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The Journal of Emergency Medicine, Vol. 61, No. 5, pp. e103–e107, 2021
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0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2021.07.014

Clinical Communications: Adult

COVID-19 Acute Respiratory Distress Syndrome and Pulmonary Embolism: A Case Report of Nebulized Nitroglycerin and Systemic Thrombolysis For Right Ventricular Failure

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□ **Abstract—Background: Acute respiratory compromise caused by complications of COVID-19, such as acute respiratory distress syndrome (ARDS) or thromboembolic disease, is a complex syndrome with unique challenges in treatment. Management often requires time and intensive care through a multiprofessional, multispecialty approach. Initial management is particularly challenging within the limited-resource environment of the emergency department (ED). The emergency physician's toolbox of treatments with reasonably rapid onset remains limited to respiratory support, prone positioning, steroids, and anticoagulation. Case Report: We present a case of a patient with COVID-19 complicated by ARDS and bilateral pulmonary emboli with severe right ventricular dysfunction and systemic hypotension treated with nebulized nitroglycerin and systemic thrombolytic therapy in the ED. Serial evaluation of right ventricular function using point of care ultrasound over the next 2 h showed improvement of function with both agents as well as improvement in the patient's respiratory rate and work of breathing. Why Should an Emergency Physician Be Aware of This?: This case describes a novel use of a widely available medication for patients with COVID-19–induced right ventricular dysfunction. Nebulized nitroglycerin may be an option to improve right ventricular function when other inhaled pulmonary vasodilators are not available in the initial ED setting. © 2021 Elsevier Inc. © 2021 Elsevier Inc. All rights reserved.**

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□ **Keywords—ARDS; COVID-19; nebulized nitroglycerin; pulmonary vasodilator therapy; right ventricular failure; thrombolysis**

Introduction

The respiratory compromise caused by COVID-19 pneumonia can be profound, and complicated by severe hypoxia, thromboembolic disease, and acute respiratory distress syndrome (ARDS). Treatment in the acute setting consists of respiratory support, corticosteroids, and anticoagulation. The pathogenesis of severe respiratory compromise in COVID-19 is at least partly related to thrombotic events in the pulmonary microvasculature (1). Pulmonary hypertension (PH) and right ventricular dysfunction (RVD) have been shown to correlate with more severe COVID-19 symptoms and worse in-hospital clinical outcomes (2). RVD and PH can be assessed using transthoracic echocardiography through the measurement of right ventricular diameter, right ventricular systolic pressure, and tricuspid annular plane systolic excursion (TAPSE) (2,3). TAPSE is a measurement of the distance traveled by the tricuspid valve along its longitudinal axis during a cardiac cycle (3). This measurement is used to describe right ventricular systolic function. TAPSE values <1.7 cm are associated with RVD (2,3).

Received: 1 March 2021; Final submission received: 19 May 2021;
Accepted: 3 July 2021

Inhaled pulmonary vasodilator medications have been described as therapy for refractory hypoxia caused by PH. One trial of inhaled epoprostenol for COVID-19–induced ARDS with refractory hypoxia showed benefit in the most severe cases (4). Similar agents have been studied for acute PH with RVD caused by pulmonary embolism (PE) with some benefit in the ED setting (5). Inhaled nitric oxide is being explored as a potential treatment for ARDS caused by COVID-19 and has been shown in small studies to improve arterial oxygenation (6,7).

The logistics of administering inhaled or intravenous pulmonary vasodilators is cumbersome and often not possible outside of an intensive care unit (ICU). Nitroglycerin is widely available in most EDs. Inhaled nitroglycerin (iNTG) has been studied for the treatment of PH as it acts rapidly as a pulmonary vasodilator via nitric oxide donation mechanisms when applied to the pulmonary vasculature (8). In the perioperative setting, iNTG has been shown to be a potent pulmonary vasodilator without causing systemic vasodilation (9). It has been discussed as a treatment for massive PE outside of the setting of COVID-19 but has not been systematically studied.

Case Report

During the COVID-19 pandemic, a 56-year-old man with no known medical history presented to the ED by ambulance. He described a 1-week history of generalized malaise and 1 day of worsening dyspnea. He denied a history of smoking or previous venous thromboembolic events. He denied experiencing lower extremity swelling, syncope, or palpitations. He reported a positive COVID-19 test the day before.

