

Optical coherence tomography for microvascular lung vessels obstructive thromboinflammatory syndrome assessment in patients with COVID-19: an exploratory study.

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Signature:

Background

Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) infection represents a pandemic emergency of dramatic proportions. The clinical course of SARS-CoV-2 infection often meets the criteria for acute respiratory distress syndrome (ARDS), with progressive severity ultimately leading to a rapid death. It appeared that the progressive worsening lung function of patients infected with SARS-CoV-2 was potentially driven by host immune response. SARS-CoV-2 replication in lung epithelial cells causes direct cellular damage and release of pro-inflammatory alarmins from dying cells. The successive complement system activation causes massive local release of pro-inflammatory cytokines and consequent severe collateral tissue injury and massive vascular endothelial and alveolar epithelial cell damage and microvascular thrombosis. Functional implications of this peculiar ARDS pathogenesis include a progressive worsening of ventilation/perfusion imbalances and a loss of hypoxic vasoconstriction reflexes, with a marked component of microvascular pulmonary thrombosis, as suggested by lactate dehydrogenase and D-dimer elevations. In the late stages of ARDS, the progression of endothelial damage with microvascular thrombosis can spread locally in the lung and potentially extends the systemic inflammatory reaction involving the microvascular bed of the kidneys, brain and other vital organs¹. A new mechanism of lung damage was recently proposed, with dramatic alveolar endothelial damage leading to a progressive endothelial pulmonary syndrome with microvascular thrombosis and suggests MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as an atypical ARDS working hypothesis¹.

In fact, thromboembolic events rate in COVID-19 patients appears not negligible², and a prophylactic utilization of low molecular weight heparin (LMWH) should be considered³.

Several biomarkers are under investigation to better determine the risk of thromboembolic events and to determine the patients who could benefit more of a prophylactic therapy with LMWH. Among others, D-Dimer is often elevated in COVID-19 patients^{3,4} and should be used as the most important

parameter for thromboembolic risk stratification, together with other inflammation index like C-reactive-protein, interleukin 6 (IL-6) and ferritin.

Nevertheless, a not negligible part of patient with COVID-19 pneumonia presents high D-dimer level with computed tomography (CT) scan negative for pulmonary embolism. Despite these patients could presents pulmonary microvascular thrombosis (MicroCLOTS)¹, it has never been proven and an aggressive anticoagulant treatment is currently not utilized.

A diagnostic technique more sensible than the CT scan on the small pulmonary arteries could theoretically allow the detection of MicroCLOTS thus justifying a more aggressive anticoagulant regimen.

Optical coherence tomography

The optical coherence tomography (OCT) is a near-infrared light source-based imaging technique with a resolution of 10–20 μm ⁵. It acquires longitudinal sequences of cross-sectional images (100 frames/s) in a blood-free environment, resulting in sharp border definition between lumen and vessel wall. It is routinely used in percutaneous coronary intervention (PCI) to better characterize vessel anatomy, as well as ascertainment of full stent deployment and expansion⁶.

Moreover, OCT has been shown to have a good correlation with histology even in the evaluation of pulmonary artery morphology, particularly in the evaluation of pulmonary arterial wall thickness⁷. Furthermore, OCT has been used to better characterized distal Type Chronic Thromboembolic Pulmonary Hypertension⁸, and to guide its treatment with percutaneous transluminal pulmonary angioplasty⁹.

Hong et al¹⁰ evaluated with OCT three patients who were highly suspected for peripheral pulmonary arteries thrombi but had negative CT scan for pulmonary embolism. Thrombi were found in most of imaged vessels in these patients. Red and white thrombi can be differentiated, according to features of the thrombus on OCT images. After anticoagulation treatment, these patients' symptoms and hypoxemia improved. Repeated OCT imaging showed that most thrombi disappeared or became smaller.

OCT was also used in evaluation of pulmonary arterial vasculopathy in Systemic Sclerosis, showing an unexpected evidence of pulmonary artery thrombus formation in 19% of systemic-sclerosis patients with pulmonary arterial hypertension¹¹.

There are sufficient data showing OCT to be a useful tool to identify intravascular thrombi in patients with chronic thromboembolic pulmonary hypertension, together with an increase in vessel wall thickness in most patients with pulmonary hypertension^{12,13}.

Aim of the study

To evaluate by intravascular OCT study the presence of microvascular pulmonary thrombosis in patients with COVID-19, high D-dimer levels and contrast CT scan negative for pulmonary thrombosis. We'll also evaluate the extension of microvascular pulmonary thrombosis in patients with contrast CT scan positive for pulmonary embolism in areas where contrast CT scan was negative.

Inclusion Criteria (part A)

- Age ≥ 18
- Severe pulmonary coronavirus disease 19 (COVID 19) with suspect for MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) **AND**
- Contrast CT scan negative for pulmonary thrombosis **AND**
- D-Dimer > 10 mcg/mL **OR**
- $5 < \text{D-dimer} < 10$ mcg/mL and either C Reactive Protein (CRP) > 100 mg/dL or IL-6 > 6 pg/mL or ferritin > 900 ng/L

Inclusion Criteria (part B)

- Age ≥ 18
- Severe pulmonary coronavirus disease 19 (COVID 19) with suspect for MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) **AND**
- Contrast CT scan positive for pulmonary thrombosis

Exclusion Criteria

- Age < 18
- Pregnancy or breastfeeding
- Known allergy to iodinated contrast dye
- Hemodynamic instability
- Glomerular Filtration rate < 30 ml/min
- Active bleeding or absolute contraindication to anticoagulant therapy

OCT procedure

- Femoral vein echo-guided puncture; 6 Fr 11 cm sheath insertion.

