Aggregometry and thromboelastography to identify the timing to trach a COVID-19 patient receiving both antiplatelet therapy and enoxaparin

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Abstract

In COVID-19 patients receiving enoxaparin and antiplatelets therapy, aggregometry and thromboelastography might be considered an adjunctive tool to identify the time to perform procedures at risk of bleeding, such as tracheostomy.

KEYWORDS

aggregometry, COVID-19, SARS-CoV-2, thromboelastography, tracheostomy

1 | INTRODUCTION

SARS-CoV-2 infection promotes an aggressive inflammatory response and induces a hypercoagulability status requiring enoxaparin and antiplatelet therapy. This is challenging when procedures at risk of bleeding, such as tracheostomy, are necessary. In this patient, after suspension of antiplatelet therapy, we identify the time to trach, through aggregometry and thromboelastography.

In late December 2019, clusters of patients with interstitial pneumonia of unknown cause have been reported by some local health facilities in Wuhan (China). On 7 January, the Chinese Centre for Disease Control identified a novel coronavirus (SARS-CoV-2),[1] consequently declared a pandemic disease (COVID-19) by the World Health Organization on 11 March.

COVID-19 mainly affects male patients, with a median age of about 50 years; 40% of patients develop a severe acute respiratory failure (ARF), 5% requiring intensive cares.[2,3] COVID-19 is also characterized by a high intensive care unit (ICU) mortality rate, with a death rate higher among older patients.[4] The most common symptoms are fever followed by dry cough, shortness breath, dyspnoea, chest pain, fatigue, and myalgia.[5] Less common symptoms include headache, dizziness, abdominal pain, diarrhea, sputum production, abdominal pain, nausea, and vomiting.[5] Approximately 75% of patients show bilateral pneumonia.[6] Different from other coronavirus infections, COVID-19 has grater preference for infecting lower respiratory tract, with severe forms of ARF complicated by shock and acute organ failures.[5,6]

SARS-CoV-2 is characterized by the presence of a viral protein Spike that interacts with the angiotensin-converting

enzyme-2 receptor in the host [7]; this protein is highly expressed in lungs, intestine, oral mucosa, and liver. SARS-CoV-2 infection stirs up an aggressive inflammatory response, described as a "cytokine storm," throughout the release of pro-inflammatory cytokines, such as the tumor necrosis factor-a, interleukin-6 (IL-6), and IL-1β. Besides causing directly organ failures, cytokine storm induces alteration of coagulation pathways, the "so called" COVID-19 coagulopathy.[3,8,9] On the opposite, a few is known on platelet function and the role of their activation in SARS-CoV-2 infection.[10]

In COVID-19 patients, coagulopathy may frequently complicate with deep vein thrombosis, pulmonary embolism, systemic arterial embolism, and also disseminated intravascular coagulation, which may lead to death.[10,11] Furthermore, at hospital admission, COVID-19 patients commonly show increased D-dimer concentration, which is one of the predictors of mortality if markedly increased.[11,12] Therefore, an accurate monitoring of coagulation and platelet aggregation may be fundamental to guide the clinician into anticoagulant and antiplatelet therapies. In particular, thromboelastography and aggregometry might be useful to help the physician to choose the right and safe time to perform invasive procedures at risk for bleeding, such as percutaneous dilatational tracheostomy. We report a mechanically ventilated COVID-19 patient, in which we interrupted clopidogrel and maintained anticoagulant therapy, and we chose the time to perform a percutaneous dilatational tracheostomy, guided by thromboelastography and aggregometry.

2 | CASE REPORT

On 23 March 2020 (Day 0), an 85-year-old Caucasian man (78 kg of actual body weight, 175 cm of height) was admitted to the Emergency Department for progressive respiratory symptoms and fever (38.5°C). In the 12 days preceding hospital admission, the patient reported fever and sore throat. Due to the medical history, a nasal and pharyngeal swab was performed and SARS-CoV-2 infection confirmed. Therefore, further investigations (such as bronchoalveolar lavage and/or serological tests) were not considered necessary. Comorbidities were arterial hypertension treated with amlodipine and untreated prostatic hypertrophy.

