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# **A Brief Review on Failed Hybrid Treatment for Massive Pulmonary Embolism: Catheter-Directed Thrombolysis (CDT) and Pharmacomechanical Thrombolysis (PMT)**

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**Abstract:** Acute massive or high-risk pulmonary embolism (PE), described as a lung arteries occlusion by an embolus, causes a significant compromise of hemodynamic stability and could lead to a lethal event. Systemic fibrinolytic therapy has been accepted as the standard reperfusion therapy in massive PE, except when there is an increased risk of bleeding. Catheter-based mechanical strategies (thrombofragmentation, thromboaspiration with catheter-guided thrombolysis) are described as options when there are absolute contraindications to systemic thrombolysis. We briefly reviewed clinical situations when patients with severe pneumonia due to COVID-19 are complicated by a

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**high-risk saddle pulmonary embolism and underwent repeated pharmacomechanical thrombolysis and high-flow oxygen therapy. There are scarce reports of failed catheter-guided pharmacomechanical thrombolysis in patients with PE secondary to COVID-19. Re-administration of systemic thrombolysis and alteplase (15 mg dose) can show favorable results. (Curr Probl Cardiol 2022;47:101294.)**

## Introduction

**A**cute massive or high-risk pulmonary embolism (PE) is described as lung arteries occlusion by an embolus, causing a significant compromise of hemodynamic stability and could lead to a lethal event.<sup>1,2</sup> While massive, submassive, and non-massive pulmonary embolism is related to the hemodynamic state, saddle pulmonary embolus is only a radiologic term.<sup>3</sup> Even though thrombolytic agents have been included in the primary treatment of PE, some patients are not candidates for systemic thrombolytic management, and catheter-based approaches must be considered a safer choice where expertise is available.<sup>1,2</sup>

## Epidemiology

PE is the third most common underdiagnosed cardiovascular disorder in North America. The annual incidence rate of PE in Western Europe, North America, Australia, and Latin America, ranges between 75 and 269 cases per 100,000 of the general population, according to a study of 70-year-old and older subjects.<sup>4</sup>

In December 2019, the first reports of a new coronavirus infection emerged from Wuhan, China. The disease, known as COVID-19, had spread worldwide in just four months.<sup>5</sup> COVID-19 is associated with a prothrombotic state, with embolic complications involving potentially any organ. A complication with high morbidity and mortality is venous thromboembolism.<sup>6</sup>

Studies analyzing PE incidence in patients admitted to the intensive care unit (ICU) with severe COVID-19 pneumonia have found rates between 25% and 43%.<sup>6,7</sup> Rates of PE in tertiary-care hospitals might be similar,<sup>8</sup> but its presence is related to worse results despite thromboprophylaxis.<sup>9</sup>

## *Classification of Pulmonary Thromboembolic Disease*

Acute PE is risk stratified as high risk (massive), intermediate-high/intermediate-low risk (submassive), and low risk (minor) based on the degree of hemodynamic compromise and right heart dysfunction. High risk and intermediate-high risk cases are significantly associated with mortality, and thrombolysis is advocated for selected patients to reduce the right ventricular (RV) afterload and improve pulmonary perfusion.<sup>10</sup>

## *Systemic Fibrinolytic Therapy*

It has been accepted as the traditional reperfusion therapy in massive PE.<sup>10</sup> According to current guidelines, it is recommended that high-risk PE patients (patients with a state of shock or profound hypotension) undergo systemic thrombolysis, except when there is an increased risk of bleeding. Catheter-based mechanical strategies [thrombofragmentation and thromboaspiration with catheter-directed thrombolysis (CDT)] are described as options when there are absolute contraindications to systemic thrombolysis.<sup>10</sup> Unsuccessful thrombolysis is defined by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 hours; it has been described in 8% of high-risk PE patients.<sup>10</sup>

