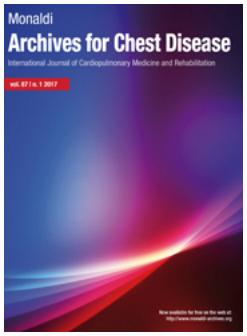

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SARS-CoV-2 pneumonia and Eisenmenger's Syndrome: doubling the challenge

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Abstract
Eisenmenger's syndrome (ES) is the most severe phenotype of pulmonary arterial hypertension (PAH) secondary to congenital heart disease. In these cases, a significant systemic-to-pulmonary (left-to-right) shunting triggers the development of pulmonary vascular disease (PVD) and pulmonary hypertension. In cases of acute hypoxemic respiratory failure in patients with ES, high flow nasal cannula (HFNC) oxygen therapy should be considered as a first-line approach in order to avoid pulmonary complications and right ventricular overload related to positive pressure ventilation. Here, we report a case of HFNC use in a patient with COVID-19 infection and ES.

Key words: pulmonary hypertension; HFNC; COVID -19; noninvasive ventilation, intensive care.

Introduction
Eisenmenger's Syndrome (ES) is considered to be the most severe phenotype of pulmonary arterial hypertension (PAH) secondary to congenital heart disease. Ventricular septal defect, atrial septal defect, single ventricles anomalies, patent arterial duct (PAD) and several other alterations are responsible for its development [1].
In these cases, a significant systemic-to-pulmonary (left-to-right) shunting triggers the development of pulmonary vascular disease (PVD) and pulmonary hypertension, leading to a multi-systemic disorder with multiple complications and poor survival.

Case Report
Here we report a case of COVID-19 severe infection in a woman affected by ES, where the use of high flow nasal cannula (HFNC) oxygen therapy greatly contributed to her recovery. Informed written consent was obtained from the patient before publishing her clinical data. A SARS-CoV-2 non-vaccinated 67-year-old woman presented to the emergency department of the University Hospital of Bari with complaints of fatigue, dyspnoea and dry cough. The patient was affected by a ventricular septal defect leading to ES. She underwent periodical check-ups at the Regional Centre for Pulmonary Hypertension of the University Hospital of Bari. Prior to admission, her medications included tadalafil, inhaled iloprost, macitentan, bisoprolol, amiodarone, furosemide and levothyroxine. In addition, home oxygen therapy (6 L/min via a non-Venturi oxygen facemask) was necessary 24 hours a day.
On arrival, the arterial blood gas (ABG) parameters revealed an hypoxic-hypercapnic respiratory failure with PaO_2 and FiO_2 ratio (PaO_2/FiO_2) of 137 (pH 7.4, pCO2 50 mmHg, $_{pO2}$ 45 mmHg HCO_3 32 mmol/l).
After a thorough assessment and a PCR swab confirming SARS-CoV2 infection, she was commenced on oxygen therapy via a Venturi-mask FiO_2 0.35, in order to achieve a target oxygen saturation (SpO_2) of at least 90%.
Taking in consideration the potential high risk of complications, intubation was avoided, and the patient was admitted to the Respiratory Intermediate Intensive Care COVID-19 Unit (RICU).
On RICU admittance, the patient was alert and conscious. Clinical examination revealed tachypnoea (respiratory rate of 35/min), noninvasive blood pressure 100/65 mmHg, heart rate 65 bpm, SpO_2 84% and peripheral cyanosis. Pulmonary arterial hypertension medications were continued, maintaining a target SpO_2 of 85-90% in consideration of her congenital heart disease [3]. Microbiological samples (blood, urine and sputum) were collected in order to exclude bacterial superinfections [3]. The echocardiographic assessment revealed marked dilatation of both right atrium and ventricles with severe pulmonary hypertension. Table 1 compares right heart catheter measurements before and after hospital admission. Chest CT-

