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In Situ Pulmonary Thrombolysis and Perfusion Lung Angiography in Severe COVID-19 Respiratory Failure

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OBJECTIVES: A proof-of-concept study using thrombolysis with catheter-directed tissue plasminogen activator (tPA) and pulmonary angiography imaging was performed to visualize perfusion deficits and reperfusion/therapeutic effects of tPA.

DESIGN: A prospective, open-label, compassionate study. Descriptive statistics were presented for categorical variables and as means with SDs for continuous variables. The Wilcoxon test was used to determine the differences between the two-related samples and a *t* test for continuous variables. Statistical significance was set at *p* value of less than 0.05. Agreement between observations was evaluated using the Kappa Cohen index and overall agreement using the Fleiss Kappa coefficient.

SETTING: A single COVID-19 ICU of Mexico´s General Hospital Dr Eduardo Liceaga.

SUBJECTS: Fifteen patients with severe Delta variant severe acute respiratory syndrome coronavirus 2 infection, 18–75 years old, requiring mechanical ventilation with a persistent FIO_2 requirement of 70% or higher and PaO_2/FIO_2 ratio (or imputed ratio) less than 150 for more than 4 hours. The coagulation inclusion criteria were International Society on Thrombosis and Haemostasis score greater than 5, and presence of a D-dimer greater than 1,200, with viscoelastic testing using rotational thromboelastometry (Instrumentation Laboratories, Mexico City, Mexico) showing both hypercoagulability (EXTEM amplitude at 5 min > 65 FIBTEM > 30) and hypofibrinolysis (EXTEM maximum lysis < 8%).

INTERVENTIONS: Catheter-directed tPA angiography and iFlow system analysis to assess pre-tPA baseline pulmonary perfusion and changes in response to thrombolysis.

RESULTS: Nine patients had microvascular filling defects demonstrated by angiography, and good agreement was found with iFlow analysis ($\kappa = 0.714$). Statistically significant differences were identified in the area under the curve (AUC) region of interest/AUC reference tissue with and without filling defects in phase 2 DM −0.09206 (SD ± 0.16684) ($p = 0.003$). The PaO_2/FIO_2 values measured immediately and 48 hours after the procedure were significantly higher ($p = 0.001$ and $p = 0.005$, respectively). Statistically significant differences were found in D-dimer values ($p = 0.007$), FIO_2 ($p = 0.002$), and oxygen saturation in arterial blood/FIO_2 ($p = 0.045$), as well as in the number of patients who required prone positioning before, immediately after the procedure, and at 48 hours after the procedure ($p = 0.002$).

CONCLUSIONS: Thrombolysis with catheter-directed tPA resulted in imaging evidence via pulmonary angiography and iFlow technology of improved lung perfusion in COVID-19 patients with severe respiratory failure.

KEY WORDS: COVID 19; microvascular thrombosis; thrombolysis

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Early in the course of Delta variant COVID-19, patients with respiratory failure have relatively normal lung compliance and elevated dead-space ventilation, a hallmark of diffuse pulmonary microvascular thrombosis (1–3). Autopsy studies of patients who died of COVID-19 have documented microthrombi in the pulmonary circulation (4–7). These alterations are driven by a systemic prothrombotic state compounded by fibrinolysis shutdown, leading to extensive small vessel thrombosis and major thromboembolic events (3, 4). In hospitalized patients with COVID-19 who are not yet critically ill, therapeutic anticoagulation has been shown to improve outcomes (8), whereas if not initiated until the patients become critically, the benefit of therapeutic anticoagulation is lost, as such patients have already formed a significant clot burden (8–11). In patients with COVID-19, ventilation/perfusion (V/Q) mismatch is observed in patients without massive or submassive pulmonary embolism (PE), suggesting diffuse pulmonary small vessel/microthrombotic occlusion, consistent with the observations seen uniformly in COVID-19 autopsy specimens (12, 13).

For these reasons, a proof-of-concept study was conducted using thrombolysis with catheter-directed tissue plasminogen activator (tPA), with pre- and post-tPA pulmonary angiography imaging and image analysis using the Syngo iFlow software to visualize perfusion deficits and reperfusion/therapeutic effects of tPA.