## *High-Flow Oxygen Therapy*

Hypoxemia is a feature of severe PE primarily due to the discrepancy between ventilation and perfusion. Administration of supplemental oxygen is suggested in patients with PE and  $\text{SaO}_2 < 90\%$ . Auxiliary oxygenation techniques should also be considered, including high-flow oxygen and mechanical ventilation in cases of extreme instability.<sup>10</sup> Oxygen therapy with high-flow nasal cannulas (HFNC) has been described as a bridge to improve respiratory distress, while thrombolytics improve ventricular function by decreasing afterload.<sup>11</sup>

## *Clinical Findings*

A 65-year-old female with a previous diagnosis of Diabetes mellitus type 2, hypertension, chronic renal insufficiency, and obesity presented to the pneumology department with 20 days of cough and shortness of breath which worsened 2-5 days preceding her presentation.

On examination, she was tachycardic (123 beats per minute), hypotensive (90/60 mmHg), tachypneic (27 breaths per minute), and hypoxic, saturating 83% on room air, with bilateral lower extremity edema.

## Laboratory Findings

Arterial gasometry was taken with the following values: pH 7.35 mmHg, pCO<sub>2</sub> 32.4, pO<sub>2</sub> 70 mmHg, HCO<sub>3</sub> 17.6 mmol/L, Lactate 2.8 mmol/L. PCR test confirmed a positive result for COVID-19. She also presented markers of inflammation and myocardial damage. CPK 103 U/L, creatin-kinase isoenzyme MB 11 U/L, troponin 195.7 pg/ml, B-type natriuretic peptide 184.6 pg/ml, D-dimer 41367 ug/L and myoglobin 76 ng/ml.

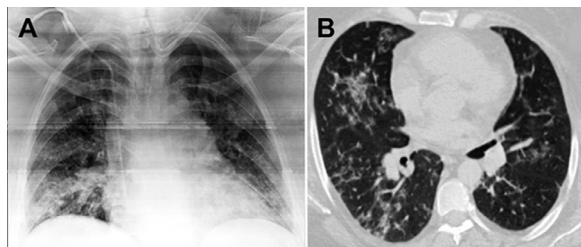
## Imaging Findings

Anteroposterior chest X-ray (Fig 1A) displayed bilateral diffuse basal opacities, mediastinal widening, central venous catheter, and pulmonary artery cone, with prominent cardiomegaly. Thorax CT in the axial plane with lung window (Fig 1B) revealed multiple nodular areas of pulmonary consolidation alternating with numerous regions of tarnished glass pattern of subpleural and peripheral distribution.


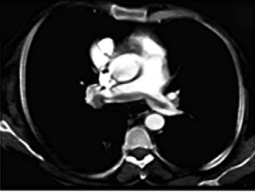
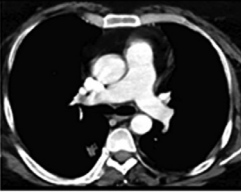
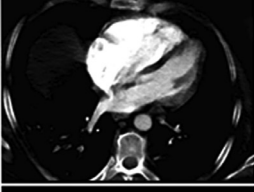

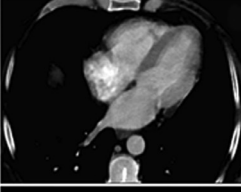
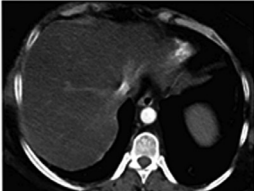
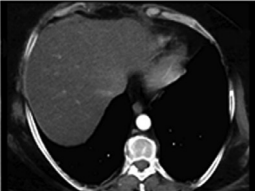
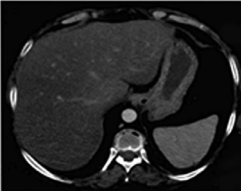
Due to suspicion of PE, CT pulmonary angiography (CTPA) was requested and revealed a saddle embolus in the bilateral basal lobar and trunk arteries leading to dilation of the right ventricle and hepatic reflux (Fig 2). Unfractionated heparin infusion, vasopressor support with norepinephrine, and high-flow nasal cannulas (HFNC) were initiated because the patient presented respiratory failure and was hemodynamically unstable.

