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COVID-19 Infection and High Intracoronary Thrombus Burden

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ABSTRACT

Coronavirus 2019 (COVID-19) is an acute respiratory disease that has rapidly spread around the world and been declared a global pandemic by the World Health Organization. Emerging evidence demonstrates a strong association with a pro-thrombotic state and we present the first patient admitted with COVID-19 and an inferior ST-segment elevation myocardial infarction (STEMI) with evidence of high intracoronary thrombus burden. We review the mechanism of the high thrombus burden, which may be driven by the significant cytokine storm, endothelial dysfunction, increase risk of coronary plaque rupture and hypercoagulability.

Contents

1. Introduction

Coronavirus 2019 (COVID-19) is an acute disease that primarily targets the respiratory system [1]. However, mounting evidence suggests that cardiac involvement is common, particularly in hospitalized patients, with a substantial increase in morbidity and mortality [1,2]. A meta-analysis of six studies from China, including 1527 patients with COVID-19 found an overall mortality rate of 2.3% with a higher risk in patients with hypertension (6%), diabetes (7.3%), and cardiovascular disease (10.5%) [2]. Emerging research has also demonstrated a pro-thrombotic state with various presentations including acute cerebral infarctions [3], venous sinus thrombosis [4], pulmonary embolism [5] and deep vein thrombosis [6]. We present the first patient admitted with inferior ST-segment elevation myocardial infarction (STEMI) with evidence of high intracoronary thrombus burden and provide a review of potential underlying mechanisms.

A 43 year old Caucasian male attended the Emergency Department with a one week history of fever, dry cough and breathlessness. He was an ex-smoker with a ten pack year history and well controlled asthma. On examination he had widespread crepitations bilaterally with a respiratory rate of 40/min and oxygen saturations of 70% on room air and 97% on 15 L/min of oxygen through a non-rebreather mask. He was febrile at 38.1 degrees Celsius. Blood pressure and heart rate were 146/81 mmHg and 153 beats per minute respectively. His arterial blood gas on room air demonstrated severe type 1 respiratory failure (pH 7.46 [7.35–7.45], pO2 5.9 kPa [10–13 kPa], pCO2 3.53 kPa [4–6 kPa], bicarbonate 22 mmol/L [22–26 mmol/L], base excess −5 mmol/L [−2 to +2], lactate 5.2 mmol/L [0–2 mmol/L]) and routine blood tests demonstrated leukocytosis of 17.22×10^9/L [$3.5–11 \times 10^9$/L] with lymphopenia of 0.82×10^9/L [$1–4 \times 10^9$/L] and neutrophilia of 12.7×10^9/L [$1.7–7.5 \times 10^9$/L]; elevated serum concentrations of ferritin and C-reactive protein (respectively 3, 486 micrograms/L [30–340 micrograms/L], and 289 mg/L [0–5 mg/L]); and deranged liver function tests with an alanine aminotransferase of 109 unit/L [10–50 unit/L] and alkaline phosphatase of 132 unit/L [0–129 unit/L]. Blood test results were not consistent with disseminated intravascular coagulation (platelets 321×10^9/L [$150–450 \times 10^9$/L], fibrinogen 6.8 g/L [1.5–4.5 g/L], d-dimer 6828 nanograms/mL [0–400 nanograms/mL]). Chest radiograph demonstrated widespread bilateral consolidation with patchy peripheral

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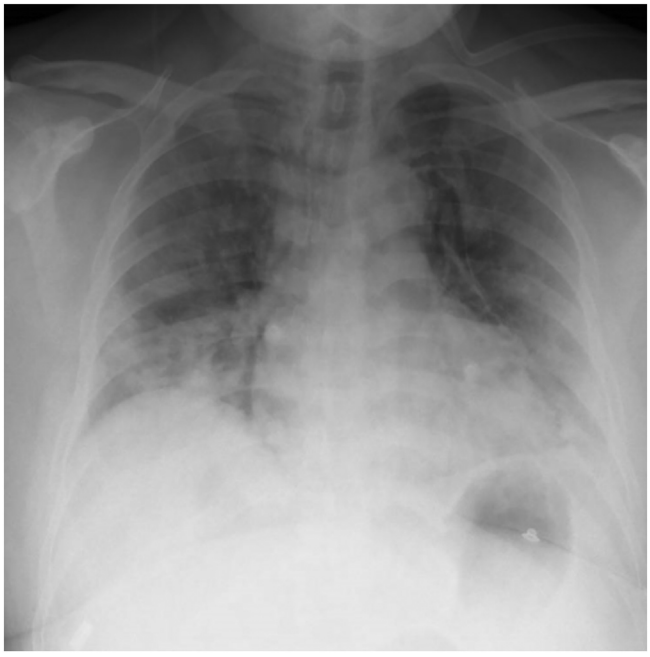

Fig. 1. Chest radiograph with typical coronavirus 2019 (COVID-19) changes.