The study objective was to determine whether thrombolytic therapy would improve microvascular pulmonary perfusion due to microthrombosis in patients with severe COVID-19 infection requiring mechanical ventilation (MV).

METHODS

The ethics and research committee at the Hospital General de México "Dr. Eduardo Liceaga" approved a prospective, open-label, compassionate 15-patient study, authorization number DI-222-2020, registered on ClinicalTrials.gov (NCT04926428). Due to the severity of the illness, the legally authorized representative signed informed consent in all patients enrolled in the study.

Intervention

Selective catheter-directed thrombolysis with tPA (alteplase, Actilyse Boehringer Ingelheim Promeco Sa de CV, Mexico City, Mexico) was performed in each main pulmonary artery under fluoroscopic guidance using right common femoral vein access, and images were acquired and analyzed using Syngo iFlow. The procedure was executed in a hybrid operating room equipped with Siemens Artis Zeego equipment. A dose of 0.5 mg/kg of tPA was administered transcatheter divided into two doses, one for each pulmonary artery in a continuous infusion for 30 minutes (total time 1 hr). Immediate angiographic assessment was performed using the same protocol. The pressure and velocity of the contrast during the pre- and post-tPA angiography were controlled using an automated injector. If a macrovascular thrombus (segmental, subsegmental, or aortic thrombosis) was found during the procedure, the Syngo IFlow analysis was omitted.

Outcome Measurements

Vascular reperfusion was evaluated using 2D perfusion angiography (2DPA), which creates a 2D color map and a time density curve (TDC) of the digital subtraction angiography (DSA) images. Image analysis was performed using the Siemens Healthineers Syngo WP post-processing iFlow software (Version VD20B; Siemens Healthcare, Erlangen, Germany). First, a 2DPA color map was created from the DSA images. Then, the TDC of the contrast input and output in a selected region of interest (ROI) was extracted from this color map. The ROI was located between the origin of each pulmonary artery and the subsegmental artery of the affected pulmonary segment. Finally, the ROI TDC was exported to a comma-separated value file and imported into MATLAB 2018a (Version 9.4; MathWorks, Natick, MA) for measurement extraction. Five measurements were calculated from the TDC: time of arrival, time to peak (TTP), mean transit time, area under the curve (AUC), and washout rate. The interpretation of the angiography and iFlow images was performed by two independent interventional radiologists; if there was a disagreement, a third interventional radiologist was consulted to obtain consensus. Coagulation status (partial thromboplastin time [PTT], prothrombin time [PT]/international normalized ratio [INR], thrombin time [TT], fibrinogen, D-dimer) and oxygenation assessment (Pao_2/Fio_2, oxygen saturation in arterial blood [Sao_2]/Fio_2, Pao_2, $Paco_2$, Fio_2, ventilator settings including compliance) were measured to evaluate the clinical impact and its correlation with the acquired images.

Inclusion Criteria

Patients were eligible for inclusion in the study if they met the prespecified pulmonary and coagulation criteria. The pulmonary inclusion criteria were patients with severe acute respiratory syndrome coronavirus 2 infection, 18–75 years old, requiring endotracheal intubation, MV with a persistent FIO_2 requirement of 70% or higher and PaO_2/FIO_2 ratio (or imputed ratio) less than 150 for more than 4 hours. The coagulation inclusion criteria were International Society on Thrombosis and Haemostasis score greater than 5, and presence of a D-dimer greater than 1,200, with viscoelastic testing using rotational thromboelastometry (Instrumentation Laboratories, Mexico City, Mexico) showing both hypercoagulability (EXTEM amplitude at 5 min > 65 FIBTEM > 30) and hypofibrinolysis (EXTEM maximum lysis < 8%).