## Rational Diagnosis and Treatment

With the findings mentioned above, a patient would presumably be diagnosed with massive saddle pulmonary thromboembolism. Systemic



**FIG 1.** (A) An anteroposterior thorax X-ray displayed bilateral diffuse basal opacities of right predominance, mediastinal widening, central venous accessory and pulmonary artery cone, and prominent cardiomegaly. (B) A CT in axial cut with lung window revealed pulmonary parenchyma with multiple nodular areas of pulmonary consolidation alternating with numerous regions of increased density in tarnished glass pattern of subpleural and peripheral distribution, with random involvement of all lung segments.

Date	02.23.2022	02.26.2022	03.01.2022
Thrombus			
RV/LV Relation			
Value	1.6	0.93	1.05
Hepatic Reflux			
Class	III	I	I

**FIG 2.** Basal CTPA showed a saddle thrombus into the main pulmonary arteries, RV/LV relation of 1.6, and hepatic reflux class III. A 72-hours later, CTPA displayed thrombus fragmentation, but CDT exhibited the persistence of a smaller saddle thrombus, RV/LV relation of 0.93, and hepatic reflux class I. The last CTPA showed no evidence of saddle thrombus after the second CDT with alteplase; there was an RV/LV relation of 1.05 and hepatic reflux class I.

thrombolysis was not performed in this example since the patient was considered at high risk for bleeding because of her medical history (age, chronic renal failure). Urgently underwent right heart catheterization (RHC) for thrombus fragmentation and CDT. Thrombofragmentation and CDT were performed with an alteplase infusion at 15mg in 100 cc, saline solution 0.9% to pass to 8 hours single dose. Subsequently, 72 hours after, a control CTPA depicted the persistence of the central thrombus. The embolus was smaller, the ratio between the diameter of both ventricles improved, and there was no hepatic reflux (Fig 2). However, the patient persisted with a need for HFNC and vasopressor management. The medical team discussed treatment options and decided to do a second intervention for catheter-directed thrombofragmentation and CDT. The same dose of thrombolytic (15 mg in 100cc saline solution 0.9% to pass to 8 hours single dose) was applied without complications. Seventy-two hours later,

a third CTPA showed the absence of the saddle thrombus, the relationship between both ventricles was two, and there was no liver reflux. The results of the multiple RHC are presented in [Table 1](#).

In the control imaging study after the second catheterization, the presence of the thrombus was not observed ([Fig 2](#)). In addition, the system of HFNC was changed by nasal tips with low oxygen flow, and noradrenaline support was suspended. The oral anticoagulant treatment was initiated with rivaroxaban every 12 hours. The patient was discharged from the pneumology service with clinical improvement.

