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High Flow Nasal Cannula Oxygenation Successfully Used as Bridge Therapy for Systemic Thrombolysis in COVID-19 Associated Intermediate-high Risk Pulmonary Embolism

María F. Aguilar-Piedras[a,b], Mateo Porres-Aguilar[c], Debabrata Mukherjee[d], Guillermo Cueto-Robledo[a,b,*], Ernesto Roldan-Valadez[e,f], and Patricio A. Tapia-Vargas[a,b]

From the [a] Department of Cardiopulmonary Emergencies and Pulmonary Vascular Disorders Clinic; General Hospital of Mexico "Dr. Eduardo Liceaga"; Mexico City; Mexico, [b] National Autonomous University of Mexico (UNAM); Mexico City, Mexico, [c] Department of Medicine; Division of Hospital and Adult Thrombosis Medicine; Texas Tech University Health Sciences Center and Paul L. Foster School of Medicine; El Paso, TX, [d] Department of Medicine, Division of Cardiovascular Diseases; Texas Tech University Health Sciences Center and Paul L. Foster School of Medicine; El Paso, TX, [e] Directorate of Clinical Research; Hospital General de Mexico "Dr. Eduardo Liceaga", Mexico City, Mexico and [f] Department of Radiology, I.M. Sechenov First Moscow State Medical University (Sechenov University); Moscow, Russia.

Abstract: The risk of venous thromboembolism (VTE) in COVID-19 patients is a growing problem. Thromboembolic complications are associated with the infection by SARSCoV-2, with an estimated incidence up to 25%-30% of VTE in patients with severe COVID-19 pneumonia. Here in, we present a case of a patient with severe pneumonia due to COVID-19 who is admitted with mild pneumothorax secondary to COVID-19 and high-intermediate-risk pulmonary embolism (PE), who underwent successfully a highflow nasal cannula (HFNC) oxygenation bridge with subsequent successful half-doses of systemic thrombolysis with intravenous alteplase. Prospective studies are warranted in this subset of patients with intermediate-

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high and high-risk PE, to further explore HFNC oxygenation with or without diverse reperfusion strategies, with the aim to identify the best individualized therapeutic approach in each patient with significant COVID-19 associated VTE and optimize outcomes. (Curr Probl Cardiol 2022;47:101000.)

The risk of venous thromboembolism (VTE) in the novel coronavirus disease 2019 (COVID-19) represents a growing problem. Thromboembolic complications are associated with the infection by *SARS-CoV-2*, with an estimated incidence up to 25%-30% of VTE in patients with severe COVID-19 pneumonia, increasing its severity and conferring a worse prognosis.[1] Pulmonary embolism (PE) is predominantly segmental and peripheral in nature, with the novel theory of provoking pulmonary vascular *in situ* macro or micro thrombosis,[2] unlike the usual classic VTE which originates in the lower limbs in up to 90%-95% of all cases. Existing data on VTE associated with COVID-19 published are scarce, so perhaps we are facing very different and novel pathophysiological aspects in this new epidemiological context.[3]

Patients with intermediate-high risk pulmonary embolism (PE) can progress to high-risk requiring hemodynamic support and respiratory support with mechanical ventilation, which could be counterproductive because of positive pressure on venous return.[4] High flow is a modality of ventilatory assistance in patients with respiratory failure, it has taken peak during the COVID-19 pandemic, however, the formation of aerosols has limited its use.[5] Here in, we present a case of a patient with severe pneumonia due to COVID-19 who is admitted with mild pneumothorax secondary to COVID-19 and high-intermediate-risk PE, who underwent a high-flow nasal cannula (HFNC) oxygenation and systemic thrombolysis (ST) with half doses of intravenous Alteplase.

Case Presentation

53-year-old man with significant past medical history of long-standing type 2 diabetes, occasional smoking, and occasional alcohol use. In May 2021 he received the first dose of vaccination against SARS-CoV-2 (Sputnik); however, by his own decision he did not go to the second dose.

Seventeen days prior to his admission with a dry cough, fever of 37.5 C°, myalgias, arthralgias, stabbing headaches associated with photophobia. He came for evaluation due to rapidly progressive acute dyspnea to mild-moderate efforts, productive cough with greenish expectoration, as well as

nonquantified fever for the past 3 days. Oxygen saturation (O2Sat) at room air (RA) was 70%. The rapid test and subsequently the PCR were reported positive for *SARS-CoV-2*.