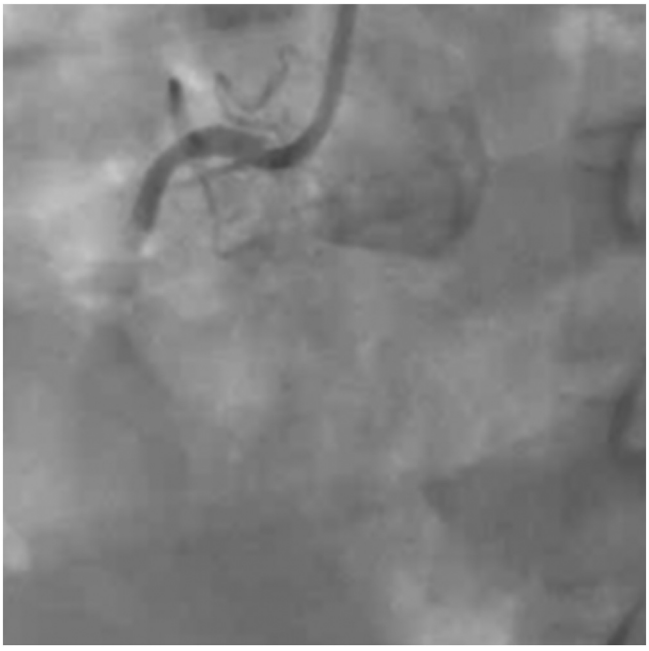

Fig. 3. Coronary angiogram: proximal right coronary artery thrombotic occlusion.

ground glass changes, highly suggestive of COVID-19 (Fig. 1). His initial 12 lead electrocardiogram (EKG) was reported as showing no ischemic changes.

The patient's condition rapidly deteriorated and his oxygen saturation diminished to 88% on 15 L/min oxygen through a non-rebreather mask. He was therefore commenced on continuous positive airway pressure with a fraction of inspired oxygen (FiO2) of 100% and positive end-expiratory pressure of 10cmH_2O. An hour later he became more fatigued with increased respiratory effort and was intubated and ventilated. Four minutes later he sustained a cardiac arrest with pulseless electrical activity (PEA). Following 4 cycles of cardiopulmonary resuscitation (CPR) and intravenous adrenaline, cardiac output was re-established, and his subsequent 12 lead EKG demonstrated inferior STEMI (Fig. 2).

Further to discussion with the cardiology team, he was transferred to the cardiac catheterization laboratory for consideration of emergency coronary angioplasty. Coronary angiogram showed mild atheroma in the left coronary system and a thrombotic occlusion of the proximal segment of a dominant right coronary artery (RCA) (Fig. 3). A whisper extra support guidewire (Abbott Vascular, California) was advanced to the distal RCA and an Export Advance™ aspiration catheter (Medtronic, California) was subsequently used. A high burden of mixed red and white thrombi was aspirated, however Thrombolysis in Myocardial Infarction (TIMI) flow remained 0. Intracoronary glycoprotein IIb/IIIa (gpIIb/IIIa) was delivered via the aspiration catheter. Serial balloon inflations with 2.5 mm and 3.0 mm semi-compliant balloons improved flow to TIMI I up to the to mid-vessel with evidence of significant residual thrombus (Fig. 4). Multiple further aspirations were performed albeit with no change in flow (Fig. 5). Intracoronary thrombolytic agent was then administered through a FineCross® MG microcatheter (Terumo, U.S.A.) with again no improvement in TIMI flow (Fig. 6).