Upon presentation, the patient was in severe respiratory distress with increased work of breathing and accessory muscle use. Lung sounds were diminished bilaterally. Physical examination was otherwise without tracheal deviation, jugular venous distension, or lower extremity edema. Initial vital signs were notable for a heart rate of 131 beats/min and a blood pressure of 116/67 mm Hg. Oxygen saturation was 62% on room air and 94% on a nonrebreather mask at 15 L/min with a respiratory rate of 48 breaths/min. Bilevel positive airway pressure was initiated and set to provide 5 mm Hg of expiratory positive airway pressure, an additional 7 mm Hg of inspiratory positive airway pressure, and 100% FiO_2, which improved the patient's work of breathing. The patient's pulse oximetry improved to 95% after intervention. He remained tachycardic at a rate of 129 beats/min with blood pressure of 100/60 mm Hg. Higher inspiratory pressures were considered, but it was felt that an inspiratory pressure of 12 mm Hg adequately improved the patient's work of breathing and that higher pressures did not warrant the risk of further hypotension.

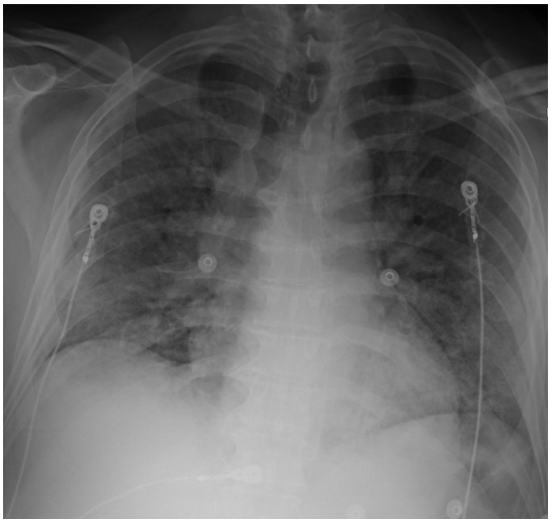

Figure 1. Anteroposterior single view chest radiograph with diffuse patchy opacities.

An upright chest radiograph revealed bilateral multifocal patchy airspace disease consistent with his known COVID-19 infection (Figure 1). An electrocardiogram was performed immediately after stabilization showing sinus tachycardia and an incomplete right bundle branch block without any acute ischemic changes. Initial laboratory results revealed renal dysfunction with creatinine of 1.5 mg/dL presumed to be acute, leukocytosis to 20,300, a troponin elevation at 0.29 ng/mL (normal range <0.04 ng/mL), a B-natriuretic peptide level of 274 pg/mL (normal range ≤100 pg/mL), and a quantitative D-dimer value that was above the upper bound of the facility's assay of 20 mcg/mL. In-hospital testing confirmed infection with COVID-19. No arterial blood gas analysis was performed in the acute setting. The patient's SpO_2/FiO_2 ratio was 95, which is 94% specific for diagnosis of severe ARDS (10).

The patient demonstrated worsening hypotension within his first hour of arrival, with a systolic blood pressure of 80 mm Hg. Pulmonary computed tomography angiography as interpreted by the radiologist revealed bilateral segmental pulmonary emboli and extensive bilateral ground glass opacities consistent with COVID-19 pneumonia. Point-of-care echocardiography performed by the emergency physician demonstrated right ventricular dilation with systolic septal bowing of the interventricular septum into the left ventricle, TAPSE of 1.08 cm (Figure 2A–C), and right ventricular systolic pressure of 39.66 mm Hg. These markers of RVD are associated with increased morbidity and mortality in the setting of PE and have been shown to correlate with increased morbidity and mortality in COVID-19 (2).

