SHORT REPORT

Using lysis therapy to treat five critically ill COVID-19 patients who show echocardiographic criteria of right ventricular strain

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1 INTRODUCTION

The case-fatality rate of COVID-19 patients characterized clinically as mild is 0%, while it reaches 50% in those patients who are clinically characterized as critical [1,2]. These numbers indicate a critical point in the pathogenesis of COVID-19 against which the current therapeutic approach proves to be ineffective. Over the past several months, our understanding of the disease has been changed by multiple landmark achievements that highlight the role of COVID-induced hypercoagulability in patients’ outcomes [3–6]. Coagulopathy associated with COVID-19 may be driven by the production of prothrombotic autoantibodies [7] in addition to microthrombogenic responses that occur when endothelial insult takes place [8]. This reaction is aggravated causing enhanced platelet activation [9], and the microthrombotic pathway is maintained by the activation of both the coagulation factors and the endothelium [6]. Therefore, in situ immune-thrombosis plays a significant role as a primary mechanism explaining the micro- and macrothrombotic manifestations of the disease [10]. Additionally, the COVID-19 patients have additional risk factors for increased thrombosis such as hypoxia, and immobility in prone positioning [11–13].

The purpose of this study was to evaluate the clinical effects of using lysis therapy, to unplug the pulmonary vasculature, administered to mechanically ventilated, hemodynamically unstable COVID-19 patients depending on the noninvasive echocardiographic assessment of the right ventricle-to-pulmonary vascular coupling.

2 METHODS IN BRIEF

Laboratory-confirmed COVID-19 patients who had any of the following were considered in a critical condition: (i) shock, identified by implementation of vasopressor therapy and elevated lactate levels (> 2 mmol/L) despite adequate fluid resuscitation, (ii) respiratory failure requiring mechanical ventilation, or (iii) failure of other organs necessitating admission to the intensive care unit.
TABLE 1 Characteristics of COVID-19 patients who received lysis therapy

| Patients | 1 | 2 | 3 | 4 | 5 |
|----------|---|---|---|---|---|
| Age | 49 | 40 | 53 | 83 | 70 |
| Sex | M | M | M | F | M |
| Weight | 81 | 64 | 87 | 78 | 73 |
| Smoking | No | No | No | No | No |
| Comorbid diseases | None | None | DM | DM | IHD |
| Disease presentation | ARDS | ARDS | ARDS | ARDS | ARDS |
| Clinical classification | Critical | Critical | Critical | Critical | Critical |
| Treatment | | | | | |
| Antivirals | None | None | None | None | None |
| Antibiotics | Yes | Yes | Yes | Yes | Yes |
| Steroids | Dexamethasone | Methylprednisolone | Dexamethasone | Dexamethasone | Dexamethasone |
| Tocilizumab* | Yes | Yes | Yes | Yes | Yes |
| Anticoagulant** | Yes | Yes | Yes | Yes | Yes |
| Status*** | Extubated, transferred to ward | Extubated, transferred to ward | Extubated, transferred to ward | Extubated, transferred to ward | Extubated, transferred to ward |
| Total length of hospital stay, d | 40 | 62 | 25 | 50 | 58 |

M, male; F, female; DM, diabetes mellitus; HTN, hypertension; ARDS, acute respiratory distress syndrome; MODS, multiorgan dysfunction syndrome; MOF, multiorgan failure.
*Tocilizumab was received as a single IV dose of 8 mg/kg (max 800 mg) within 3 days of hospitalization.
**Anticoagulation therapy was administered in a prophylactic dose.
***All patients continued to receive oxygen therapy at the ward, and Patient 5 was discharged from the hospital on home oxygen.

2.1 | Patients

COVID-19 patients were eligible to receive lysis therapy if they fulfilled the following criteria: (i) had a rapidly progressive severe pneumonia, (ii) were currently supported by mechanical ventilation, (iii) \( \text{PaO}_2/\text{FiO}_2 \) ratio < 300 (wherein \( \text{PaO}_2 \) measured in mmHg and \( \text{FiO}_2 \) is the fraction of inspired oxygen expressed as a decimal), and (iv) the echocardiographic examination showed one or more criterion of right ventricular strain.

2.2 | Lysis therapy

A low-dose protocol of recombinant tissue-type plasminogen activator [14] was implemented, wherein Alteplase (Activase®, Genentech) was intravenously infused over 15 min with a dose of 0.6 mg/kg (the maximum dose is 50 mg) [15].