Vital signs upon admission were heart rate of 117 bpm, respiratory rate of 35 x minutes, 100 of 65 mm Hg. Temperature 35.8. O2Sat at RA 70%. Neck with subcutaneous emphysema on the right lateral side. Anterior aspect of the right hemithorax with soft tissue crepitation due to subcutaneous emphysema. Respiratory sounds decreased in a generalized way, with bilateral diffuse crackles and rales and increased voice transmission all throughout. Rhythmic heart with tachycardia. Abdomen and extremities without any significant abnormalities. Given the clinical suspicion of pneumothorax, we decided to start respiratory support with a simple mask supplemental O2 at 10 liters x minutes. A right sided internal jugular ultrasound-guided central venous line was placed.

Laboratories was remarkable for leukocytosis of 13.9 × $10e^{3/}$uL, mild lymphopenia of 0.83 × 10e3 /uL, platelets at 420,000 x mm^3, hemoglobin 16.2 g/dL, glucose 174 mg/dL, urea 26.9 mg/dL, creatinine 0.59 mg / dL, LDH of 350 U/L. Coagulation profile within normal limits (PT of 13.3 sec, INR 1.1, aPTT 25.1 sec), fibrinogen 928 mg / dL, ESR 20.00 mm/hr, ferritin 787.23 ng/mL, CRP 159.00 mg/L, troponin-I 55.0 pg/mL, BNP 160.70 pg/mL; elevated D-dimer at 4551 ug/L (200-550 ug/L). procalcitonin 0.09 ng/mL. Arterial blood gas (ABGs) at RA showed pH 7.46, $PaCO_2$ 30.6 mm Hg, PaO_2 37.2 mm Hg, HCO3 21.7 mmmol/L, $SatO_2$ 72.5%, Lactate 2.08 mmol/L.

Despite the increase in the PaO_2/FiO_2 ratio at10-L simple face mask, tachypnea and tachycardia persisted. Chest radiography showed a small right-sided laminar pneumothorax with pneumopericardium and pneumomediastinum, in addition to bilateral diffuse alveolo-interstitial infiltrates (Fig 1A). 12-lead electrocardiogram showed sinus tachycardiac with "backward tip pattern," new complete right bundle branch block, as well as late "R" in AVR and presence of "R" wave in lead V-1 (Fig 1B). Computed tomographic angiography (CTA) of the chest for acute PE protocol showed soft tissue range images in the right interlobar pulmonary artery and right basal pulmonary artery trunk up to its bifurcation, as well as in the bifurcation of the left main pulmonary arterial trunk in relation to thrombosis. Severe multifocal pneumonia with commonly reported findings in SARS-CoV2 pneumonia. Subcutaneous emphysema in the thoracic wall and cervical region, as well as in the right perirenal space. (Fig 1C and 1D).

Rapid multimodality risk stratification classified our patient as intermediate-high risk acute PE, given that it had systolic greater than 90 mm

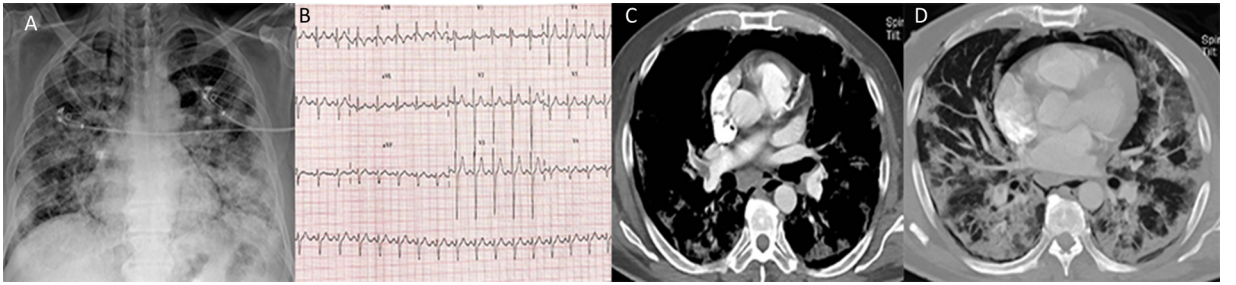

Fig. 1. **(A)** Chest radiograph showing confluent infiltrates, pneumopericardium, pneumomediastinum, and right laminar pneumothorax. **(B)** Initial 12-lead ECG showing sinus tachycardia, *"backward tip pattern,"* incomplete right bundle branch block and late "R" in AVR. **(C)** CTA of the chest demonstrating thrombus in the right interlobar and left subsegmental arteries. **(D)** CTA of the chest with confluent areas and ground glass in both hemithorax.