Exclusion Criteria

Ischemic cardiovascular disease, presence of abnormal neurologic examination, active bleeding, myocardial infarction within the previous 3 weeks or cardiac arrest during hospitalization, cardiac tamponade, endocarditis, uncontrolled hypertension (systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg), history of stage 4 cancer, history of brain tumor or cerebral arteriovenous malformation or ruptured aneurysm, major surgery or major trauma within the previous 2 weeks, pregnancy, fibrinogen less than 200 mg/dL, blood dyscrasias, or thrombocytopenia (platelet count < 30 × 10^3/uL).

Presence of macrovascular thrombosis (segmental or subsegmental pulmonary embolism or aortic thrombosis) precluded patients from iFlow analysis because the changes in perfusion areas using iFlow technology would cause bias in interpretation; however, these patients received in situ thrombolysis for outcome measures.

Statistical Analysis

Descriptive statistics were presented as numbers and percentages for categorical variables and as means with SDs for continuous variables. The Wilcoxon test was used to determine the difference between two-related samples (which did not meet normality criteria), while a *t* test was used for continuous variables (standard). One-way analysis of variance was used to compare the means of three samples that met the normality criteria, while the Friedman test was used for samples that did not meet this criterion. Cochrane's Q test was used to compare the three groups with dichotomous variables. Statistical significance was set at *p* value of less than 0.05. Agreement between observations was evaluated using contingency tables and the Kappa Cohen index, while the overall agreement was evaluated using the Fleiss Kappa coefficient. For statistical analysis, Microsoft Excel (Version 2016; Microsoft Corporation, Mexico City, Mexico) (Computer Software) and IBM SPSS (Version 25; IBM, Mexico City, Mexico) (Computer Software) were used.

RESULTS

Descriptive Angiography Findings

Eighteen patients were consented for this study. Three patients died before the intervention, with the remaining 15 patients undergoing the study protocol. The characteristics of the patients are summarized in **Table 1**. Five patients (33.3%) had macrovascular thrombosis on initial angiography (one segmental and three subsegmental PE, one aortic thrombus) and therefore were excluded from the study and received standard of care for their macrothrombotic findings. The remaining 10 patients underwent angiography with catheter-directed tPA thrombolysis for severe COVID-19 respiratory failure. Of the 10 patients who underwent angiography and catheter-directed pulmonary tPA, seven completed the iFlow protocol for analysis due to technical issues with implementing use of the new technology at our institution.

From the pulmonary angiography reports of the 10 patients without macrothrombosis, nine (90%) of the subjects had peripheral filling defects suggestive of microvascular thrombosis. Bilateral involvement was evident in three (33.3%) of the nine subjects with peripheral filling defects. Eight patients (80%) had immediate imaging evidence of improved perfusion (reduced filling defects) after catheter-directed tPA, six patients (60%) had partial improvement of filling defects post-thrombolysis, and three (30%) had near-complete resolution of filling defects. One patient had no improvement in filling defects.

When the pre- and post-angiography values were compared with iFlow, a good agreement was found between the observations by both methods ($\hat{k} = 0.714$) (**Figs. 1** and **2**).

TABLE 1.
Characteristics of the Patients

Variables	Total (n = 10)
Age (yr)	55.0 (49.0–63.0)
Sex = male	8 (80)
Female	2 (20)
Hispanic ethnicity	10 (100)
Body mass index (kg/m^2)	29.44 (21.6–39.54)
Myocardial infarction	1 (10%)
Cardiac disease	1 (10%)
Stroke	0
Hypertension	7 (70)
Diabetes	8 (80)
Chronic obstructive pulmonary disease	1 (10)
Cancer	0
Immunosuppression	0
Dementia	0
Hyperlipidemia	3 (30)
Coagulation disorder	0
Other comorbidities	0
Number of comorbidities	3.0 (0.0–3.0)
Remdesivir	0 (0)
Dexamethasone	10 (100)
Vasopressors/inotropic	
1	1 (10)
2	1 (10)
3	8 (80)
Acute kidney injury	6 (60)
1	4 (66.6)
2	0 (0)
3	2 (33.3)
Renal replacement therapy	2 (33.3)
Acute Physiology and Chronic Health Evaluation II	16.5 (14–18)
Sequential Organ Failure Assessment	5 (5–5)
International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score	5 (5–5)
Ferritin (ng/mL)	2,434 (1,210–3,079)
D-dimer (µg/L)	2,826 (1,320–5,245)
Polymerase chain reaction (mg/L)	191 (122–274)
Troponin (pg/mL)	15.2 (2.2–33)

