Original Article

Endothelial dysfunction assessed by brachial artery flow-mediated dilatation predicts severe COVID-19-related disease

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Abstract

Background: Endothelial dysfunction, inflammation, and hypercoagulability are hallmarks of severe COVID-19 related disease. Endothelial function can be measured non-invasively by flow-mediated dilatation in the brachial artery. We planned a study to measure it as a marker of the severity of COVID-19 disease. **Objective:** To evaluate the association of clinically recognizable endothelial dysfunction in COVID-19 disease and its usefulness as a marker of severe COVID-19-related disease. **Methods:** 20 COVID-19 patients being admitted to our unit were analyzed for endothelial dysfunction and correlated with disease severity as per computed tomography (CT) chest score. Patients with diabetes, atherosclerotic coronary artery disease, dyslipidemia, chronic renal disease, and infections other than COVID-19 were excluded. Endothelial dysfunction was measured by flow-mediated dilatation in the brachial artery. **Results:** The mean age was 46.4 ± 16.5 years; 70% were males. The mean CT severity score was 22 ± 8; 60% required supplemental oxygen and steroids. The incidence of endothelial dysfunction was more in patients with a computed tomography severity score of >19.5 or oxygen saturation of <93% at room air as compared to mild cases ($P = 0.003$). Endothelial dysfunction was more evident >7 days after onset of disease as compared to early (<7 days) disease ($P = 0.016$). There was negative correlation between % flow-mediated dilatation in brachial artery and severity of lung involvement and prolonged symptomatic phase. **Conclusions:** Endothelial dysfunction as measured by impaired brachial artery flow mediated dilatation correlates with disease severity.

Keywords: COVID-19, CT severity score, endothelial dysfunction, flow mediated dilatation

Introduction

Endothelial dysfunction, inflammation, and hypercoagulability are hallmarks of severe COVID-19 related disease.[1] Coronavirus disease (COVID-19) accesses host cells via the protein angiotensin-converting enzyme 2 (ACE2). This protein is abundant in the lungs[2] and is expressed by endothelial cells[2,3], and resultant endothelitis causes impaired ability of the endothelium to maintain vascular homeostasis.[3] Apart from direct infection, the pro-inflammatory cytokines cause vascular endothelial cell apoptosis, increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant, and pro-adhesive changes, and microvascular dysfunction, which further compromises microvascular blood flow and thrombosis in various organs, such as lungs. Vascular endothelitis and angioplasty associated with coagulation and inflammation and

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resultant widespread thrombosis seem to be pathophysiology of changes leading to major organ dysfunction.[4] Therefore, the recognition of endothelial dysfunction non-invasively may be an important feature to predict severe disease. Endothelial function can be assessed non-invasively using flow-mediated dilatation technique.[5] We planned a study to find the correlation between endothelial dysfunction measured by this technique and the severity of COVID-19 disease.

Objectives

1. To study the association of endothelial dysfunction with COVID-19 disease.
2. To study the frequency of endothelial dysfunction in mild and severe disease.

Methods

Study design

We conducted an observational case control study involving COVID 19 patients admitted at our tertiary care hospital and research institute. The study was approved by the institutional ethics committee AIIMS/IEC/20/680 and the clinical trial registry of India (CTRI/2020/10/028361, 12/10, 2020). All methods in this study were carried out in accordance with the principles of the Declaration of Helsinki (latest version 2013) after informed consent.