3 | RESULTS

Five patients (age range, 40–83 years; 1 woman) were treated with lysis therapy. None of whom was a smoker, and three patients had preexisting medical conditions in the form of diabetes mellitus, hypertension, and ischemic cardiomyopathy. All five patients had received tocilizumab (within 3 days of hospitalization) and low-dose steroids without antiviral treatments (Table 1).

All five patients were mechanically ventilated at the time of lysis therapy administration, all of them were weaned from mechanical ventilation and extubated postlysis (Table 1). Patient 5 was receiving ECMO at the time of lysis therapy administration but did not require ECMO within 6 days postlysis. All patients were transferred to the ward and eventually discharged from the hospital; length of stay was 40, 62, 25, 50, and 58 days, respectively (Patient 5 discharged on home oxygen due to pulmonary fibrosis).

3.1 | Change in hemodynamics

At the time of lysis therapy administration, all patients were hemodynamically unstable on circulatory support in the form of norepinephrine plus or minus vasopressin. The resultant mean arterial blood pressure (MAP) ranged from 60 to 70 mmHg. Upon administration of lysis therapy, all patients were gradually weaned from the circulatory support, and the MAP gradually increased over 80 mmHg within a time period that ranged from 7 to 12 days (Table 2, Figure 1A).
FIGURE 1 Temporal changes of mean arterial pressure (MAP), PAO2/FIO2 ratio, SOFA score, and body temperature in patients receiving lysis therapy. Wherein (A) change in mean arterial blood pressure (lowest value during the day was recorded) from day 0 to day 12 postlysis. (B) Change in PAO2/FIO2 ratio of the treated patients from day 0 to day 12 after treatment. (C) Represent change in Sequential Organ Failure Assessment (SOFA) score of the patients during the same duration (range 0–24, with higher scores indicating more severe illness). (D) Change in body temperature of the 5 patients prior to and postlysis.

3.2 | Change in PaO2/FiO2 values

All five patients were receiving mechanical ventilation at the time of lysis therapy administration, and all patients were extubated after receiving the lysis therapy protocol within a time period of 2 weeks. Patient 5 was receiving ECMO at the time of lysis therapy initiation but did not require ECMO within 6 days postlysis. Prior to receiving the lysis therapy, the PaO2/FiO2 values of all patients were below 300 and ranged from 107 to 211. Upon administration of the lysis therapy, the PaO2/FiO2 values of all patients gradually increased over 350 within a time period that ranged from 7 to 12 days (Table 2, Figure 1B).

3.3 | Change in SOFA score

The SOFA score ranged from +6 to +10 prior to receiving lysis therapy and decreased to a range of +1 to +5 at the twelfth day (the seventh day for Patient 1) following administration of lysis therapy (Table 2 and Figure 1C). The SOFA score is calculated using six systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system, and kidney; and the worst value on each day was recorded.

3.4 | Change in laboratory markers and body temperature

All five patients had high-sensitivity cardiac troponin levels that ranged from 0.35 to 3.3 ng/L at the time of lysis therapy administration. The values of D-dimer were significantly high in all five patients prior to lysis therapy (a value less than 250 ng/ml is considered normal); these values markedly decreased postlysis within 7 to 12 days, except for Patient 4 who showed a mild variation. The serum levels of inflammatory markers such as serum ferritin, lactate dehydrogenase, and procalcitonin eventually decreased, but not normalized, within 7 to 12 days postlysis, except for Patient 4 who showed mild variations (Table 2). Body temperature ranged from 37.2 to 39.0°C prior to lysis therapy and declined to the normal ranges on the third-day postlysis, except for Patient 2 which regained fever by day 2 postlysis which then eventually normalized by the eleventh-day postlysis (Table 2 and Figure 1D).
### Clinical indices, circulatory support, and laboratory results of COVID-19 patients before and after lysis therapy