Hg, PESI score for Class-III, abnormal biomarkers of myocardial damage and CTA of the chest with objective findings of right ventricular dysfunction with an abnormal RV/LV ratio >0.9, as well as rectification of the interventricular septum. Inferior vena cava reflux corresponds to class II. (Fig 2A and 2B). Bova score was calculated to be Class-III, implying the possibility of short-term 30-day morbidity and mortality between 20% and 25%. After multidisciplinary discussion by a designated pulmonary embolism response team, it was decided to administer half doses of systemic thrombolysis (ST) with Alteplase (total infusion of 50 mg IV in 1 hour), as well as to migrate to a high-flow nasal cannula (HFNC) to limit the effects of positive pressure from noninvasive MV on the existing laminar pneumothorax. Post-ST clinical course was favorable, vital signs within the first 6 hours reported normotension with BP at 117 of 79 mm Hg, HR of 76 bpm, RR 22 x min, temperature 36.8, O_2Sat at 93% (Fig 2C), as well as significant improvement and changes in the 12-lead EKG post ST (Fig 2D). ABGs 2 hours post-ST with HFNC (FiO2 75% Flow at 50 L/min): pH 7.47, pCO2 30.5 mm Hg, pO2 76.4 mm Hg, HCO3 21.8 mmol / L, SaO2 92.3%, Lactate 1.37 mmol / L. Subcutaneous therapeutic enoxaparin was started at 1.5 mg/kg of body weight, with no significant major bleeding events post-ST for 5 days, and the patient was discharged on full VTE therapeutic doses of rivaroxaban for at least 3 months, with close follow-up in our post PE multidisciplinary clinic.

Discussion

HFNC oxygenation therapy represents a cornerstone element for the treatment of acute hypoxemic respiratory failure. Its superiority over noninvasive ventilation and conventional oxygen therapy is well established since it reduces mortality, avoids intubation, shortens days of stay in intensive care and hospitalization in some patients with severe hypoxemia.[6,7]

The use of HFNC has been described in many clinical scenarios. An early improvement in respiratory distress is reported in terms of oxygenation and respiratory rate, as we were able to observe in our patient. This relief from respiratory failure appears to be the key to the safety and efficacy of HFNC. Several mechanisms explain the benefits of HFNC over conventional oxygenation modalities; among these, being able to provide the necessary flow and being able to graduate the inspired fraction of oxygen unlike low-flow systems.[7] There are few reports of cases of acute PE treated with HFNC, in fact, they are limited to a series of cases and a case report.[8,9] In PE, mechanical ventilation (MV) increases intrathoracic

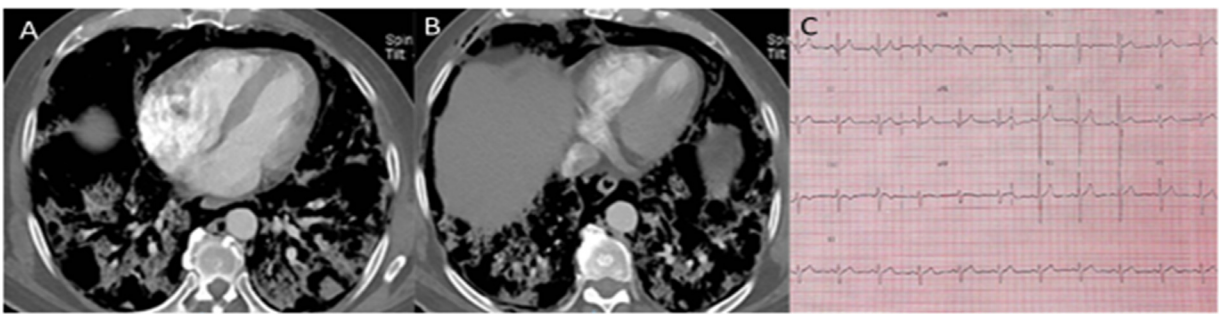

Fig. 2. **(A)** CTA of the chest showing loss of the relationship between RV / LV and rectification of interventricular septum. **(B)** Axial section with class II hepatic venous reflux. **(C)** 12-lead ECG post systemic thrombolysis, persistent *"heart toe back"* pattern, heart rate of 66 bpm, absence of right bundle branch block.