Patient population and protocol

COVID-19 patients [confirmed with nasopharyngeal aspirates for identification of SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR)] admitted in our unit between age 18 to 80 years who were nondiabetic, non hypertensive, no evidence of coronary artery disease or dyslipidemia were included in the study. Patients with any other infection except COVID-19, renal failure (CrCl <60 mL/min/1.73 m^2) or need for hemodialysis, pregnancy, anemia, diabetes, known coronary artery disease, dyslipidemia, smoking were excluded. Diabetes, hypertension, dyslipidemia, coronary artery disease, renal failure, infections other than COVID-19 were excluded as they are *per se* are associated with endothelial dysfunction.[6-9] COVID-19 cases generally have symptoms such as fever cough, sore throat, dyspnea, and chest imaging showing lung opacities.[10-12] Disease was defined as mild when patients have subtle clinical symptoms and no lung opacities on chest imaging. Severe cases should meet any of the following criteria: (1) respiratory distress, respiratory rate (RR) of ≥30 beats/min; (2) resting blood oxygen saturation of ≤93%; or (3) partial pressure of arterial blood oxygen (PaO_2)/oxygen concentration (FiO_2) of ≤300-mm Hg or evidence of thrombotic disease - acute coronary syndrome, thrombotic stroke, pulmonary embolism any vascular thrombotic complication, acute respiratory distress syndrome, shock, multiple (>2) organ dysfunction, cytokine storm, new-onset liver, renal or respiratory failure. Critical patients need to meet one of the following conditions: (1) respiratory failure and need mechanical ventilation; (2) shock; (3) other organ failure needing intensive care unit (ICU) monitoring treatment.[12] The computed tomography severity score (CTSS) is a method used to describe ground-glass opacity, interstitial opacity, and air trapping, which was correlated with clinical and laboratory parameters in patients.[13,14] According to the anatomical structure, the 18 segments of both lungs were divided into 20 regions. The posterior apical segment of the left upper lobe was subdivided into apical and posterior segmental regions, and the anteromedial basal segment of the left lower lobe was subdivided into anterior and basal segmental regions. The lung opacities in all of the 20 lung regions were subjectively evaluated on chest CT using a system attributing scores of 0, 1, and 2 if parenchymal opacification involved 0%, less than 50%, or equal or more than 50% of each region, respectively. The CTSS was defined as the sum of the individual scored in the 20 lung segment regions, which may range from 0 to 40 points.[13,14]

Depending on the timing of onset of symptoms, cases were categorized as early (0–7 days) or late clinical manifestations (>7 days).[12]

Electrocardiography was done in all as per recommendations.[15] Echocardiography was performed at the bedside by an expert cardiologist using a commercially available ultrasound system (Epic, Philips, Andover, MA, USA). The echocardiograms parameters included two-dimensional, M-mode, and Doppler studies, ejection fraction by Simpson method as recommended by the American Society of Echocardiography.[16]

Endothelial dysfunction

Endothelial function was assessed by flow-mediated dilatation (FMD) using the Phillips Epic ultrasound system as described and recommended by European society guidelines.[9] In brief, the brachial artery was imaged using a 10-MHz linear array probe. The right brachial artery was imaged above the antecubital fossa in the longitudinal plane (approximately 4 cm above the bifurcation). A segment with a clear anterior and posterior interface between the lumen and vessel wall for 2D-gray scale imaging was chosen and a baseline image at rest was acquired. Reactive hyperemia was induced by inflating a pneumatic cuff placed around the distal forearm to a pressure of 50 mmHg above systolic blood pressure for 5 min, followed by rapid deflation of the cuff. FMD was measured as the maximal percentage increase in brachial artery diameter from baseline at 90 s after cuff deflation. FMD of <7.5% was taken as abnormal.[17]

Blood tests

All patients underwent baseline complete blood counts, renal, and liver function tests. Few severe disease patients also had D dimer and IL 6.

Treatment

The treatment of COVID-19 patients was as per institutional COVID policy as per recommendations of the Indian Council of Medical Research and National Institute of Health and was not interfered.

Outcomes

The primary endpoint was the frequency of endothelial dysfunction associated with COVID-related disease, and the secondary endpoint was the frequency of endothelial dysfunction in mild and in patients with severe disease and early disease (<7 days of symptom onset) vs. late disease (>7 days of symptom onset).

Sample size

Twenty consecutive COVID patients admitted to our unit were included. Twelve had severe disease and eight had mild disease as per the criteria already mentioned. Owing to health hazards to research staff and health care professionals, sample size was small.