- Unfractionated heparin administration (70 - 100 U/kg) to achieve an activated clotting time (ACT) between 250 and 300 seconds.
- Pulmonary artery cannulation with 5 Fr Multipurpose (MP) catheter (Cordis, Dublin, Ohio) and Storq wire (Cordis).
- Pulmonary artery pressure measurement
- Selective pulmonary artery cannulation and angiography
 - The choice of the pulmonary arteries to be cannulated will be driven by “ground glass” area at CT scan
- 5Fr MP catheter will be changed for 6Fr MP guiding catheter over the Storq wire.
- Storq wire removal and 0.014” Balance wire distally advanced.
- OCT images acquisition
 - In order to remove all the blood, as well as to obtain clear images, iodinated contrast is infused at a flow rate of 5 mL/s over 4 s, at 400 psi of pressure (Acist, Eden Prairie, Minnesota). Automatic pullback at 20 mm/s.
- If needed, blood samples can be taken through Recover catheter (Hexacath, Rueil-Malmaison, France)
- The same procedure will be performed:
 - on “healthy” (without ground glass appearance at CT scan) area in the same lung
 - on contralateral lung, both in “ground glass” and “healthy” areas according to CT scan.

PRIMARY ENDPOINT

- Overall safety of OCT procedure in COVID-19 pneumonia patients
- Presence of microvascular pulmonary thrombosis at OCT assessment in COVID-19 patients, both in “ground glass” and “healthy” ventilated areas.

SECONDARY ENDPOINT

- Pulmonary artery vessel anatomy characterization in COVID-19 patients
- Correlations with single trans-thoracic echocardiography (TTE) pulmonary hypertension (PH, estimated systolic pulmonary artery pressure > 35 mmHg) and right ventricular dysfunction (RVD: tricuspid annular plane systolic excursion < 17 mm or Doppler tissue imaging S wave < 9.5 cm/sec).
- Dynamic correlations with standard inflammatory, coagulation and tissue damage

Study design, sample size, statistical analysis

The study is an open label, prospective, interventional clinical study of the safety, tolerability and potential diagnostic value of optical coherence tomography for microvascular lung vessels obstructive thromboinflammatory syndrome assessment in patients with COVID-19 pneumonia.

This is a proof of concept exploratory study and will be conducted in 10 patients with mild-to-severe ARDS.

The sample size calculation was designed for safety assessment based on a reference population of last 100 patients who underwent OCT at our Institution for coronary Artery Disease (CAD) in which a rate of SAEs lower than 1% have been recorded (personal communication)

Primary endpoint

As for safety analysis, the number of imaging related complications (expected/unexpected) and serious events (SAEs) (expected/unexpected and/or related/not related) and the percentage of subjects experiencing imaging related event (IRE) and SAEs in the study will be summarized by severity and within body system involved. Narratives will also be presented.

Secondary endpoints

Continuous variables will be summarized with indices of location (i.e. mean or median) and dispersion (i.e. standard deviation or interquartile range), as appropriate. All relevant estimates will be reported with the corresponding 95% Confidence Intervals (CI).

Patients will be censored at study closure, withdrawn of consent or loss to follow-up.

Withdrawal and Premature Termination or Suspension of Study

Investigators may terminate a study subject's participation in the study if:

- Any clinical AE, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion, either newly developed or not previously recognized (except those caused by ARDS and SARS-CoV-2 infection), that precludes further study participation.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects;

Adverse events (AE)

AE is defined as any untoward medical occurrence in a patient or clinical investigation subject who underwent to a clinical procedure regardless of its causal relationship to the clinical procedure itself. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the performing of the clinical procedure. The occurrence of an AE may come to the attention of study personnel during the hospitalization period, or during follow up visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

Each AE will be recorded only once on the “Adverse Event” CRF page, with seriousness and maximum intensity that occurred over the duration of the event. Each event will also be evaluated with respect to causality and actions taken. All AEs will be monitored and recorded throughout the study. For all adverse events that require the subject to be discontinued from the study, the event(s) will be followed until final resolution or stabilization of the event(s).

The Investigator will classify and evaluate each AE as follows:

- Description of event (if the event consists of a cluster of signs and/or symptoms, record a diagnosis [e.g.: “flu”] rather than each sign and symptom)
- Onset date
- Stop date (if resolved)
- Seriousness (see definition of serious adverse events below)
- Intensity (“Mild” [does not interfere with daily activities]; “Moderate” [interferes with daily activities]; “Severe” [prevents daily activities])
- Relationship to study intervention (Not Related, Possibly Related, Probably Related)
- Action taken (None, Required concomitant treatment, Permanent discontinuation of study intervention, Other [explain])
- Outcome (recovered without sequelae, Resolved with sequelae, Ongoing, Unknown, Death)

Serious Adverse Events (SAE)

An SAE is an AE that meets 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires or prolongs in-patient hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect or malignancy
- Is medically important
- Requires medical intervention to prevent permanent impairment or damage

Imaging-related events

Intra-procedural adverse events will be recorded and considered as potential imaging-related events (IRE). IRE will be defined as the occurrence of clinical symptoms (worsening of respiratory failure, requiring invasive mechanical ventilation, hemoptysis), adverse angiographic outcomes (dissection, perforation, vasospasm, thrombus formation, abrupt closure), requiring interruption of the imaging procedure during intra-polmonary imaging and will be routinely registered by the operator. Major peri-procedural adverse events will be also be recorded: death, acute kidney injury, major bleedings, contrast media reaction, access-site related complications.

Fundings: The procedure will be covered by SSN. The other costs (see attached table of costs) will be covered by COVID BIOB funds.

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