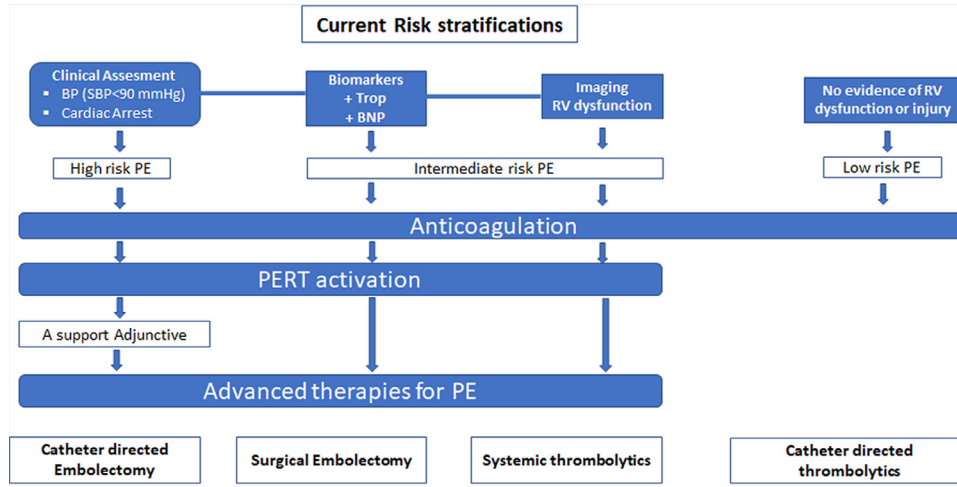
## Discussion

PE is responsible for more than 100,000 cardiovascular disease-related deaths annually in the United States.<sup>12</sup> Despite its incidence and mortality, there has historically been a relative lack of data on risk stratification and effective treatment strategies to guide clinical decision-making, leading to variability in managing a potentially preventable cause of death. In the last decade, there has been increased interest in optimizing acute PE management with the development of novel endovascular technologies and the establishment of PE response teams (PERTs). The standard of care for acute PE.<sup>13</sup> ([Fig 3](#)) remains hard to define given the broad spectrum of clinical presentations and the multitude of pharmaco-mechanical treatment options available.<sup>12</sup>

Catheter interventions can be performed when thrombolysis has failed to improve hemodynamics in the acute setting.<sup>14</sup> Catheter-based

**Table 1.** Hemodynamics results from the basal and subsequent RHC. Both procedures reduced HR, CI, and the mean pulmonary artery pressure. The final catheterization improved the relationship between ventricles and hepatic reflux eradication

	Attempt 1	Attempt 2	Attempt 3
HR	103	89	82
RA mmHg	4	1	2
RVs/d mmHg	36/2	31/5	26/3
PAP s/d/m mmHg	36/12/21	31/8/18	26/6/15
CI l/min/m <sup>2</sup>	3.5	2.7	2.7
PCWP mmHg	3	2	2
PVR mmHg	2.6	3.0	2.4
PvO <sub>2</sub> mmHg	33	30	35
SvO <sub>2</sub> mmHg	62%	56%	36%
PaO <sub>2</sub> mmHg	47	47	58
SaO <sub>2</sub> mmHg	83%	83%	89%



**FIG 3.** Algorithm management strategies include including PERT in the management of PE care.



approaches have generated interest due to the limitations of anticoagulation in intermediate and high-risk patients and the high risk of bleeding with systemic thrombolysis. Broadly, there are two strategies within the catheter-based therapies: CDT and catheter-based embolectomy. Multiple factors are weighed when deciding the appropriate treatment, including thrombus burden, location, patient hemodynamics, patient comorbidities, patient bleeding risk, institutional and operator experience, and device availability.<sup>12</sup> They operate by two primary mechanisms: direct mechanical action to break apart large emboli or percutaneous thrombectomy.<sup>11</sup>

The catheter-based therapy goals involve the following events: rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance (PVR); improving systemic perfusion; and helping RV recovery.<sup>14</sup>

The strategy of CDT is reasonably safe and highly effective for massive PE.<sup>11</sup> CDT fundamental principles are mechanical clot fragmentation, clot aspiration, and intra-clot thrombolytic injection.<sup>2,15</sup> These allow to make a channel through the obstruction and help expose a larger surface area of the thrombus to the effects of the local thrombolytic drug.<sup>11</sup> The overall procedural success rates (described as hemodynamic stabilization, correction of hypoxia, and survival to hospital discharge) of percutaneous catheter-based therapies reported in several studies have reached 87%.<sup>16</sup>

Retrospective comparative studies suggested that pharmacomechanical CDT offers comparable clot-removal efficacy to drug-only CDT but with significant (40%-50%) reductions in the needed thrombolytic drug dose, infusion time, and hospital resource use.<sup>14</sup>

According to the SEATTLE II study, lower-dose thrombolytics in CDT have been reported to produce minor bleeding than high-dose systemic thrombolytic treatment.<sup>17</sup> The main reasons for choosing CDT or intrapulmonary therapy rather than systemic thrombolytic treatment are: the thrombolytic drug can be in a higher concentration in the area most needed; since the dose of a thrombolytic agent is more restricted, there might be fewer side effects, and it could be used in subjects with contraindications to systemic therapy; there might be a faster dissolution of the clot because of the concentrated dose; and finally, the treatment can start almost immediately as the access is already obtained by the angiogram used for diagnosis.<sup>18</sup>