Statistical methods

Values are expressed as mean ± standard deviation (SD) unless otherwise stated. Endothelial dysfunction was correlated with the severity of chest CT score by dividing the data into two groups: CT score of >19.5 and <19.5. The difference between groups was calculated using *t* test. Linear regression analysis was done between disease severity as per CT score vs. percentage FMD and duration of disease vs. percentage FMD. Early disease (<7 days from symptom onset) and late disease (>7 days from symptom onset) were compared to the severity of endothelial dysfunction (% FMD) by *t* test. All statistical analyses including multiple imputations were performed using IBM SPSS statistics (SPSS version 24, Chicago, IL, USA).

Results

Participants

Forty-five consecutive patients admitted to our unit with COVID positive requiring admission were screened and 20 were confirmed eligible and included in the study and analyzed. Ten were excluded because of diabetes, three because of chronic renal failure, two had coronary artery disease, ten had active infection other than COVID-19.

Baseline characteristics

The mean age was 46.4 ± 16.5 years, the majority were males (70%). Fever, cough, and dyspnea being the most common clinical features. As we are a tertiary referral center, majority of patients were symptomatic and presented at >7 days from symptom onset. The mean CT severity score was 22 ± 8, and 60% required supplemental oxygen and steroids [Table 1]. All patients had normal renal functions. Liver function was normal in the majority except for five patients having mildly elevated liver enzymes. Electrocardiography was normal in 95% of patients (n = 19) except one with T inversion in V1, V2. Echocardiography was normal in all except one with severe left ventricular dysfunction and normal coronaries on CT coronary angiography. He had evidence of endothelial dysfunction on FMD and elevated D dimer and IL 6. One patient had evidence of deep vein thrombosis of the lower limb. Most of the patients with resting oxygen saturation of <93% received supplementary oxygen therapy, steroids, and low molecular weight heparin [Table 1].

Endothelial function as assessed by percentage FMD from baseline was worse with increasing severity of lung involvement by COVID-19 as assessed by chest CT score [Table 2, Figures 1 and 2]. Symptomatic late disease was associated with more impairment of percentage flow-mediated dilation ($P = 0.016$) [Table 3, Figure 3].

Discussion

COVID-19 pandemic has created a grave health care problem across the globe. COVID-19 infection results in self-limited febrile illness lasting few days in the majority of patients

Table 1: Baseline characteristics

	n=20
Age (years) (mean±SD)	46.4±16.5
Females	30% (*n*=6)
Healthcare workers	25% (*n*=5)
Fever	100% (*n*=20)
Cough	90% (*n*=18)
Dyspnea	60% (*n*=12)
Duration of illness >7 days	70% (14)
Hb. (mean±SD)	12.7±1.08
TLC (mean±SD)	8.6±5.2
Neutrophils (mean±SD)	74.04±16.92
Lymphocytes (mean±SD)	16.86±13.67
Monocytes (mean±SD)	7.04±3.7
Eosinophils (mean±SD)	0.63±0.93
Basophils (mean±SD)	0.39±0.49
Platelets (mean±SD)	216±67
CT score (mean±SD)	22±8 (n=14)
Dexamethasone	60% (12)
Azithromycin	30% (6)
Tamiflu	5% (1)
Low molecular weight Heparin	60% (12)

CT: Computed tomography, Hb: Hemoglobin, TLC: Total leukocyte count, SD: Standard deviation

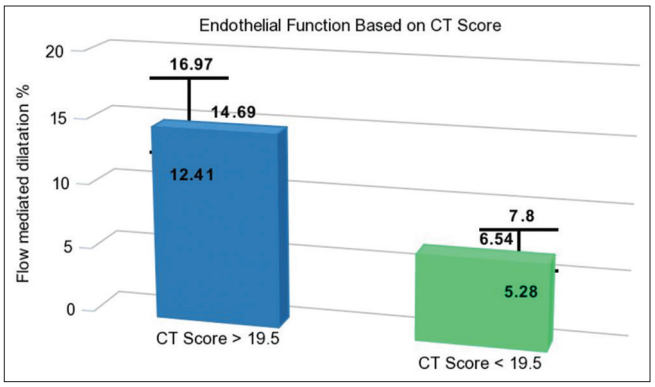

Figure 1: Endothelial dysfunction in relation to severity of lung involvement as assessed by CT Severity Score. CT : Computed Tomography

