kinetics method. Each box refers to a single patient enrolled in the study. The color scale refers to perfusion change (l/min) 15 minutes after administration of inhaled Nitric Oxide at the pixel level. Red color= perfusion increase; Blue color= perfusion decrease.

Figure 2

Linear regression analysis. iNO: inhaled Nitric Oxide; PaO_2: Partial Pressure of Oxygen in the arterial blood; FiO_2: Fraction of Inspired Oxygen.

Table 1 - Population characteristics

	n=10
At ICU admission	
Age, years	65 [56-75]
Male, n (%)	6 (60)
BMI, Kg/m^2	32 [28-41]
PBW, Kg	66 [56-69]
SAPS II	46 [40-53]
SOFA	7 [6-9]
PaO_2/FiO_2	84 [70-115]
Mild ARDS, n (%)	0
Moderate ARDS, n (%)	4 (40)
Severe ARDS, n (%)	6 (60)
ICU mortality, n (%)	4 (40)
On study day	
Days from intubation, n	10 [4-20]
PaO_2/FiO_2	86 [76-101]
PaO_2, mmHg	60.3 [58.2-63.5]
Tidal volume/PBW, ml/kg	5.9 [5.7-6.6]
Respiratory rate, n/min	24 [23-28]
PEEP, cmH_2O	13 [10-16]
C_{RS}, ml/cmH_2O	26 [25-37]
iNO responsiveness, n (%)	6 (60)

Data are expressed as number (percentage) or median [interquartile range].

BMI: Body Mass Index; PBW: Predicted Body Weight; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; ARDS: Acute Respiratory Distress Syndrome; PaO_2: Partial Pressure of Oxygen in the arterial blood; FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End-Expiratory Pressure; C_{RS}: Compliance of the Respiratory System; iNO: inhaled Nitric Oxide.

Table 2 – Respiratory and hemodynamics variables before and 15 minutes after initiation of inhaled nitric oxide.

	iNO 0 ppm	iNO 20 ppm	*P*
Respiratory			
PaO_2/FiO_2	86±16	110±30	0.001
SpO2, %	90±3	95±3	<0.001
$PaCO_2$, mmHg	53.2±5.8	51.2±5.5	0.09
$etCO_2$, mmHg	37±3	38±3	0.09
Venous admixture , %	51±8	45±7	0.0045
Dead Space, %	29±8	25±6	0.008
$PAlv\text{-}artO_2$, mmHg	392±67	378±72	0.003
Ventilation Distribution (Ant.%/Post.% ratio)	1.02±0.41	1.10±0.50	0.39
Hemodynamics			
HR, beat/min	88±16	86±16	0.21
MAP, mmHg	79±13	81±11	0.53
CVP, mmHg	11±3	11±3	0.11
CO, l/min	7.6±1.9	7.7±1.9	0.66
CI, l/min/m^2	3.7±0.6	3.7±0.6	0.58
SVI, ml/m^2/beat	43±9	45±7	0.15
GEDVI, ml/m^2	730±126	699±106	0.28
EVLWI, ml/kg	11.2±6.7	10.8±7.7	0.37
ITBVI, ml/m^2	912±158	900±187	0.64
SVRI, dyn*s*cm^{-5}*m^2	1445±622	1486±594	0.67

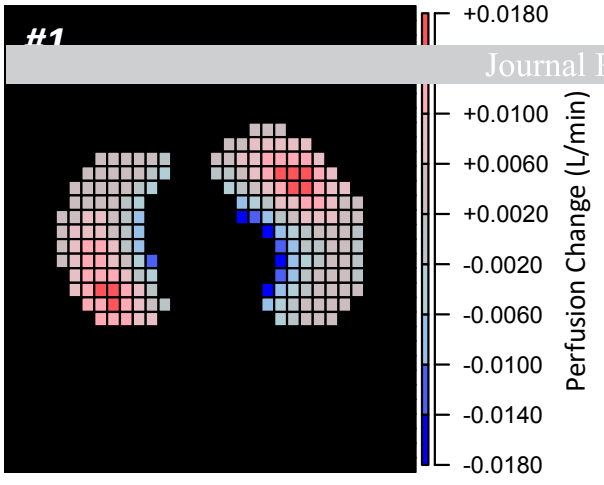
Data are expressed as mean ± standard deviation.