Re-administration of a thrombolytic agent is only recommended when patients are unresponsive to the initial thrombolysis. The echocardiogram shows signs of RV dysfunction persistence combined with poor clinical tolerance.<sup>19</sup> Failed thrombolysis is not rare; in a retrospective study

carried out in 2006 by Meneveau et al., it occurred in 8.2% of patients, and although the literature suggests the use of surgical procedures instead of repeating systemic thrombolysis, the authors opted to repeat the process in all 37 patients, but with a different thrombolytic agent. Streptokinase was used in those cases where alteplase was used as the first option, and alteplase was used when streptokinase was the first thrombolytic.<sup>19</sup>

In 2020, Kaese1 and Lebiedz retrospectively registered 12 consecutive patients admitted to the ICU with fulminant pulmonary embolism who did not respond to thrombolysis and were treated with extracorporeal life support (ECLS). Thrombolysis was achieved using either 8000 IU tenecteplase or 100mg of rtPA with prior application of 5000 IU heparin. They recorded the following outcomes: 6 of 12 patients (50%) died during treatment, and the rest were discharged from the hospital. Their results may indicate an improved survival rate in this subgroup of PE patients; however, further studies are required to confirm the usefulness of ECLS therapy in patients with severe PE even without definitive treatment such as thrombolysis.<sup>20</sup>

Kucher et al. investigated whether ultrasound-assisted catheter-directed thrombolysis (USAT) was superior to anticoagulation alone in reversing RV dilatation in intermediate-risk patients. They compared conventional heparin-based treatment and a catheter-based therapy merging ultrasound-based clot fragmentation with low-dose in situ thrombolysis in 59 patients with intermediate-risk PE in a randomized control trial in 2014. In that study, USAT was linked with a more significant reduction in the RV/LV diameter ratio at 24 hours, without an increased risk of bleeding.<sup>21</sup>

The OPTALYSE-PE trial (A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism) also showed a comparable reduction in RV/LV ratio in intermediate-risk PE patients that were randomized to 4 different infusion doses of ultrasound-facilitated CDT.<sup>22</sup>

In the clinical case described, it is essential to note that repeated CDT and the same thrombolytic agent were used. Initially, the patient had systemic thrombolysis contraindicated because she had multiple risk factors for bleeding. Hence, the hospital team decided to use thrombofragmentation with CDT as the treatment of choice. The results were unsatisfactory after the first procedure because the administration of vasopressors had to be continued. In the second CT angiography, performed 72 hours later, the saddle thrombus remained smaller, and the ratio between ventricles and suprahepatic reflux decreased significantly.

The limitations to emergency surgical thrombectomy in some tertiary-care hospitals can make clinicians decide to repeat thrombofragmentation with CDT in this patient.<sup>23</sup> In our example, the results were excellent in the second procedure because the thrombotic load decreased, and the saddle thrombus disappeared, which allowed the withdrawal of vasopressor and switching oxygen therapy from high-flow oxygen therapy ventilation to oxygen therapy with nasal tips and reservoir bag.

Before the hybrid treatment of thrombofragmentation and CDT, RHC showed tachycardia, a mean pulmonary artery pressure of 21 mmHg with wedged pressure of less than 15 mmHg; however, this patient did not meet the PH criteria because her RVP was reported as less than 3 UW.

The patient remained with regular HF. However, she had a gas exchange compromise, and the angiotomography revealed a loss of the relation between ventricles and liver reflux. The second RHC before repeat fragmentation and thrombolysis showed a decrease in heart rate, the mean pressure of the pulmonary artery by 18 mmHg, and the PVR, raised to 3 Woods units in a reduction in cardiac output, which explained the gas exchange. However, RV dilation and tricuspid insufficiency improved, pulmonary pressures were reported as standard and better gas exchange.