Categorical variables are expressed as n (%), while numerical variables are expressed as median (interquartile range).

iFlow Analysis

Pre-treatment was compared with the post-treatment of healthy and diseased lung tissue to identify differences in the PEAK ROI/PEAK reference (REF), TTP, and AUC ROI/AUC REF in phase 1 and phase 2. A statistically significant difference was identified in the TTP of healthy tissue in phase 1, medium density (MD) −4.18 ± 0.685 (p = 0.092) (**Supplemental Material 1**, http://links.lww.com/CCX/A959), and in the AUC ROI/AUC REF of healthy tissue in phase 2, MD −0.09 ± 0.166 (p = 0.003). When we compared the same values grouped by tissue filling defect status, phase, and affected lung segment, statistically significant differences were identified in the AUC ROI/AUC REF of tissue with filling defects when compared with tissue without filling defects in phase 2 of the middle (p = 0.041) and lower (p = 0.013) segments and in the PEAK ROI/PEAK REF of healthy tissue in phase 2 of the lower segment (p = 0.041). No statistically significant differences were found in the other comparisons (**Supplemental Material 2**, http://links.lww.com/CCX/A960).

No statistically significant difference was found when the MD of the PEAK ROI/PEAK REF, TTP, and AUC ROI/AUC REF values of the pre-treatment and post-treatment, tissue, with filling defects and tissue without filling defects were compared.

Clinical Outcomes

The Pao_2/Fio_2 values immediately after the procedure and after 48 hours were significantly higher than the values before the procedure (p = 0.001 and p = 0.005, respectively). In addition, statistically significant differences were found in D-dimer (p = 0.007), Fio_2 (p = 0.002), and Sao_2/Fio_2 (p = 0.045) taken before the procedure, immediately after the procedure, and at 48 hours post-procedure, as well as in the number of patients who required prone positioning before the procedure, immediately after the procedure, and at 48 hours after the procedure (p = 0.002). No statistically significant differences were found in the values of PTT, PT, INR, TT, fibrinogen, Pao_2, Sao_2, and $Paco_2$ (**Table 2**). Six (60%) of the study patients died.

DISCUSSION

A key clinical feature of severe COVID-19 is a highly prothrombotic state linked to excess arterial and