At this point the patient developed complete heart block with a rate of 30 beats per minute and therefore a temporary pacing wire was inserted. The blood pressure was 80/60 mmHg which was being augmented with metaraminol boluses and following discussion within the team, it was decided to stop the procedure at this stage and continue with systemic gpIIb/IIIa infusion. Whilst still in the catheterization

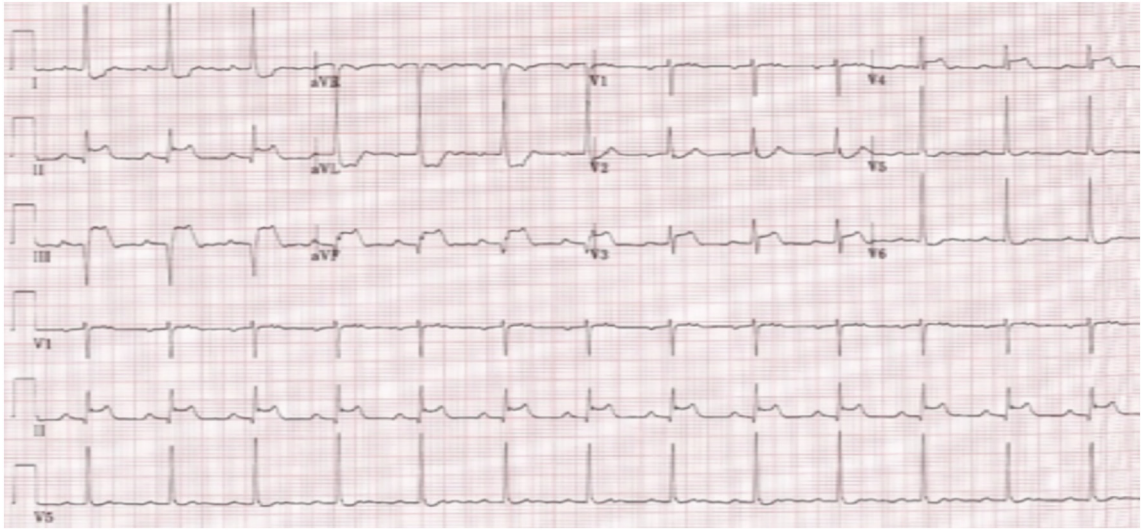

Fig. 2. 12 lead electrocardiogram: inferior ST-segment elevation.

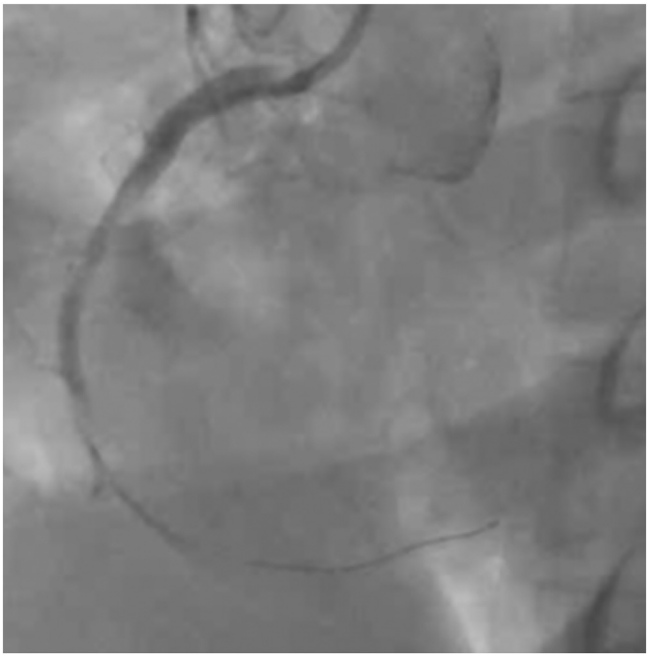

Fig. 4. Coronary angiogram following catheter aspiration and balloon inflations.

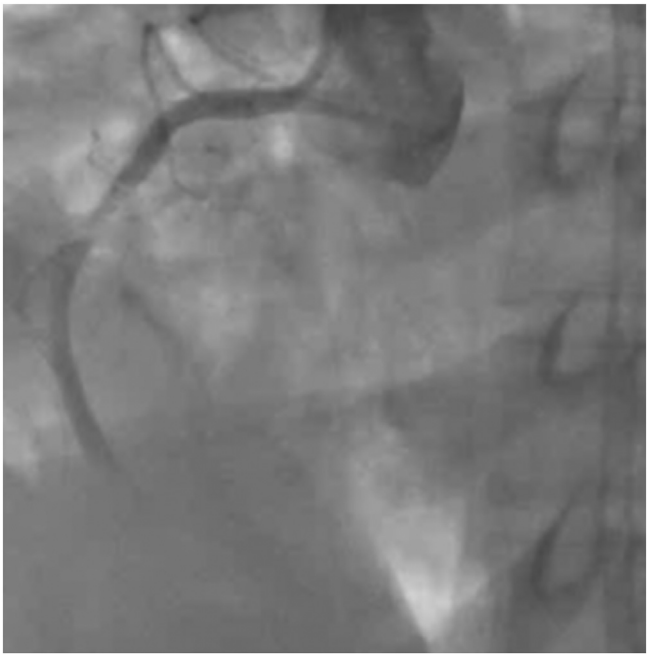

Fig. 6. Coronary angiogram: post intracoronary thrombolysis.