#### TABLE 2

| Patients | 1 | 2 | 3 | 4 | 5 |
|----------|---|---|---|---|---|
| **Clinical indices** |   |   |   |   |   |
| MAP |   |   |   |   |   |
| Day 0 before lysis | 63 | 60 | 70 | 61 | 60 |
| Day 1 postlysis | 90 | 95 | 83 | 79 | 67 |
| Day 3 postlysis | 93 | 94 | 74 | 78 | 96 |
| Day 7 postlysis | 84 | 78 | 86 | 70 | 83 |
| Day 12 postlysis | 93 | 79 | 81 | 112 |   |
| P/F ratio |   |   |   |   |   |
| Day 0 before lysis | 182 | 211 | 107 | 179 | 173 |
| Day 1 postlysis | 363 | 325 | 162 | 332 | 186 |
| Day 3 postlysis | 376 | 282 | 262 | 353 | 238 |
| Day 7 postlysis | 437 | 389 | 370 | 326 |   |
| SOFA score |   |   |   |   |   |
| Day 0 before lysis | +6 | +10 | +7 | +9 | +7 |
| Day 1 postlysis | +4 | +5 | +8 | +9 | +6 |
| Day 3 postlysis | +4 | +5 | +6 | +8 | +4 |
| Day 7 postlysis | +2 | +3 | +7 | +7 | +5 |
| Day 12 postlysis | +1 | +2 | +5 | +4 |   |
| Body temperature (°C) |   |   |   |   |   |
| Day 0 before lysis | 37.2 | 38.8 | 39 | 37 | 38 |
| Day 1 postlysis | 37.6 | 37.5 | 38.7 | 36.5 | 37.1 |
| Day 3 postlysis | 37.1 | 38.6 | 36.8 | 37.3 | 37.5 |
| Day 7 postlysis | 36.7 | 38 | 36.9 | 36.8 | 36.9 |
| Day 12 postlysis | 37.4 | 37.2 | 36.9 | 37 |   |
| Circulatory support |   |   |   |   |   |
| Norepinephrine (mcg/kg/h) |   |   |   |   |   |
| Day 0 before lysis | 0.3 | 0.18 | 0.8 | 0.2 | 0.5 |
| Day 1 postlysis | 0.2 | 0.1 | 0.3 | 0.4 | 0.15 |
| Day 3 postlysis | 0.08 | 0.02 | 0.3 | 0.05 | 0.05 |
| Day 7 postlysis | 0 | 0.02 | 0.01 | 0 | 0.04 |
| Day 12 postlysis | 0 | 0 | 0 | 0 | 0 |
| Dobutamine (mcg/kg/min) |   |   |   |   |   |
| Day 0 before lysis | – | – | – | – | 3 |
| Day 1 postlysis | – | – | – | – | 3 |
| Day 3 postlysis | – | – | – | – | 0 |
| Day 7 postlysis | – | – | – | – | 0 |
| Day 12 postlysis | – | – | – | – | 0 |
| Vasopressin (U/min) |   |   |   |   |   |
| Day 0 before lysis | 0.04 | 0.04 | 0.04 | 0.04 | – |
| Day 1 postlysis | 0.04 | 0.04 | 0.04 | 0.04 | – |
| Day 3 postlysis | 0.04 | 0 | 0.04 | 0 | – |

#### TABLE 2 (Continued)

| Patients | 1 | 2 | 3 | 4 | 5 |
|----------|---|---|---|---|---|
| hs-Cardiac troponin (ng/L) |   |   |   |   |   |
| Day 0 before lysis | 0.54 | 0.35 | 1.63 | 0.99 | 3.3 |
| D-Dimer (ng/ml) |   |   |   |   |   |
| Day 0 before lysis | 3788 | 5156 | 7172 | 1212 | 4003 |
| Day 1 postlysis | 1484 | 8291 | 6324 | 1630 | 6242 |
| Day 3 postlysis | 972 | 4738 | 2000 | 1090 | 5520 |
| Day 7 postlysis | 613 | 1331 | 1165 | 890 | 3335 |
| Day 12 postlysis | 864 | 682 | 1036 | 1100 |   |
| Serum ferritin (ng/ml) |   |   |   |   |   |
| Day 0 before lysis | 619 | 1006 | 1265 | 761 | 1030 |
| Day 1 postlysis | 853 | 1186 | 843 | 1235 | 4227 |
| Day 3 postlysis | 576 | 791 | 820 | 1550 | 2246 |
| Day 7 postlysis | 382 | 476 | 360 | 1443 | 551 |
| Day 12 postlysis | 311 | 269 | 996 | 328 | 493 |
| Lactate dehydrogenase (U/L) |   |   |   |   |   |
| Day 0 before lysis | 995 | 1167 | 795 | 615 | 415 |
| Day 1 postlysis | 676 | 1003 | 798 | 557 | 666 |
| Day 3 postlysis | 597 | 830 | 571 | 690 | 679 |
| Day 7 postlysis | 626 | 485 | 496 | 583 | 891 |
| Day 12 postlysis | 302 | 342 | 601 | 324 | 294 |
| Procalcitonin (ng/ml) |   |   |   |   |   |
| Day 0 before lysis | 2.98 | 1.6 | 0.6 | 4.3 | 3.5 |
| Day 1 postlysis | 3.19 | 1.1 | 3.18 | 4.5 | 4.6 |
| Day 3 postlysis | 2.61 | 1.8 | 2.16 | 4.1 | 4.0 |
| Day 7 postlysis | 1.32 | 1.2 | 0.7 | 4.8 | 2.21 |
| Day 12 postlysis | 0.6 | 0.2 | 2.4 | 1.0 |   |

MAP, mean arterial pressure; P/F ratio, PaO₂/FiO₂ ratio; SOFA score, sequential organ failure assessment score.