At admission, he was spontaneously breathing in room air, with a respiratory rate >25 breaths/min; the oxygen arterial partial pressure (PaO_2) to inspired fraction (FiO_2) ratio (PaO_2/FiO_2) was 290 mm Hg, as assessed through arterial blood gases (ABGs) analysis. Hemodynamic was stable (ie, a mean arterial blood pressure (MAP) >65 mm Hg), while sequential organ failure assessment (SOFA) score was 4.

At admission, a general inflammatory status with alterations of part of coagulation tests was observed, in the absence of kidney, liver, and heart injuries. The patient was therefore admitted to a COVID-19 ward and treated with antibiotic at broad spectrum (ceftriaxone 2 g once daily till Day 8), hydroxychloroquine, and oxygen through a Venturi mask with a FiO_2 at 30%.

On Day 3, CT scan showed bilateral, patchy alveolar opacities progressing to diffuse consolidations, with a "white lung" appearance and widespread ground-glass opacities and moderate bilateral pleural effusions. On Day 4, patient's condition progressively worsened and continuous positive airway pressure (CPAP) through helmet was attempted.[13] Azithromycin 500 mg twice daily was also introduced; furthermore, according to an ongoing trial, tocilizumab 8 mg/kg was administered intravenously and repeated after 12 hours.

Antibiotic therapy was then modulated according to bacteria isolation. On Day 15, due to isolation of Acinetobacter baumannii in the sputum, gentamicin (480 mg/daily) and aerosolized colistin (3 billion-unit trice/daily) were initiated.

At Day 23, clinical condition suddenly precipitated; PaO_2/FiO_2 was 103 mm Hg, deeming necessary ICU admission and CPAP resuming. Due to the lack of gas exchange improvement and onset of kidney and heart failure, the patient was intubated and mechanically ventilated with a protective ventilation strategy. Prone position was applied for prolonged (>16 hours) sessions.[14] Norepinephrine from 0.1 to 0.6 mcg*kg/min was started and titrated according to the hemodynamics, in order to target a MAP >65 mmHg. Table 1 reports the blood test at ICU admission and along the first month of ICU stay. Due to the hypercoagulability related to COVID-19, Enoxaparin 8000 UI twice daily was administered subcutaneously; in addition, we also administered clopidogrel 75 mg once daily.

Since the clinical conditions barely improved and extubation was not possible due to the permanence of poor gas exchange, on Day 37 we decided to tracheostomy the patient, with a percutaneous single-stage dilatational technique (Ultraperc®, Portex; Smiths Medical Inc). Of note, this clinical decision kept with the more recently published guidance on tracheostomy in COVID-19 patients.[15] However, due to the anticoagulant and antiplatelet therapies, we decided to stop the administration of clopidogrel, while keeping enoxaparin, and to monitor the coagulation status with thromboelastography (TEG®6S; Haemonetics) and platelet function (PlateletMapping® ADP, Haemonetics).

As shown in Table 2, measurements were done at Day 37 (when tracheostomy was decided and clopidogrel stopped), Day 38, 40 (day of tracheostomy), and 42 (24 hours after clopidogrel resumption). In addition, we also investigated the following: (a) the coagulation with laboratory tests, that is, prothrombin time (PT), partial thromboplastin time (PTT),