laboratory the patient became more hypoxic and sustained a second PEA arrest. A focused transthoracic echocardiogram showed no evidence of pericardial effusion. Several cycles of CPR were attempted to no avail and unfortunately the patient passed away. Subsequently, it was confirmed that the patient's nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse-transcriptase–polymerase-chain-reaction assay.

2. Discussion

The outbreak of COVID-19 occurred in December 2019, in Wuhan, Hubei, China and it has spread rapidly around the world and been declared a global pandemic by the World Health Organization [1]. Severe COVID-19 has been defined as respiratory distress with a respiratory rate >30 per minute, oxygen saturations ≤93% at rest or a PaO2/FiO2 ≤ 300 mmHg [1]. However, research has also demonstrated an associated pro-thrombotic state resulting in an increased risk of death [7].

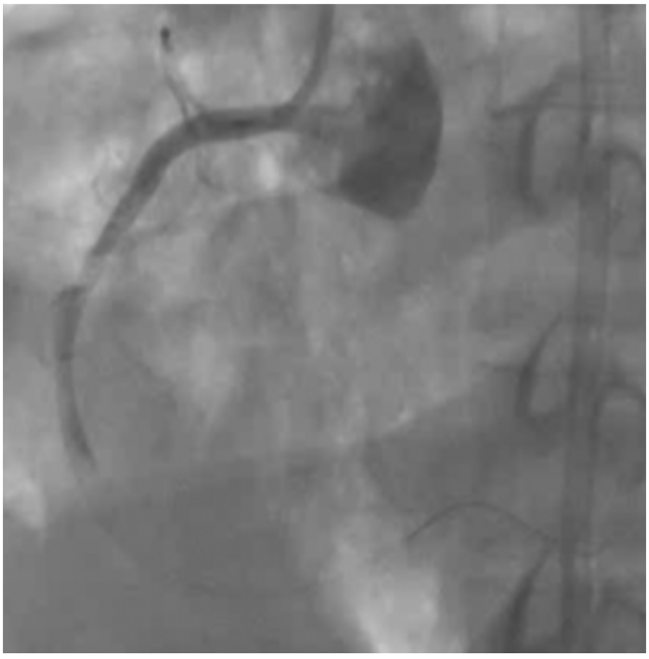

Fig. 5. Coronary angiogram following multiple runs with aspiration catheter.

There are emerging theories regarding the mechanism of increased thrombus burden seen in COVID-19, central to which seems to be a significant pro-inflammatory state [8]. This stems from the excess production of inflammatory cytokines tumor necrosis factor, interleukin (IL)-6 and IL-1β resulting in a cytokine storm which ultimately leads to activation of coagulation pathways, vascular hyperpermeability, multi-organ failure and an increased risk of death [9,10]. One of the central components in this is thrombin, which usually promotes clot formation by activating platelets and converting fibrinogen to fibrin [11]. Thrombin generation is regulated by feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system [11]. During inflammation these mechanisms can become dysfunctional, with reduced anticoagulant concentrations due to diminished production and increased demand. This predisposes to the development of thrombosis, disseminated intravascular coagulation, and multiorgan failure [8,12].

Furthermore, the circulating cytokines may also lead to atherosclerotic plaque instability and rupture [13]. Systemic inflammation as well as increased shear stress due to increased coronary blood flow can precipitate plaque rupture resulting in acute myocardial infarction [13]. In related viral studies, the influenza virus induced acute arterial wall inflammation that was associated with plaque destabilization [14]. Limited evidence also shows that the SARS coronavirus may also be associated with an increased risk of plaque instability [15]. Plaque rupture results in an increase in tissue factor (TF), collagen and platelet activation causing increased fibrin production and a higher thrombus burden [16].

Complement is a key component of the innate immune response to viruses and initiates several pro-inflammatory responses. Pathogenic activation of the alternative and lectin pathways has been documented in patients with COVID-19 disease [17]. This results in membrane attack complex mediated microvascular endothelial cell injury and activation of the clotting pathway leading to fibrin deposition and an increased thrombus burden [18].