#### 3.5 Change in chest imaging

Chest x-rays of these five patients demonstrated severe pneumonia prior to lysis therapy and showed gradual resolution of pulmonary lesions after administration of lysis therapy within a time period of 2 weeks (Supplementary figures).

#### 3.6 Safety and adverse effects

The implemented low-dose protocol of alteplase seems to be effective and well tolerated. All five patients did not suffer significant side effects or bleeding.
In this report, thrombolytic therapy was used to treat five hemodynamically unstable, mechanically ventilated COVID-19 patients who showed echocardiographic signs of right ventricular strain. This therapeutic intervention showed a durable result in the form of restoring hemodynamic stability and increasing the ventilation capacity of the treated patients. The clinical conditions of these patients improved, as indicated by restoring circulatory rigor, improved PAO2/FIO2, decreased SOFA score, body temperature reduction, and chest imaging. All treated patients, who had been receiving mechanical ventilation and ECMO, were no longer in need of respiratory or circulatory support, and then transferred to the ward within days of receiving the lysis therapy.

The rationale for use of thrombolytic therapy in critical COVID-19 patients is straightforward. Patients diagnosed with COVID-19 infection are at increased risk for developing thrombotic vascular occlusions and the histopathological examination often reveals fibrin-based obstructions in the lungs’ small vasculature of patients who succumb to severe forms of the disease [13, 16]. COVID-19 is a newly emerged viral infection and studies that implemented lysis therapy in the treatment of the disease are scarce. Multiple case studies, which recruited hospitalized patients with COVID-19 infection, reported an improvement of patients’ oxygenation after using thrombolytic therapy [17, 18]. A retrospective cohort study of 12 decompensated patients with severe COVID-19 treated using alteplase concluded that the mortality rate decreased from 88% to 41.6%, which represents a significant improvement in patients requiring advanced respiratory support [19]. These studies have methodological limitations including unclear patient selection protocols, lack of reporting for patient baseline characteristics, inadequate duration of follow-up, and partial reporting of outcomes. Our study improves the methodological limitations in the previous literature by giving clear indications and inclusion criteria for patients eligible to receive lysis therapy, reports patients’ baseline characteristics prior to lysis therapy administration, defines the dosing and therapeutic protocol, and delineates detailed clinical outcome postlysis therapy with adequate follow-up duration.

All enrolled patients did not receive antiviral agents and the SARS-CoV-2 virus was still detectable in all 5 patients at the time of extubation. Therefore, the study results highlight the possibility that lysis therapy has contributed to the observed clinical improvement.

4.1 Recommendations

The main recommendations of this report are the following: (i) bedside echocardiography can be a beneficial tool in the urgent assessment of the right ventricle-to-pulmonary vascular coupling in mechanically ventilated COVID-19 patients and (ii) a low-dose protocol of lysis therapy may be beneficial in mechanically ventilated, hemodynamically unstable COVID-19 patients who show echocardiographic criteria of right ventricular strain. The decision of implementing lysis therapy should weigh the current mortality rate of this patient subset in the absence of a specific antiviral treatment, besides the proposed benefits of clinical improvement against the possible bleeding complication of such intervention.

4.2 Limitations

This study has following limitations: (i) a case series included no controls and (ii) alteplase was administered immediately after fulfilling the patient inclusion criteria; whether a different timing of administration would have been associated with different outcomes cannot be determined.

5 Conclusion

In this case-series of five mechanically ventilated, hemodynamically unstable COVID-19 patients who show echocardiographic criteria of right ventricular strain, administration of low-dose protocol of alteplase as a lysis therapy was followed by improvement of the patients’ clinical parameters. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require further evaluation in clinical trials.

CONFLICT OF INTEREST

The authors declare that the article was prepared in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

AM, RT, and NJ performed the therapeutic intervention. EA developed the theory, designed the study, and wrote the manuscript with support from AM and RT. HF revised the manuscript and supervised the study. All authors contributed equally to this work, and all authors have read and approved the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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