TABLE 1 Blood test during the first month of ICU admission

	Normal range	ICU admission (Day 23)	Day 30	Day 35	Day 37	Day 42	Day 51
WBC (10^9/L)	4.5-11	4.42	5.11	13.86	13.22	10.66	12.70
RBC (10^5/mm^3)	4.7-6.1	4.37	3.90	3.28	3.68	3.03	3.01
Platelet (10^3/mm^3)	150-450	135	113	322	438	337	204
Creatinine clearance (mL/min)	88-128	98.8	78.3	68.3	80.2	38.7	86.1
AST (UI/L)	8-40	32	19	24	18	19	14
ALT (UI/L)	8-40	57	21	25	13	33	12
Lactate dehydrogenase (UI/L)	140-280	301	225	265	285	363	178
IL-6 (pg/mL)	0-16.4	4226	463	90.6	752	90.6	100
Procalcitonin (ng/mL)	<0.2	0.08	0.22	0.28	0.26	0.83	0.52
C-reactive protein (mg/dL)	<10	31.4	10.50	77.8	123	79.1	76.8
Glycemia (mg/dL)	70-130	115	117	187	126	163	162
Troponin (ng/L)	<0.04	<0.012	0.081	0.073	0.029	0.068	0.081
Fibrinogen (mg/mL)	200-400	202	270	400	619	432	327
D-dimer (ng/mL)	0-50	386	280	328	542	469	457

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; IL-6 interleukin; RBC, red blood cell; WBC, white blood cell.

activated partial thromboplastin time (aPTT), and D-dimer; and (b) the IL-6 blood concentrations.

During the whole hospitalization, the patient underwent periodical SARS-CoV-2 swab surveillance tests. Complete viral shedding with the first pharyngeal swab negative for SARS-CoV-2 was detected on Day 50. Patient was weaned-off invasive mechanical ventilation on Day 48,[16,17] and he was discharged from ICU on Day 56.

3 | DISCUSSION

We report a case of COVID-19 patient receiving both anticoagulant and antiplatelet therapies, in which the choice of the timing for tracheostomy was also guided by aggregometry and thromboelastography.

SARS-CoV-2 infection has been initially reported in the literature as a viral and interstitial pneumonia[1]; advances of research and knowledge on pathophysiology suggest that SARS-COV-2 infection promotes a cytokine storm and a COVID-19–related hypercoagulability condition.[3,8,9] Indeed, COVID-19 patients are characterized by a state of hypercoagulability, as compared to healthy adults.[18,19] In

particular, as compared to controls, *R* and *K* values have been reported to be shorter in 50% and 83% COVID-19 patients, respectively. Moreover, K and MA angle were also higher in 72% and 83% in COVID-19 population, as compared to controls. Finally, Lys-30 was lower than reference population in all patients affected by SARS-CoV-2 infection.[18] Spiezia et al reported that, compared to controls, COVID-19 patients are characterized by higher fibrinogen and D-dimer plasma levels, with markedly hypercoagulable ROTEM profiles characterized by significantly shorter clot formation time in the evaluations of both intrinsic (INTEM) and extrinsic (EXTEM) coagulation pathways, and by a higher maximum clot firmness in INTEM, EXTEM, and in the evaluation of fibrinogen contribution to blood clot (FIBTEM).[19] In fact, thromboembolic complications represent a part of the clinical picture of COVID-19 and can be already present at the time of hospital admission.[20] For these reasons, firstly several treatments with anti-inflammatory drugs or monoclonal antibodies have been attempted to modulate the cytokine storm; however, the awareness of the hyper-coagulability has pushed physician to start also anticoagulant therapies with low-molecular-weight heparin at high dosage and, sometimes, antiplatelet therapy.[21-23]

TABLE 2 Coagulation, thromboelastography, and platelet function test

	Day 37	Day 38	Day 40	Day 42
Coagulation test				
PT (seconds)	13.00	13.20	12.80	12.80
PTT (seconds)	36.70	31.40	34.10	34.20
aPTT	1.15	0.98	1.07	1.07
D-dimer (mg/mL)	328	516	781	585
Thromboelastography (TEG®6S)				
R (minutes)	8.5	8.9	8.5	8.4
K (minutes)	1.2	1.0	1.1	1.0
Angle (°)	75.3	76.9	76	76.3
MA (mm)	66	68.1	68.6	66.3
LY30 (%)	0.00	0.00	0.00	0.00
TEG ACT	78	78.5	82	81.2
Platelet function (PlateletMapping® ADP)				
MA ADP (mm)	25.1	28	52.6	52.8
Aggregation (%)	10.9	9.7	83.5	70.6