The SARS-CoV-2 virus uses angiotensin converting enzyme 2 (ACE-2) receptors as an entry point to the cell. ACE-2 receptors are not only expressed on pneumocytes but are also expressed on endothelial cells and therefore SARS-CoV-2 can also induce endothelial cell activation and dysfunction [8]. The endothelium typically regulates the interplay of the coagulation system with the surrounding cells and tissues and when activated the cells initiate clotting and concomitantly begin recruiting platelets to the site of injury as a support surface for the formation of pro-coagulant complexes and platelet aggregation [19]. Indeed, endothelial dysfunction has previously been associated with a high coronary thrombus burden [20]. Intact endothelium typically prevents the formation of thrombi, but endothelial dysfunction or injury exposes the intima which interacts with and activates platelets and induces early pathological processes such as inflammation and thrombosis [20]. The degree of endothelial injury has been shown to correlate positively with thrombus burden [21].

Anti-phospholipid antibodies have also been detected in patients with COVID-19 [22]. The mechanism by which these antibodies create the conditions for thrombosis is not fully understood but is thought to depend upon two hits. The first is antiphospholipid antibodies binding to endothelial cells inducing a pro-coagulant and pro-inflammatory phenotype and promoting platelet aggregation. A second hit such as that caused by infection, results in complement activation and this is thought to cause thrombus formation [23]. Therefore, the conditions seen in COVID-19 would be ideal for thrombus formation in the presence of antiphospholipid antibodies.

Pathology studies have demonstrated frequent microvascular thrombi in patients with COVID-19 [24–26]. In seven patients, all autopsies revealed platelet-rich thrombi in the pulmonary, hepatic, renal and cardiac microvasculature [26]. Indeed, patients with COVID-19 have been found to have a three to six-fold increased risk of thrombosis compared to patients without COVID-19 [27] and these findings have led to recommendations of thromboprophylaxis in all COVID-19 patients [27,28]. Tang et al. [29] reported that patients with sepsis-induced coagulopathy had a lower mortality if they received heparin for seven or more days compared to those who had heparin therapy for <7 days (40% vs. 64.2%, respectively $p = 0.029$). In patients who had a d-dimer of six times or greater than the upper limit, those receiving heparin for seven days or more had a reduced risk of mortality compared to those who had heparin for less than seven days (32.8% vs 52.4% respectively, $p = 0.017$) [29].

In a cohort of 2773 COVID-19 patients, including 28% who received systemic treatment dose anticoagulant therapy [30], Paranjpee et al. found that in-hospital mortality was lower in patients receiving anticoagulation (22.5% mortality with a median survival of 21 days) compared to those who did not receive anticoagulation (22.8% mortality with a median survival of 14 days) [30]. Similarly, in patients requiring mechanical ventilation ($n = 395$), mortality was lower if they received anticoagulation (29.1% mortality with a median survival of 21 days) compared to no anticoagulation (62.7% mortality with a median survival of 9 days) [30]. Longer duration of anticoagulation therapy was also associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% CI 0.82–0.89; $p < 0.001$) [30].

Interestingly, bleeding risk in those receiving anticoagulation was no different to those not on anticoagulation (3% vs 1.9%, respectively, $p = 0.2$) [30]. However, there was an observed increased risk of bleeding events amongst patients requiring mechanical ventilation compared to those not ventilated (7.5% vs 1.35%) [30]. It should be noted that direct oral anticoagulants have been associated with an increased risk of major bleeding compared to low molecular weight heparin (LMWH) (relative risk 1.70; 95% CI, 1.02–2.82) and therefore LMWH should be prescribed in inpatients with COVID-19 [31]. Thrombosis guidelines are under continuous review with current recommendations supporting the routine prescription of thromboprophylaxis for all patients, unless contraindicated [27,28].