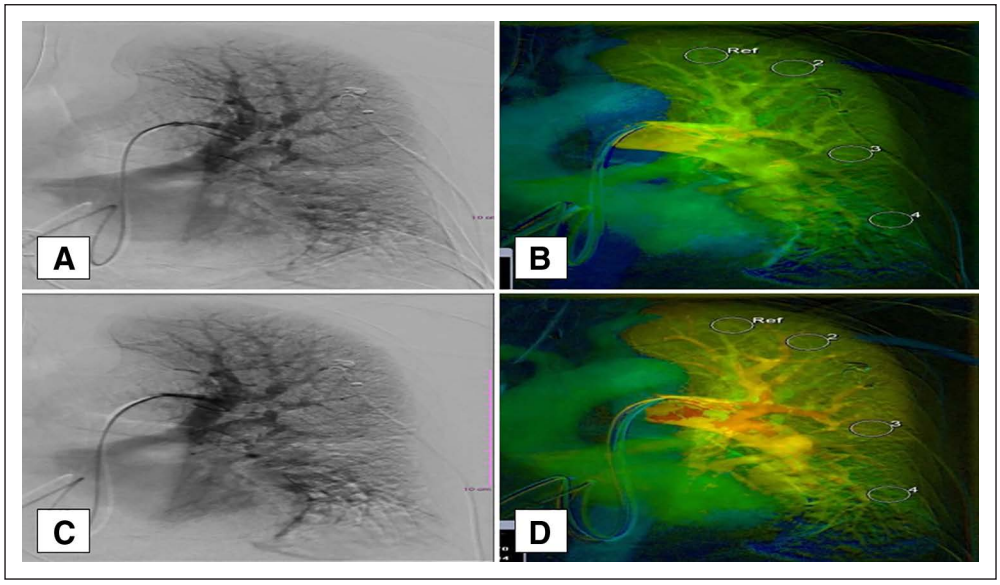

Figure 1. Pulmonary angiography and iFlow analysis. **A**, Selective angiography of the left pulmonary artery with defects of the peripheric perfusion in the superior and medial interlobar pulmonary artery pre-thrombolysis. **B**, iFlow with a *green* pattern color reflecting the pre-thrombolysis contrast flow velocity. **C**, Selective angiography of the left pulmonary artery with partial improvement of the defects of the peripheric perfusion in the superior and medial interlobar pulmonary artery post-thrombolysis. **D**, Post-thrombolysis iFlow analysis with increased pulmonary flow velocity (manifested by a change of the color codification from *green* to *orange*) and distal pulmonary artery definition augmented. Ref = reference.

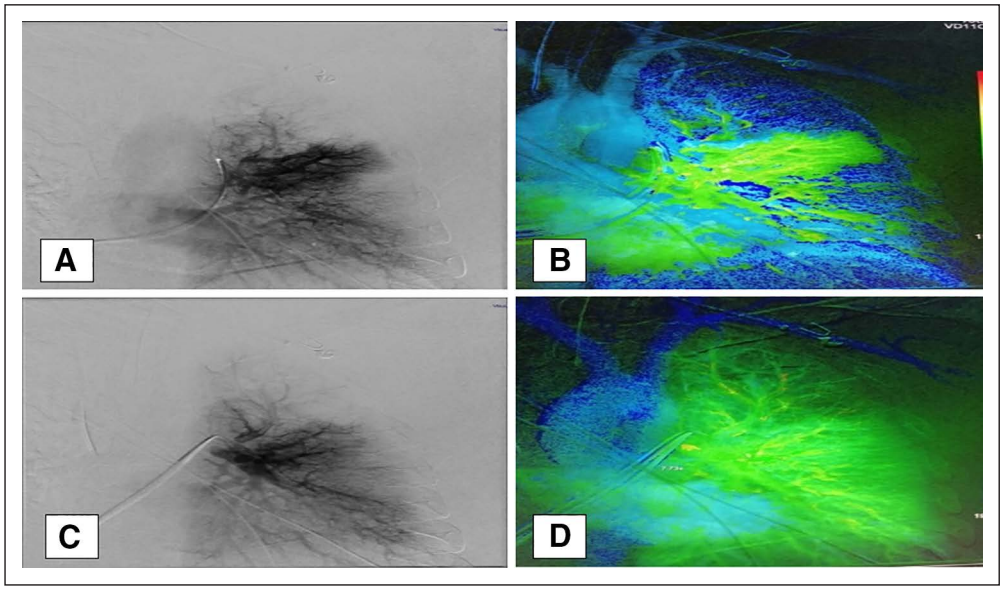

Figure 2. Pulmonary angiography and iFlow analysis. **A**, Selective angiography of the left pulmonary artery with defects of the peripheric perfusion in the superior and medial and inferior interlobar pulmonary artery pre-thrombolysis. **B**, iFlow with a *blue* pattern color reflecting the pre-thrombolysis contrast flow velocity. **C**, Selective angiography of the left pulmonary artery with partial improvement of the defects of the peripheric perfusion in the superior and medial and inferior interlobar pulmonary artery post-thrombolysis. **D**, Post-thrombolysis iFlow analysis with increased pulmonary flow velocity (manifested by a change of the color codification from *blue* to *green*).

venous microvascular and macrovascular thromboses (13–21). Patients who present with COVID-19 respiratory failure have preserved lung compliance early despite profound respiratory failure, consistent with V/Q mismatch from pulmonary microvascular thromboses. The high mortality of critically ill patients with COVID-19 infection, the presence of microvascular thrombosis on autopsy, the efficacy of anticoagulation in treating moderate disease but lack of efficacy once severe disease has occurred, collectively suggest that small pulmonary vessel thrombosis is contributory, if not the predominant reason, for the V/Q mismatch observed in COVID-19 patients (14).