scan showed bilateral and diffuse ground-glass opacities, with bilateral consolidations in the upper pulmonary lobes (Figure 1), confirming the diagnosis of moderate acute respiratory distress syndrome (ARDS). According to the indications of the physician-in-charge on the admission day, the patient was commenced on noninvasive ventilation (NIV) [4] (settings: pressure support PS: 11 cmH_2O, positive end expiratory pressure PEEP 8 cmH_2O) with an interface rotational strategy [5] and alternating prone positioning (at least 12 hours a day) and light sedation [6] with dexmedetomidine (up to 0.5 mcg /kg /h). Decision to start a NIV attempt was based on the progressive deterioration of gas exchanges, on the attempt to avoid invasive mechanical ventilation which may lead to increased pulmonary vascular resistance and worsening of hypoxemia.
As poor interface tolerance forced to discontinue NIV, the patient was switched to HFNC therapy (60 L/min, temperature 31°C) with a SpO2 target above 85% monitoring ROX index [7]. FiO_2 and flow were reduced according to clinical improvements. After 5 weeks, the patient was progressively weaned-off from HFNC therapy and was discharged home at 7 weeks after admission with indications to follow her homecare as before the acute event [8] (Figure 2).

Discussion

To the best of our knowledge, this is the first successful case of HFNC therapy after NIV failure in a patient with severe global respiratory failure and COVID-19. Only one previous study described a limited series of hypoxemic ES patients with COVID-19, treated with low-flow oxygen therapy [9].
NIV has been extensively used with alternating results in COVID-19 hypoxemic patients. Lung overdistension related to positive pressure ventilation may cause hyperinflation, directly correlating to right heart overload [9]. Thus, the use of HFNC may have contributed to decrease patient's effort without increasing right ventricular afterload.
In addition, HFNC has demonstrated to be a more tolerable therapeutic alternative when compared to NIV. While poor interface tolerance and the possible development of pressure ulcers often lead to NIV discontinuation, HFNC may be delivered continuously improving patients' therapeutic adhesion [10].
The official ERS/ATS guidelines recommend NIV for acute hypercapnic respiratory failure with acidosis (pH $\leq$7.35) secondary to COPD [11]. The HFNC may be very useful for COVID-19 patients with respiratory distress providing a small positive airway pressure, reducing the anatomical dead space and increasing pharyngeal oxygen concentration [9,12]. Therefore, its action can counterbalance severe hypoxemia improving hypercapnia, and both these mechanisms might have contributed to our patient's recovery.

Conclusions

In conclusion, treating PAH secondary to ES in the case of COVID-19 related ARDS doubles the challenge to which physicians are faced to. HFNC therapy reaffirms its benefits and therefore should be considered as a first-line approach.

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Table 1. Aortic pressure, pulmonary pressure and resistance, right ventricle pressure, pulmonary capillary wedge pressure, cardiac output and stroke volume values of the patient before (2019) and after (2021) COVID-19.

	Aortic pressure S/D/M (mmHg)	Pulmonary pressure S/D/M (mmHg)	Pulmonary vascular resistance (WU)	Right Ventricle pressure S/D/M (mmHg)	PCW mean (mmHg)	Right atrial pressure mean (mmHg)	Cardiac output (L/min)	Stroke volume (mL)
2019	166/67/97	124/37/71	6.5	128/11/27	17	12	8.23	137
2021	105/60/70	106/25/55	4.3	100/0/4	20	11	8.13	120

S: systolic; D: diastolic; M: mean; PCW: pulmonary capillary wedge pressure.

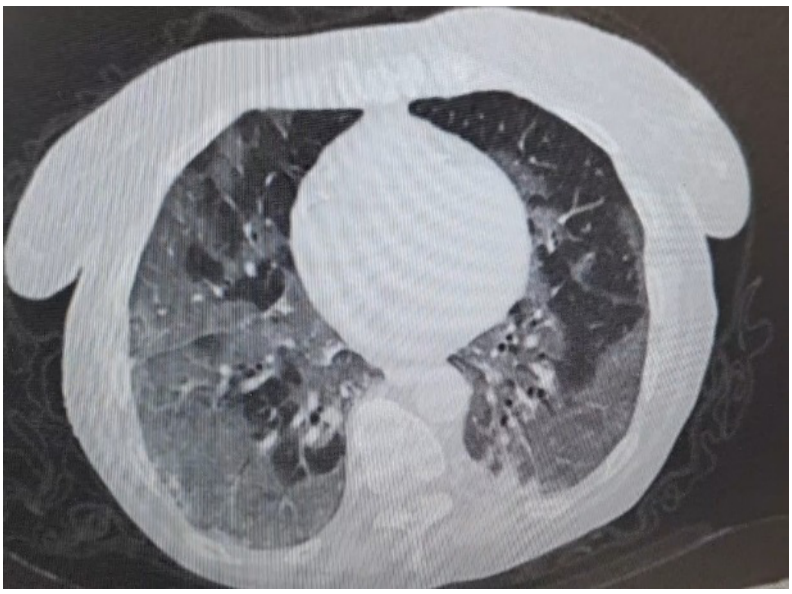

Figure 1. Chest CT-scan. Bilateral ground glass opacities and consolidations in middle and lower pulmonary lobes.