To the best of our knowledge this is the first case that reports an association between increased coronary thrombus and COVID-19. In our case, despite multiple runs with an aspiration catheter and aggressive intracoronary and systemic pharmacotherapy we were unable to reduce the clot burden and re-establish coronary flow reflecting the challenge in this patient group. High thrombus burden in myocardial

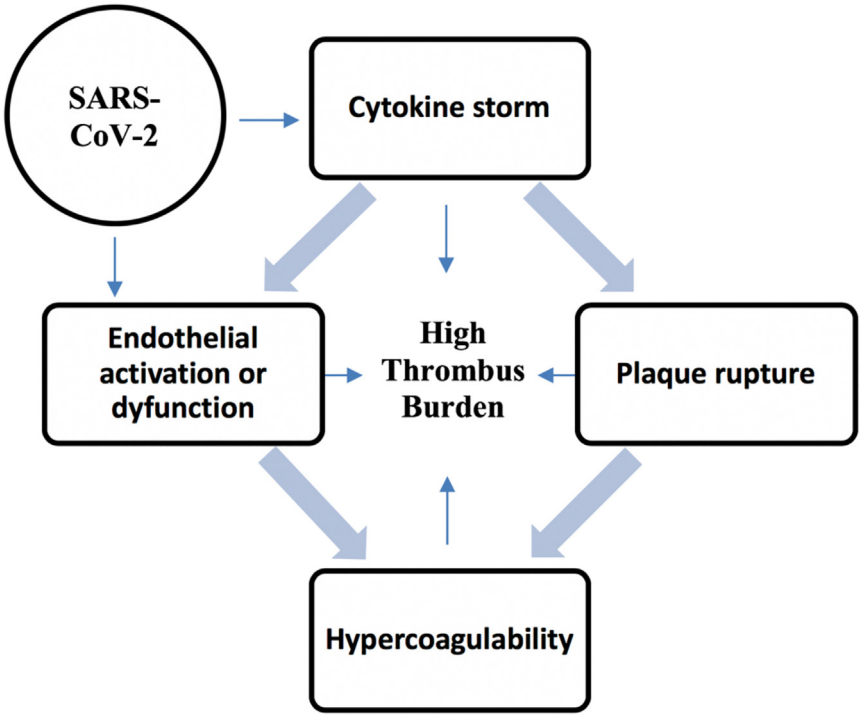

Fig. 7. Possible mechanism of high intracoronary thrombus burden in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

infarction is a real challenge and has an increased risk of no reflow, slow reflow, and distal embolization [16]. Furthermore, it may also result in a larger area of myocardial damage, cardiac rupture, malignant arrhythmias, and heart failure due to insufficient pericardial and myocardial perfusion [16].

Another potential treatment option in this case may have been intravenous cangrelor, a direct P2Y12 receptor antagonist which can achieve maximal platelet inhibition within 5 min and demonstrates continuous efficacy throughout the infusion [32]. Loading with oral ticagrelor offers maximal platelet inhibition within 2–4 h and whilst crushing tablets reduces this by around 1 h [32], this does not lead to immediate platelet inhibition [33]. Given the hemodynamic instability due to cardiogenic shock seen in this case, gastrointestinal absorption and subsequent antiplatelet effect of ticagrelor via the nasogastric tube may have been reduced [34,35]. Therefore, the intravenous administration of cangrelor may have been beneficial in our case. In a pooled analysis of the CHAMPION trials [36], cangrelor reduced the rate of stent thrombosis by 41% compared to clopidogrel or placebo (0.5 vs 0.8%, $p = 0.0008$) with no difference in primary safety outcome [36,37]. Furthermore, the early use of cangrelor may reduce the need for glpIIb/IIIa agents [37].

Unfortunately, due to the rapid nature of the patient's deterioration and respiratory arrest we were unable to consider extracorporeal membrane oxygenation (ECMO), with the nearest service located around 30 min away from our centre. Preliminary data from China [38,39] demonstrated that ECMO did not confer a significant survival benefit in patients with COVID-19 and adult respiratory distress syndrome [38,39]. However, more recent retrospective data from the United States demonstrated that ECMO conferred a significant clinical and survival benefit [40,41] with improvement in acute physiology and chronic health evaluation II score of 28.8 pre-ECMO and 11.8 post-ECMO ($p < 0.001$) and sequential organ failure assessment score of 10.1 pre-ECMO and 4.4 post-ECMO ($p < 0.001$) [41].

3. Conclusion

Early coronary angiography in these cases may be indicated to diagnose the high thrombus burden and facilitate immediate administration of both intracoronary and systemic anti-thrombotics. Aspiration of intracoronary thrombus may also have a role, though further guidance is required. Modulation of the cytokine storm may be a possible treatment avenue to reduce the pro-thrombotic state and trials are currently underway with therapies such as the IL-6 receptor antagonist tocilizumab which has already been used successfully in patients with cytokine storm syndrome [24]. Ultimately, more research is needed to identify the optimal management in these cases but the mechanism of high thrombus burden is progressively becoming more evident (Fig. 7).

Declaration of competing interest

None declared.

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