Our study shows in severe COVID-19 respiratory failure, using pulmonary angiography and iFlow technology, that there is imaging evidence of pulmonary microvascular perfusion defects that can be reversed, at least partially, through thrombolysis with tPA, and this corresponds with clinical improvement in oxygenation. These findings, in the context of the above literature on thrombotic phenomena in COVID patients, are highly suggestive that the peripheral filling defects seen in our series are due

TABLE 2.
Clinical or Biochemical Characteristics Before and After the Procedure

Clinical or Biochemical Characteristic	Pre, Mean (SD)	Post, Mean (SD)	48 hr, Mean (SD)	*p*
Prothrombin time	12.05 (0.79)	11.85 (0.73)	12.29 (2.15)	0.584
Partial thromboplastin time	29.03 (5.75)	28.65 (6.11)	27.17 (8.28)	0.813
International normalized ratio	1.0 (0.06)	0.98 (0.06)	1.03 (0.17)	0.554
Dilute thrombin time	22.02 (4.34)	22.25 (5.56)	20.86 (2.61)	0.836
Fibrinogen	726.50 (179.19)	671.50 (174.29)	652.33 (177.41)	0.97
D-dimer	7,006.0 (12,481.37)	4,409.40 (3,435.36)	1,729.50 (1,233.97)	0.007[a]
Sao_2	93.50 (3.37)	93.80 (1.87)	92.0 (1.24)	0.275
FIO_2	95.0 (8.16)	61.90 (18.95)	62.50 (22.01)	0.002[a]
Sao_2/FIO_2	62.50 (22.01)	98.90 (10.75)	163.30 (45.98)	0.045[a]
Pao_2	63.6 (8.09)	65.0 (10.23)	67.6 (8.73)	0.611
Pao_2/FIO_2	67.45 (10.99)	110.4 (26.03)	119.4 (38.16)	0.000[a]
PCO_2	60.28 (22.87)	60.36 (20.98)	73.75 (42.23)	0.670

Sao_2 = oxygen saturation in arterial blood.
[a]Statistical significance.

to microvascular thrombosis, rather than some other phenomena (e.g., vasoconstriction).

Our findings are consistent with the recently published STudy of Alteplase for Respiratory failure in SARS-Cov2 COVID-19 trial, which was the first prospective randomized controlled trial of fibrinolytic therapy in COVID-19 respiratory failure. This study showed significantly improved oxygenation, half the mortality and 12 more ventilator-free days in the tPA bolus group (underpowered for significance), with an acceptable risk profile when patients were carefully selected with no intracranial hemorrhages (22).

This study has several limitations. First, pulmonary arterial infusion is resource intensive and the dynamics of pulmonary perfusion have unique characteristics that require consideration of multiple complex variables in order to translate our findings obtained by iFlow before and after noncatheter-directed thrombolysis (23–26). However, delivery of tPA via a central venous catheter where the tip is near the cavoatrial junction, just proximal to the pulmonary vessels, may provide similar effects. Second, this was an uncontrolled study with respect to patients, although the pre- and post-tPA nature of the imaging served as an internal control. Finally, the impact on clinical outcomes was not feasible due to the lack of a matched control group.

In sum, our observational study provides novel insight with direct imaging evidence of the presence of perfusion alterations that improve with the application of catheter-directed thrombolysis via tPA in patients with severe COVID-19 respiratory failure.

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intellectual content and final approval of the version to be published. Guarantor of the article (to Dr. Pérez-Calatayud).

All authors consent for publication if the article is accepted. All authors confirm that the content of the article has not been published or submitted for publication elsewhere.

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This study was submitted to the Institutional Review Board for human subjects. Both ethic and research committee approved the protocol with registers number DI-222-2020. Patients were informed and signed consent before participation.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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