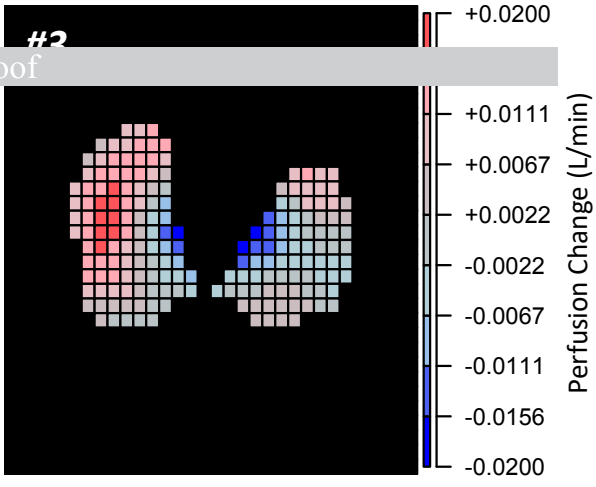
iNO: inhaled Nitric Oxide; PaO_2: Partial Pressure of Oxygen in the arterial blood; FiO_2: Fraction of Inspired Oxygen; SpO_2: Peripheral Oxygen Saturation; $PaCO_2$: Partial Pressure of Carbon Dioxide in the arterial blood; etCO2: End-tidal Carbon Dioxide; $Palv\text{-}artO_2$: Alveolar–arterial Oxygen gradient; HR: Heart Rate; MAP: Mean Artery Pressure; CVP: Central Venous Pressure; CO: Cardiac Output; CI: Cardiac Index; SVI: Stroke Volume Index; GEDVI: Global End-Diastolic Volume Index; EVLWI: Extravascular Lung Water Index; ITBVI: Intrathoracic Blood Volume Index; SVRI: System Vascular Resistance Index.

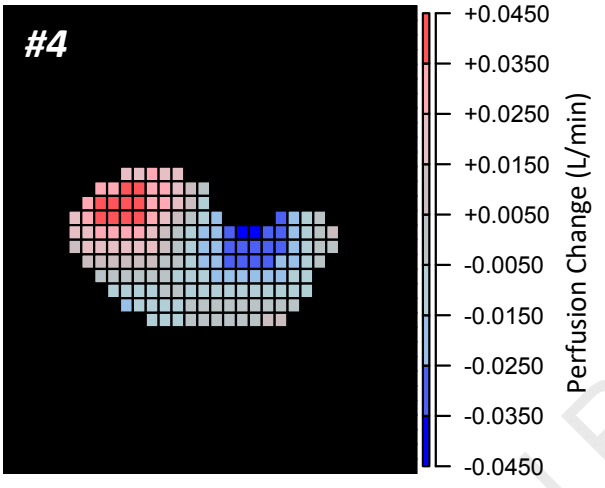
Table 3 – Respiratory, hemodynamics, and perfusion variables before and 15 minutes after initiation of inhaled nitric oxide for each patient.

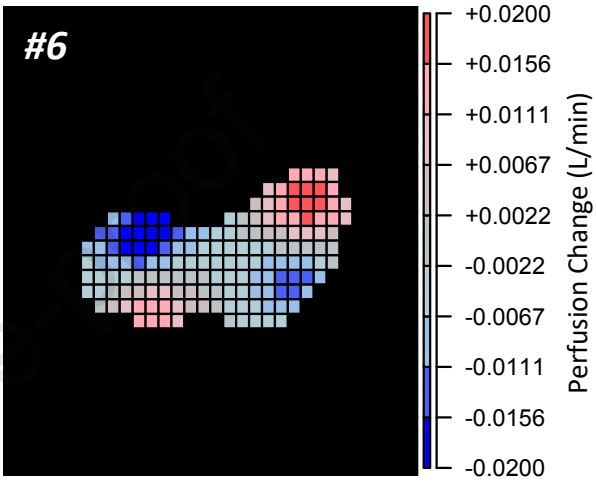
Patient	After – Before iNO					
	Qva/Qt (%)	Dead Space (%)	PaO_2/FiO_2	CO (l/min)	Ventilation / Perfusion Mismatch (% of pixels)	Positive perfusion change (% of pixels)
#1	-4.8	+1.0	+35.7	+0.6	6.6	56
#2	-4.9	+0.2	+28.8	+0.7	NA	NA
#3	-11.0	-9.5	+45.2	+0.6	3.3	50.2
#4	-3.7	-3.8	+31.5	+0.2	6.2	32.16
#5	-1.0	-6.3	+44.7	-0.5	NA	NA
#6	2.9	0.7	-2.1	-0.2	1.2	30.2
#7	-9.2	-7.8	+26.9	-1.0	3.5	50.8
#8	-4.1	-2.1	+6.8	-0.4	10.8	25.5
#9	-7.1	-7.2	+10.5	+0.5	12.5	42.5
#10	-13.0	-6.4	+13.7	+0.4	1.2	28.3