Based on this knowledge, we adopted the clinical choice to administer both anticoagulant and antiplatelet therapies to our patients in ICU. It should be noted that among severe COVID-19 patients with elevated D-dimer levels, a high incidence of thromboembolic complications, despite standard low-dose prophylaxis, has been reported.[24] For these reasons, an intermediate-intensity or full-dose anticoagulation has been routinely used, as opposed to standard low-intensity prophylaxis.[24] However, these therapies could have limited our treatment choice, in particular for most invasive procedures such as percutaneous tracheostomy at the bedside, due to the increased risk of bleeding. Indeed, bleeding is the most frequent perioperative and postprocedural complication after percutaneous dilatational tracheostomy, with a reported incidence of around 5%.[25]

It should be also criticized that we performed a late tracheostomy, instead an early strategy. In the past, a great challenge has been to assess the effectiveness and safety of early vs late tracheotomy in critically ill adults with different clinical conditions, with respect to their clinical outcomes. Early tracheotomy is defined as a procedure performed within the first 10 days from tracheal intubation, while late tracheotomy if occurring later than 10 days.[26] Results from the literature are quite contradictory. A systematic review and meta-analysis reported a moderate quality of evidence for a lower mortality rate at the longest follow-up time in the group receiving early tracheostomy, than late tracheotomy (47.1% vs 53.2%, respectively), with a statistically significant risk ratio of 0.83 (95% confidence interval 0.70–0.98; $P = .03$).[26] However, the procedure of tracheostomy should

not follow strict rules regarding time, but should be tailored to the individual patient. Furthermore, tracheostomy is an aerosol-generating procedure. So, healthcare workers are at risk of infection during insertion and subsequent care, even when appropriate personal protective equipment is used.[15] While on the one hand, delaying tracheostomy might reduce risks for staff and allow disease resolution with the possibility of weaning from mechanical ventilation and extubation, on the other hand, it prolongs duration of translaryngeal intubation, sedation, mechanical ventilation, and ICU stay.[15] After contemplating all these considerations, we decided for a late tracheostomy.

When we decided to tracheostomize our patient, we stopped antiplatelet therapy and kept the anticoagulant therapy ongoing, although some papers suggest that antiplatelet therapy may not be interrupted and mild coagulative disorders not corrected before percutaneous dilatational tracheostomy.[27,28] However, after performing advanced coagulation and aggregation tests, we obtained an objective evaluation of thromboelastography and aggregometry that lead us to act in this way. In fact, at the time the patient was admitted (end of March 2020), a few was known on the coagulative disorder correlated with SARS-CoV-2 infection. Therefore, the choice of the right time to perform tracheostomy was cautionary dictated by the daily coagulation blood test and platelet counts, in addition to thromboelastography and aggregometry. In fact, as we have shown in our case, we stopped the administration of clopidogrel, and after 3 days, the MA and the aggregation (%) fall within the normal range and percutaneous dilatational tracheostomy was safely performed at the bedside without bleeding complications. Therefore, our strategy has been revealed to be successful for our scope. Furthermore, we decided to restart antiplatelet therapy 24 hours after tracheostomy, in order to reduce as much as possible, the risk of platelet aggregation and thromboembolic events.

Although this was a successful strategy in the management of our patient, this remains a simple case report. Therefore, it should be considered as simple report, and not to be taken as a general practice to be applied in all patients. Further studies, with a proper design, are therefore required, to address whether this strategy is superior to others.

In conclusion, COVID-19 is a disease with a major coagulative disorder that requires an important anticoagulant and antiplatelet therapy. The performance of a percutaneous dilatational tracheostomy might be complicated by the required therapy. In this COVID-19 case, we decided to tracheostomy the patient guided by thromboelastography and aggregometry, after the interruption of antiplatelet drugs. This clinical choice, done in the beginning of the SARS-CoV-2 epidemic in our region, was successful and might be a strategy to be considered in complicated patients.

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