Clinical decision-making remains challenging for intermediate or high-risk PE patients with relative or absolute contraindication to thrombolytic therapy.<sup>24</sup> For patients with intermediate-risk PE, clinical endpoints in evaluations of interventions include mortality, rates of hemodynamic decompensation, and change in RV/LV ratio. The RV/LV ratio change in the first 48 hours after PE diagnosis has become a surrogate outcome since multiple observational studies have shown that RV/LV ratio > 0.9–1.0 is associated with higher 30-day mortality. While this has become the benchmark for primary outcomes in many PE-related studies, it is essential to remember that acute changes in RV/LV ratio are a surrogate endpoint and has not been proven to decrease mortality; thus, radiological improvement of RV/LV ratios should be interpreted with caution.<sup>25</sup> Furthermore, it remains unclear if a threshold of improvement in the RV/LV ratio needs to be achieved to impact outcomes. Keeping this context in mind, each catheter-directed therapy has promising data of improvements in RV/LV ratios.

After acute PE, approximately one-third of surviving patients develop chronic symptoms such as dyspnea, exercise intolerance, and impaired quality of life (QoL). “*Post-PE syndrome*” is a term that has been coined to describe the persistence of these symptoms for more than three months after acute PE despite therapeutic anticoagulation.<sup>26</sup> The syndrome

encompasses chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic disease (CTED), and dyspnea with functional limitations but without identifiable pulmonary vascular disease, sometimes called post-PE dyspnea.

CTEPH is characterized by pulmonary hypertension (PH) with radiographically evident pulmonary vascular disease; it occurs in 3%-4% of patients after the first episode of acute PE;<sup>27</sup> CTEPH can also be a sequel of severe post-covid-19 pneumonia.<sup>28</sup> It remains unclear whether intervention at the time of presentation for acute PE changes the incidence of these diseases in the intermediate- and long-term timeframes as the MOP-PET trial suggests improved RV systolic pressures at 28 months after thrombolysis. Still, the long-term PEITHO data shows no reduction in CTEPH, post-PE dyspnea, or RV dysfunction following systemic thrombolytic therapy at presentation.<sup>29,30</sup>

The ELOPE study was a prospective trial aimed at quantifying and predicting long-term functional and exercise limitations after the first acute PE. Almost half of the patients (46.5%) had exercise limitations on cardiopulmonary exercise testing at one year. This limitation was not correlated with baseline or residual clot burden. Patients with exercise limitations were also found to have significantly worse QoL and dyspnea scores and reduced 6-minute walk distance (6MWD).<sup>31</sup> A systematic review of 26 studies evaluating long-term PE outcomes with a mean follow-up of 18 months found a pooled prevalence of RV dysfunction of 18.1%, functional impairment with NYHA II-IV symptoms in 33.2%, and a mean 6MWD of 415 m, equivalent to the 4th percentile when compared to age- and sex-matched reference standards. Patients also reported reduced quality of life on the Short Form-36 Physical Component Score and Pulmonary Embolism Quality of Life Questionnaire. Thus, the long-term response to PE is clinically heterogeneous, ranging from reduced QoL and exercise intolerance to pulmonary hypertension requiring surgical intervention. More studies are needed to determine whether specific clinical factors at the diagnosis are correlated with long-term functional impairment. Likewise, future studies may aid in deciding if upfront catheter-directed therapies at the time of initial clinical presentation are associated with better or worse long-term outcomes when compared to systemic thrombolytics or anticoagulation alone.<sup>32</sup>

Complications related to PE catheter-based thrombectomy are hematoma at the puncture site, perforation or dissection of cardiovascular structures, pericardial tamponade, pulmonary hemorrhage, and cardiac arrest during pigtail catheter rotation.<sup>33</sup>

To our knowledge, there are scarce reports of failed catheter-guided pharmacomechanical thrombolysis in patients with PE secondary to COVID-19. In our experience, the procedure can be repeated with the same drug and alteplase (15 mg dose) with favorable results. There are reports of clinical cases with systemic thrombolysis and ultrasound-enhanced CDT with encouraging results, but none with the characteristics of our reported patient.<sup>9,34</sup>

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