Table 2: Endothelial dysfunction in relation to severity of lung involvement

	CTSS >19.5 (*n*=12)	CTSS <19.5 (*n*=8)	*P*
% Flow-mediated Dilatation (Mean±Standard Deviation)	6.54±4.37	14.69±6.46	0.0033

CTSS: Computed Tomography Severity Score

Table 3: Endothelial dysfunction in relation to early and late disease

	Duration of Disease <7 days	Duration of Disease >7 days	*P*
% Flow-mediated Dilatation (Mean±Standard Deviation)	15±6.78	7.58±5.27	0.016

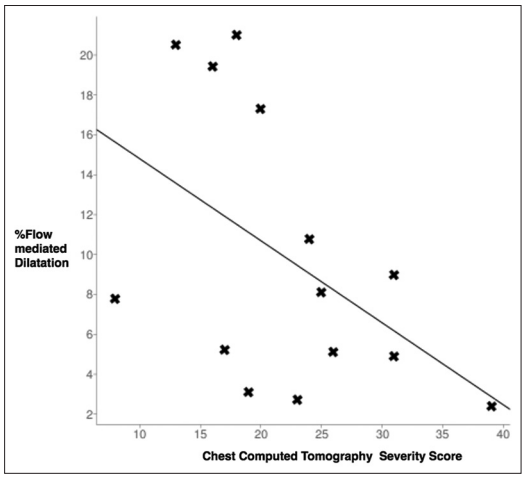

Figure 2: Percentage flow-mediated dilatation vs. computed tomography severity score

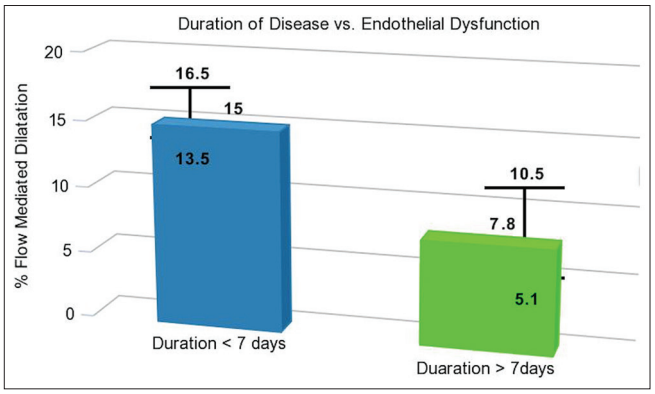

Figure 3: Symptomatic Late Disease associated with more endothelial dysfunction

but a small proportion can have potentially life-threatening complications such as acute respiratory distress, which seem to be related to endothelitis, endothelial dysfunction, inflammation, and thrombosis.[18] A lot of clinical outcome studies[10-12] have been reported but endothelial dysfunction was not measured clinically, though there was enough evidence of endothelial involvement as a major contributor to severe manifestations of disease was found on autopsy or histopathology.[19]

The important and novel findings of our study is that COVID-19 disease is associated with a measurable parameter of endothelial dysfunction, which can be measured non-invasively by brachial FMD technique. Severe respiratory disease with a CT score of >19.5 was associated more frequently with endothelial dysfunction in our study. The endothelial dysfunction may be central to pathogenesis and severe involvement not only in lungs but also in cardiac and other organs like the brain, kidney, etc.[1] One patient with deep vein thrombosis, COVID myocardial involvement with severe left ventricular dysfunction, left ventricular basal aneurysm, and clot had associated severe endothelial dysfunction. He was nonhypertensive, nondiabetic, and had no history of coronary artery disease. His CT coronary angiography revealed normal coronaries. He had significantly elevated D dimer levels. He was stabilized with anticoagulation. Endothelial dysfunction without risk factors for atherosclerosis may be a clue to COVID-related myocardial involvement due to inflammation, endothelial involvement, and thrombotic state.