pressure, which can result in a decrease in RV stroke volume and systemic blood pressure. Therefore, HFNC may have significant advantages: first, although it has been shown that lung volume increases at the end of respiration, this increase is modest and positive pressure is mainly observed during expiration, consequently unwanted hemodynamic effects related to HFNC are not observed.[8] Second, HFNC oxygenation can be seen as a *"bridge to systemic thrombolysis or reperfusion strategies"* since it allowed relief of respiratory distress, allowing extra time, widening the therapeutic window to perform ST.[9] In the case of our patient, the findings of RV dysfunction were findings of chest angiography and after placing the HFNC we decided to administer ST. The other limiting factor in our patient for MV was the presence of laminar pneumothorax, which could increase with the use of positive ventilatory pressure.

ST has been shown to reduce early morbidity and mortality in patients with high-risk acute PE, defined as PE associated with shock or hypotension with clinical features of end-organ hypoperfusion.[10] It has been established a widened thrombolysis window up to 14 days after initiation of VTE symptoms for ST; however, the closer we administer ST from symptom onset, the greater chances of obtaining successful fast systemic and pulmonary reperfusion with enhanced efficacy, with less major bleeding complications down the road.

It has been reported in the literature that using half systemic doses of thrombolytics does not increase the risk of bleeding, particularly major bleeding events; on the other hand, it has demonstrated to be superior in terms of efficacy when compared to anticoagulation alone and with comparable outcomes to full doses of ST.[11]

Scarce data exists in regards the potential role of ST in acute PE associated with COVID-19. So and colleagues performed a retrospective cohort analysis in 6095 patients hospitalized due to COVID-19; 57 patients received ST presumably due to the development of acute PE; RV strain and RV thrombus were present in 3.5% (2/57), RV strain and DVT in 5.3% (3/57). CTA of the chest was not performed in any of the patients. Following alteplase infusion, 49.1% (28/57) of patients demonstrated improvement. Six patients (10.5%) survived to discharge, of whom 2 received extracorporeal membrane oxygenation (ECMO) and were transferred to other facilities for lung transplantation, 2 were discharged home, and 2 were discharged to a rehabilitation facility. Overall mortality was 89.5%, concluding that ST for critically ill patients with COVID-19 and presumed acute PE warrants further prospective studies.[12]

Rapid and appropriate risk stratification for both, candidacy for ST as well as for potential major bleedings events post-ST, in combination with

a Bova score > 4 points (grade III) which is related to a 30-day mortality between 15% and 25%,[13] allowed in our patient to decide for half-doses of ST with 50 mg IV of Alteplase, with favorable clinical outcomes during his hospital stay.

Conclusion and Future Perspectives

We strongly believe that the use of HFNC oxygenation in patients with high-risk or intermediate-high-risk PE could be an attractive option to support acute hypoxemic respiratory failure in this type of patients, to avoid the effects of positive pressure ventilation on the RV, being a feasible option to use HFNC oxygenation as a respiratory therapeutic leverage and/or bridge if further reperfusion strategies are considered, with the possibility to avoid rapid cardiopulmonary decompensation and the need of MV. Further prospective studies are warranted in the subset of patients with intermediate-high and high-risk PE, to further explore HFNC oxygenation with or without diverse reperfusion strategies, with the aim to identify the best individualized therapeutic approach in each patient with significant COVID-19 associated VTE and optimize outcomes. Overall, our case suggests that systemic thrombolysis should be considered for the treatment of PE in appropriate patients with COVID-19.[14,15]

Relationship Disclosures

Written and informed consent was obtained from the patient and available for review if needed. The authors of this case report vouch for accuracy and integrity of the data provided.

Author Contributions

Every single coauthor designed, performed research, helped in writing, crafting, editing and critically reviewing key elements of the manuscript. All coauthors read and approved the final version of the manuscript.

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