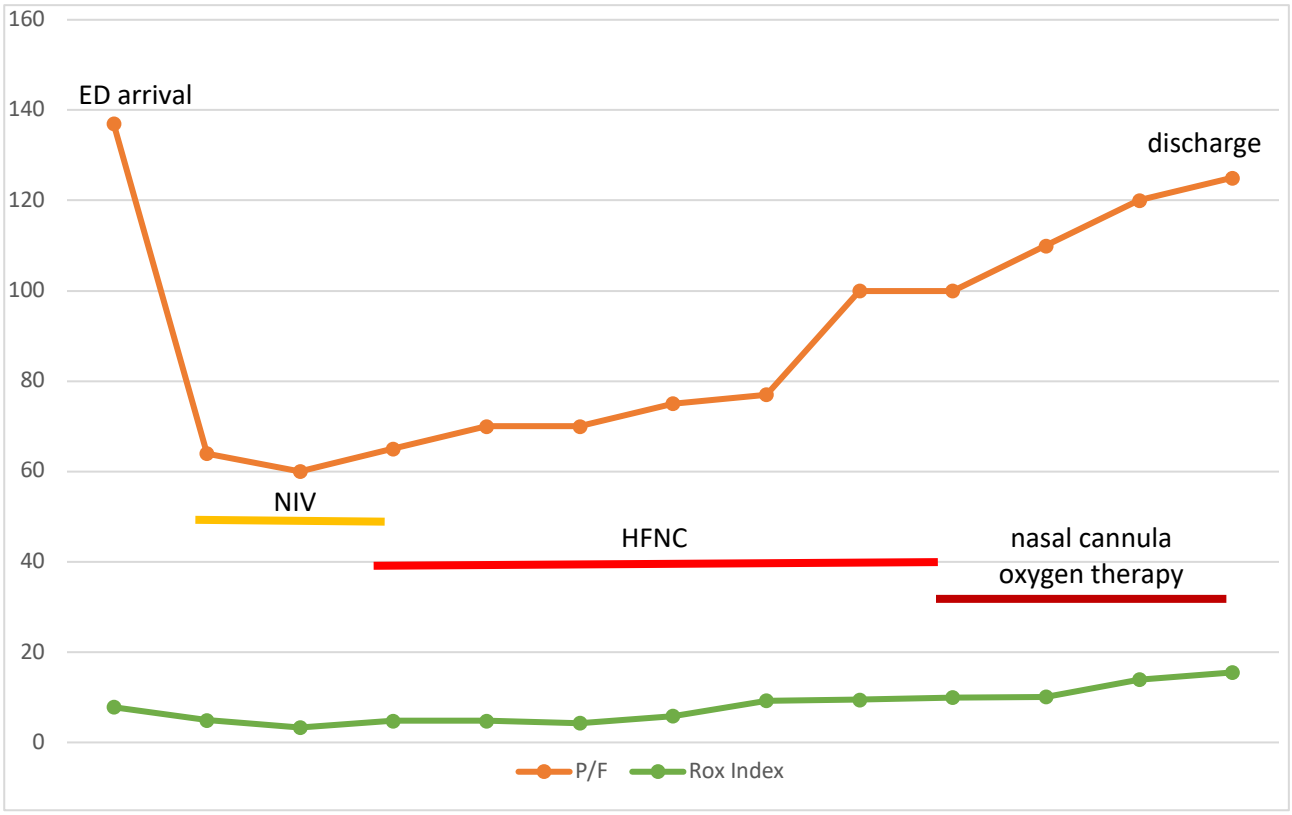

Figure 2. Oxygenation parameters trends (according to different therapeutic strategies).