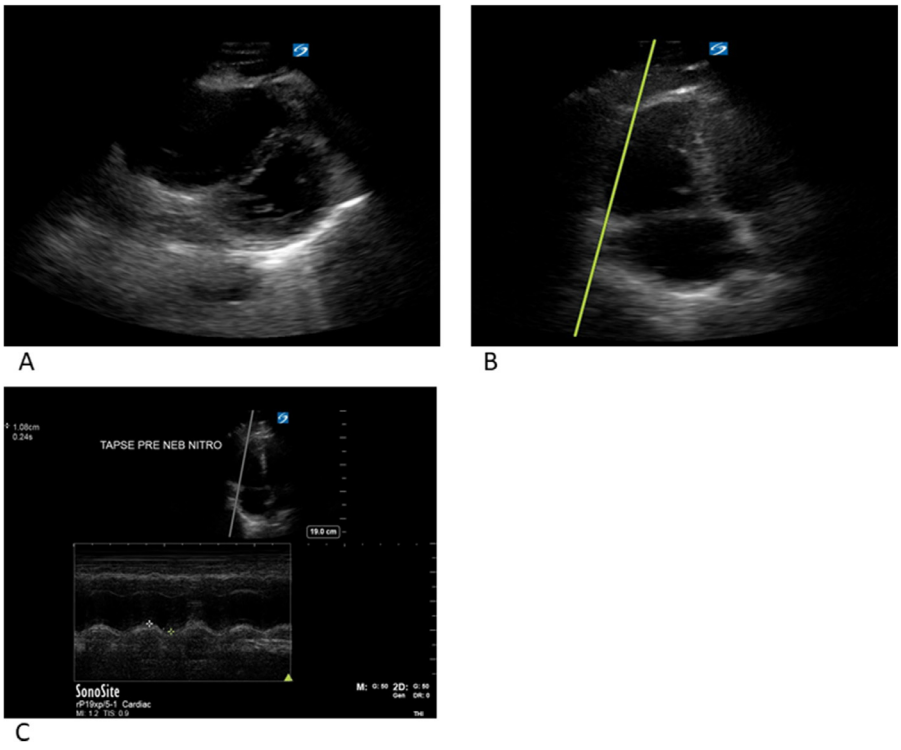

Figure 2. Point-of-care echocardiogram. (A) Parasternal short axis still image showing deviation of the interventricular septum into the left ventricle, indicative of right ventricular pressure overload. (B) Apical 4-chamber still image showing dilated right ventricle with M mode spike placed over the tricuspid plane edge for measurement of tricuspid annular plane systolic excursion (TAPSE). (C) M-mode tracing of the tricuspid plane edge for measurement of TAPSE of 1.08 cm, indicating right heart dysfunction.

Given the patient's progressive hypotension, further treatment modalities were explored. No crystalloid volume resuscitation was administered. Catheter directed fibrinolytic therapy was considered with a multidisciplinary PE team, but the patient was ultimately felt to be too unstable. Vasopressor support was held at bedside ready to deploy but was ultimately never given as the patient's mean arterial pressure did not persist under 65 mm Hg despite this significant drop in blood pressure

The patient was given iNTG 2.4 mg (200 mcg/mL) via inline closed-circuit nebulizer over the next 60 min. Minutes after initiating iNTG, RVD was reevaluated and TAPSE improved. Serial measurements are shown in Figure 3. Systemic thrombolytic infusion was started at the third data point, 12 minutes after iNTG. Alteplase 100 mg was given over 2 h without a bolus dose. The first dose of iNTG was completed after 60 min. The next evaluation of right ventricular function 13 min after the iNTG treatment was completed showed recurrent RVD. Treatment with iNTG was resumed and 10 min after resumption, RVD was again improved—see the final data point in Figure 3.

During this 2-h time period of initial treatment, noninvasive positive pressure ventilation settings were maintained at the initial pressure settings and a constant 100% FiO_2. The patient's blood pressure continued to trend upward—from a systolic blood pressure nadir of 74 mm Hg to a maximum of 86 mm Hg—and his work of breathing continued to improve, with a respiratory rate of 30 breaths/min at the time of final reassessment.

The patient was admitted to the medical ICU with steadily improving hemodynamics. Nebulized nitroglycerin (iNTG) therapy was not continued inpatient, though he was treated with standard therapies including dexamethasone, remdesivir, broad-spectrum antibiotics, and therapeutic anticoagulation. The intensivist's point-of-care echocardiogram upon ICU admission was similar to the emergency physician's with a dilated right ventricle. By day 3 of hospitalization, RVD was no longer present on a cardiology-performed echocardiogram, which showed a TAPSE of 2.6 cm and right ventricular systolic pressure of 26 mm Hg.

The patient's ICU course was protracted and complicated. His respiratory support requirement gradually worsened from intermittent bilevel positive airway pressure to full-time bilevel positive airway pressure over the course of the next week to eventually requiring intubation on hospital day 9. On hospital day 11, a cardiology-performed echocardiogram showed recurrent RVD. Inhaled epoprostenol was administered for refractory