Brachial artery FMD is a cost-effective, noninvasive, and readily available test. which can help in the current pandemic, which is creating a serious problem in low-income countries and remote primary health centers, where biochemical markers may not be readily available. Endothelial function assessment is a noninvasive test and can be done on a routine ultrasound echocardiography system available in most hospital settings. It can be easily applied even by primary physicians at remote health centers. Treatment strategies to prevent and minimize endothelial dysfunction can be studied using this modality.

Pulmonary endothelium is responsible for clearance of bradykinin, endothelin, angiotensin 1, and production of nitric oxide (NO) and prostacyclin, which are important in the regulation of vascular tone. Normal endothelium forms an anti-adhesive surface for platelets and secretes NO, prostacyclin, heparin, and activated protein C to prevent platelet aggregation and clotting.[20,21] Endothelial dysfunction, the impairment of the ability of the endothelium to maintain vascular homeostasis may be the result of direct infection of endothelial cells, the effects of pro-inflammatory cytokines resulting in vascular endothelial cell apoptosis, and leading to lung microvascular dysfunction, vascular leakage, alveolar edema, and hypoxia. Pro-inflammatory cytokines also increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and pro-adhesive changes, worsening microvascular flow, and, consequently, tissue perfusion.[22,23] These mechanisms were responsible for exudative/proliferative diffuse alveolar damage, but

endothelial tumefaction in pulmonary capillaries and fibrinous thrombi in small pulmonary arterioles and neutrophil traps were found on autopsy and histopathology studies.[24-26] The magnitude of lung involvement has been linked to disease severity and short-term prognosis.[27] We found that the magnitude of endothelial dysfunction correlates with severity of lung involvement and that pulmonary endothelial dysfunction is also associated with peripheral arterial endothelial dysfunction, which can be measured non-invasively and used as a marker of severity.

Endothelial dysfunction seems to be more associated with late disease (>7 days from symptom onset). The median time from onset of symptoms to dyspnea was eight days, acute respiratory distress syndrome nine days, and requirement for admission to ICU or mechanical ventilation was 10.5 days.[28] Being a tertiary referral care center, we received more of symptomatic and late cases. Patients without evidence of endothelial dysfunction at 10 days after symptom onset may be a low-risk group and may be discharged if stable, and those with endothelial dysfunction need more careful monitoring and to be included in trials of treatment strategies known to correct endothelial dysfunction and anticoagulation and antiplatelet strategies to prevent thrombotic events.

Pre-existing endothelial dysfunction in conditions such as diabetes, atherosclerosis, and metabolic syndrome when aggravated by the acute, noxious effects of SARS-CoV-2 over the endothelium may explain their worse outcomes in COVID-19.[4,6-9,29]

Ratchford *et al.*[30] showed a strikingly lower vascular function and a higher arterial stiffness in COVID-19 patients after 3–4 weeks of tested positive as compared with healthy controls. Ambrosino *et al.*[31] documented the improvement in endothelial function of convalescent COVID-19 patients after rehabilitation. They also showed a correlation between the severity of pulmonary and vascular disease and suggested that the improvement in endothelial function can be positively correlated with the improvement in pulmonary function. These findings are consistent with finding of your study. Our study was done on COVID 19 positive hospitalised patients during acute phase as compared to other studies which included non hospitalised recovered patients.

Statins, anti-inflammatory and immune modulating drugs can improve endothelial function.[32]

Identification of endothelial dysfunction will help in testing these drugs in future studies.

Highlights

1. COVID-19-associated severe disease is associated with endothelial dysfunction, which can be assessed non-invasively by brachial artery flow-mediated dilatation.
2. Endothelial dysfunction correlates with the severity of lung involvement and predicts prolonged illness.

Limitations

The study is limited by not being a randomized control trial and having a small sample size because of potential health hazards to healthcare workers and research staff.

Conclusion

To conclude, our study has shown endothelial dysfunction to be associated with severe lung disease. Endothelial function measured using brachial artery FMD can be a noninvasive, cost-effective, and quick method of risk prediction of severe disease and triage of COVID patients. It will be a useful tool in devising clinical trials to treat endothelial dysfunction associated with COVID-19.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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