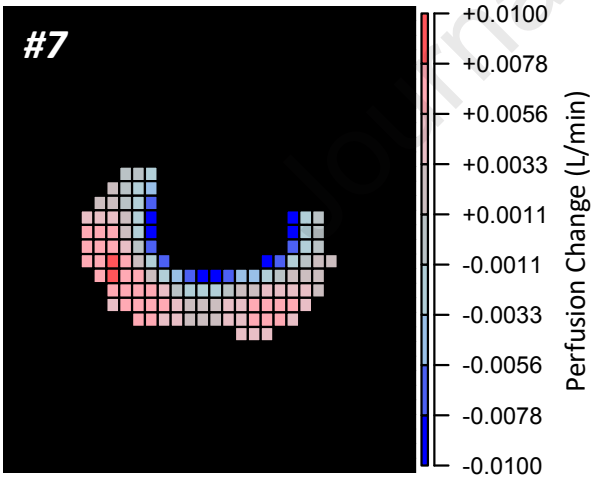
iNO: inhaled Nitric Oxide; Qva/Qt: venous admixture; PaO_2: Partial Pressure of Oxygen in the arterial blood; FiO_2: Fraction of Inspired Oxygen; CO: Cardiac Output.

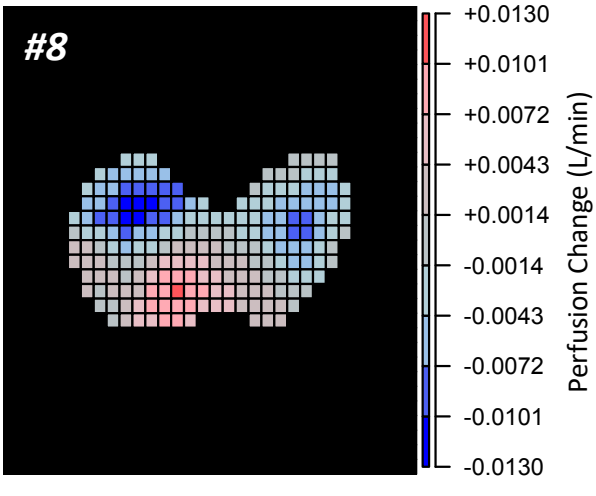


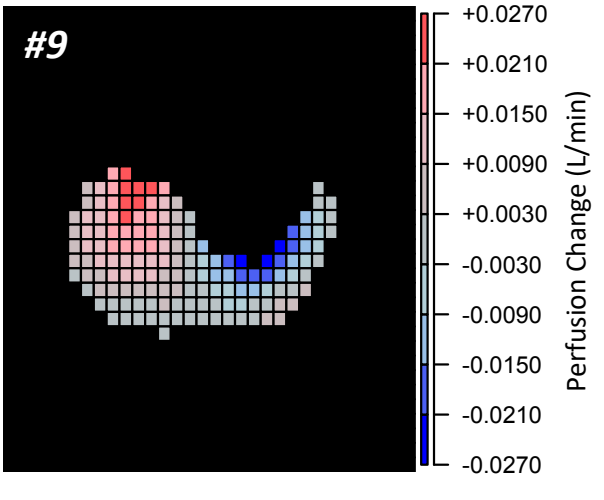


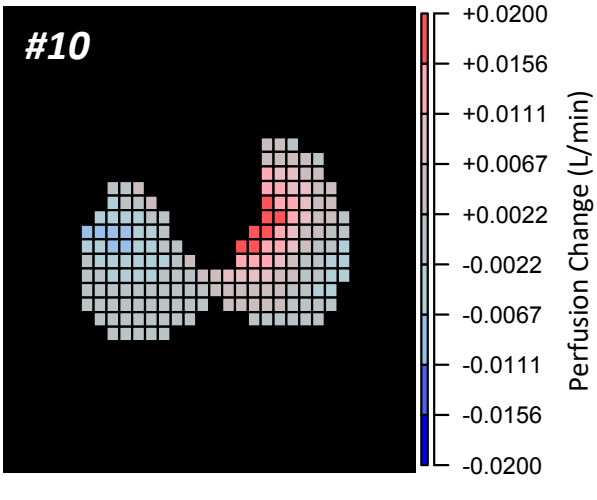


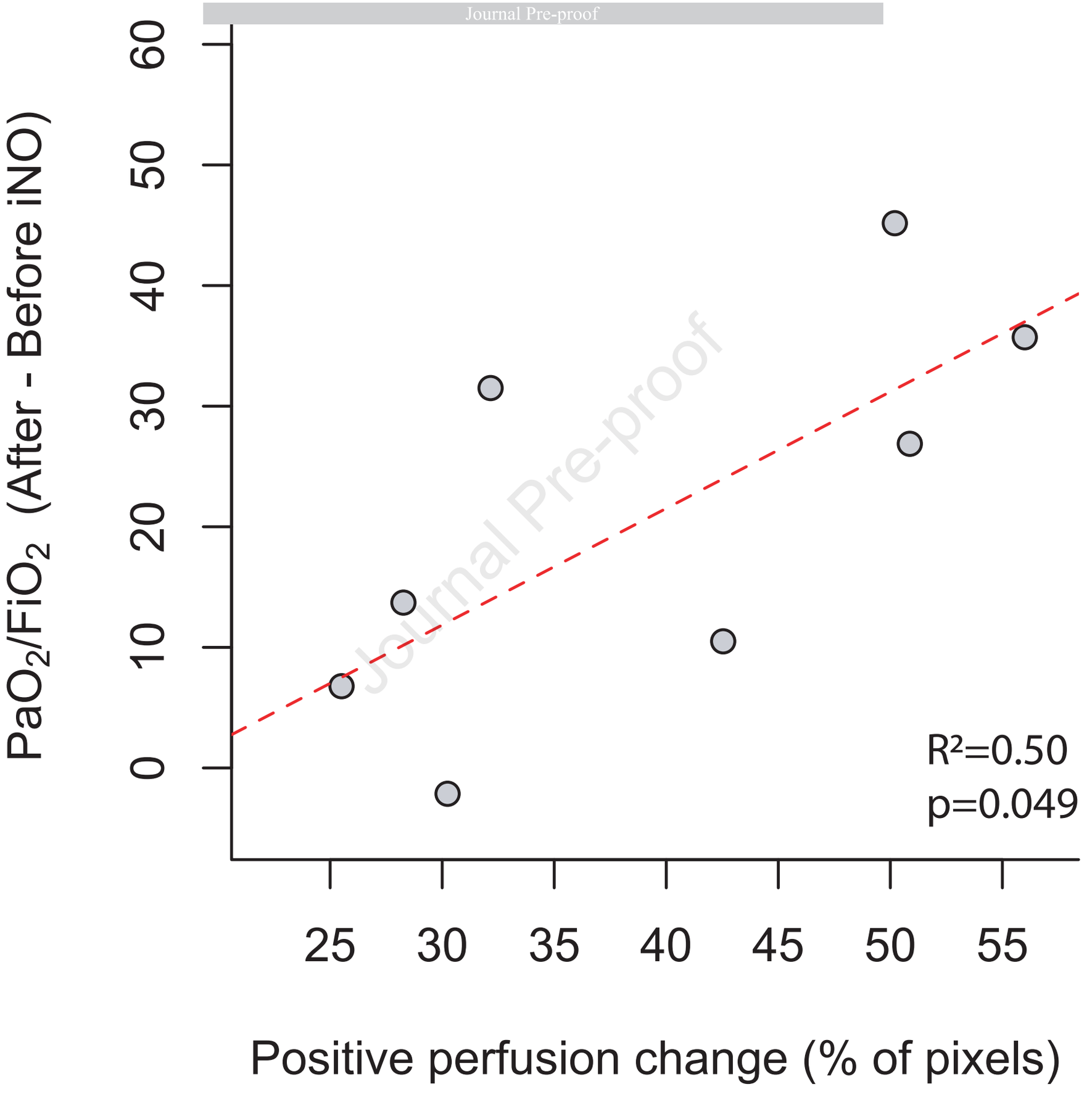












Modulation of Pulmonary Blood Flow in Patients with Acute Respiratory Failure

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Highlights:

- Hypoxemia due to impairment of pulmonary ventilation and perfusion matching is one of the most common causes of respiratory failure requiring intensive care unit admission.
- Inhaled nitric oxide is a selective pulmonary vasodilator that releases pulmonary vasoconstriction and increases perfusion in ventilated regions, whose effect is commonly estimated by improvement in blood oxygenation.
- The administration of inhaled nitric oxide led to a redistribution of blood perfusion in the lungs in all patients, recorded at the bedside and visualized *in vivo* using electrical impedance tomography, regardless of the response in blood oxygenation.
- The possibility of monitoring and modulating blood distribution lay the foundations for testing new therapies aimed at optimizing regional perfusion in the lungs.