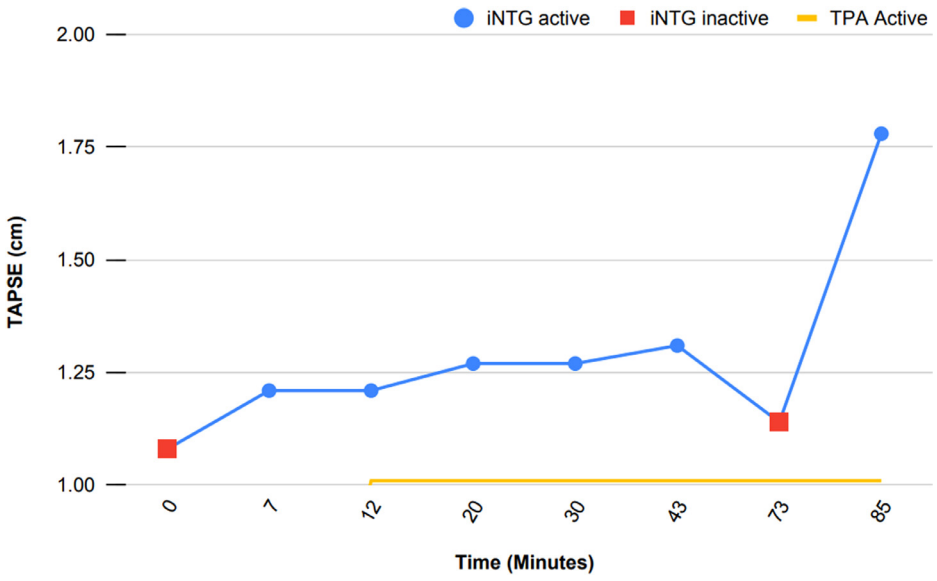

Figure 3. Plot of right heart function assessed by tricuspid annular systolic excursion (TAPSE) over time. Nebulized nitroglycerin (iNTG) was started just after the first plotted time point, iNTG dose completed at approximately 63 min, and restarted immediately after the 73-min assessment. Systemic thrombolytic therapy was started at 12 min and continued for 2 h uninterrupted. TPA = tissue plasminogen activator.

hypoxia despite aggressive respiratory support in the setting of recurrent PH. Despite these measures the patient ultimately died on hospital day 25 while intubated in the ICU.

Discussion

We describe our experience using iNTG with systemic thrombolytic therapy to treat a hemodynamically unstable patient's acute RVD that was caused by COVID-19–induced ARDS complicated by PE.

Systemic thrombolytic therapy was initiated for this patient's profound PH. The patient's PH and vital sign abnormalities were caused in part by COVID-19–induced ARDS and in part by acute PE. At the time, the treating physicians felt that the patient's hemodynamic instability and echocardiographic findings were primarily related to ARDS rather than segmental PEs. However, we also recognized COVID-19–induced ARDS may be associated with overwhelming microthromboemboli and as such the decision was made to administer full-dose alteplase 100 mg over 2 h without bolus dosing in accordance with U.S. Food and Drug Administration guidelines for the management of PE (1,12). Thrombolysis has been retrospectively reviewed in severe COVID-19 pneumonia with concern for PE by Arachchillage et al. who found significant improvement in PaO_2/FiO_2 ratios 24 h after thrombolytic therapy infusion (11). Dosing for thrombolytic therapies specific to COVID-19–induced acute PH have yet to be determined. Vasopressor support was held at bedside ready to deploy but was ultimately never used because the patient's mean arterial pressure did not persist under 65 mm Hg despite his significant drop in blood pressure.

This patient was given iNTG 2.4 mg (200 mcg/mL) via inline closed-circuit nebulizer over 60 min. This dose provided approximately 5.8 mcg/kg/min of iNTG (9). Inhaled nitroglycerin has been described as a treatment for PH in the perioperative setting but has not been rigorously studied in the ED setting (9). The rapid onset of action of this medication via nebulization at 3–5 min is well-suited to acutely ill patients in the ED setting, and the duration of effect was found to persist for ≤30 min (9). Studies of other inhaled pulmonary vasodilators for acute RVD, such as inhaled nitric oxide, are ongoing, but the logistics of providing inhaled nitric oxide in the ED setting may be onerous (5).

The addition of iNTG to this patient's treatment appears to have improved RVD and work of breathing within minutes of starting therapy (see the second data point in Figure 3). Systemic thrombolytic therapy was started at the third data point and continued for 2 h.

This case highlights the acute changes to right heart function caused by iNTG and systemic thrombolytic therapy. This is especially evident in the last 3 data points of Figure 3. The initial iNTG treatment was completed at 60 min, followed by decompensated right ventricular function upon reevaluation at 73 min. Right ventricular function improved once iNTG was reinitiated. The pharmacokinetic properties of alteplase without bolus dose

suggest that the peak effect was reached approximately 6 h after completion of the 2-h infusion (13). The majority of the improvement seen in this patient's RVD may be attributed to iNTG rather than thrombolytic therapy.

This case calls for prospective study of inhaled pulmonary vasodilators medications, such as nitroglycerin, in the ED setting for treatment of severe COVID-19–induced ARDS as well as PH caused by PE without COVID-19.

Why Should an Emergency Physician Be Aware of This?

In this case of severe COVID-19 ARDS and PE with RVD, iNTG improved this patient's acute PH. This novel use of a common medication may provide a new treatment option for acute PH which is otherwise poorly addressed by standard ED therapies. This case report serves as evidence to prospectively study both iNTG and systemic thrombolysis for the treatment of COVID-19 ARDS and PE with RVD.

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