Invasive assessment of coronary microvascular dysfunction in patients with long COVID: Outcomes of a pilot study

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INTRODUCTION

Since infections with SARS-CoV-2 have become a global public health issue, most efforts have been focused on reducing virus transmission and management of patients with acute respiratory failure. Recently diagnostic and therapeutic efforts will gradually involve post-COVID-19 survivors. Even though SARS-CoV-2 is considered a respiratory virus, the cardiovascular system is commonly involved. Up to 20% of patients hospitalized for COVID-19 have evidence of myocardial injury [1]. Direct viral infection, as well as indirect activation of the endothelial cell by inflammatory mediators, leads to endothelial inflammation and impairment of microcirculation function [2].

Numerous post-COVID-19 convalescents struggle with chronic fatigue, dyspnea, and recurring chest pain also known as long COVID-19 or post-COVID-19 syndrome, which is potentially related to prolonged endothelial dysfunction [3]. Long COVID-19 is often combined with the presence of cardiovascular risk factors, which implies the need for cardiological diagnostics. This study aimed to assess coronary microcirculation dysfunction (CMD) in symptomatic patients with post-COVID-19 syndrome without obstructive coronary artery disease (CAD).

METHODS

Study population

The study population consisted of 24 consecutive symptomatic long-COVID patients (with chest pain, dyspnea, and chronic fatigue) in whom non-obstructive CAD was diagnosed. Those patients were referred to two cooperating Cardiac Departments in the Lower Silesia Region between July 2021 and February 2022 by post-COVID outpatient care to have scheduled coronary angiography (CA) due to positive stress electrocardiography (ECG) test results. All study subjects had had positive tests for COVID-19 and undergone at least 1–3 months of recovery. All patients signed written consent to CA with subsequent CMD assessment. Since the study was observational and retrospective, ethical review and approval were waived.

Invasive coronary microcirculation assessment

After the diagnostic CA procedure, a 6F guiding catheter was inserted in the left main artery, and an intracoronary bolus of 200 µg of nitroglycerine along with a bolus of unfractionated heparin (UFH; 70 U/kg) was administered. After initial equalization, a pressure-temperature sensor guidewire (PressureWire X wired, Abbott, Chicago, IL, US) supported by the Coroventis software (Coroventis AB, Uppsala, Sweden) was used for the fractional flow reserve (FFR) and CMD measurements. The pressure sensor was placed at the distal segment of the target vessel (left anterior descending artery [LAD]). After an initial evaluation of mean transit time (Tmn) performed by three consecutive intracoronary saline injections at room temperature, hyperemia was induced

by an intravenous infusion of adenosine (140 µg/kg/min) through a central or peripheral vein. After reaching stable hyperemia, a total of 3–4 ml of saline at room temperature was rapidly injected through the guiding catheter. This procedure was repeated until 3 stable (reading within ±10% of each other) analogs thermodilution curves were obtained. If discordant values showed up, operators replaced them by repeating measurements.

Statistical analysis

The R language was used for analyses. Continuous variables were characterized by their mean and standard deviation, or median and first and third quartile dependent on their distribution, whereas frequencies were used for categorical variables. The Shapiro-Wilk test was used to verify the normality of continuous variables. The significance level was set to 0.05.

RESULTS AND DISCUSSION

The study population consisted of twenty-four patients, mainly males (70.8%). Almost one-third had been previously hospitalized for COVID-19, and approximately 20% required advanced respiratory support during COVID-19. The vast majority of patients had a high prevalence of cardiovascular risk factors — hypertension (95.8%), hyperlipidemia (91.6%), or had been previously diagnosed with CAD (41.7%). This reflects the therapies applied in the study cohort (Table 1). Regarding the echocardiographic assessment, the majority of subjects had preserved systolic function of the left ventricle (LVEF), 54.6% (11.5%). None of the patients had right ventricular dysfunction. CMD (Index of microvascular resistance (IMR) >25 or coronary flow reserve [CFR] <2) occurred in 6 patients (25%), and two of them had simultaneously incorrect IMR and CFR. All results were presented in Table 1.

This is, to the best of our knowledge, the first study aiming for invasive evaluation of CMD in subjects with symptomatic long-COVID-19 syndrome. Despite SARS-CoV-2 mainly affecting the respiratory system, endothelial cells are also susceptible to infection [3]. There is growing evidence suggesting that endothelial vasodilative dysfunction with a pro-inflammatory and pro-thrombotic state plays a crucial role in the pathogenesis of COVID-19 complications [4]. Furthermore, classical cardiovascular risk factors along with CAD and heart failure are well-known predictors of poor outcomes of COVID-19 [5] and are inextricably linked with endothelial dysfunction.

All these facts substantiate the critical role of vascular endothelium in the pathogenesis of COVID-19 and post-COVID-19 syndrome. However, exact consequences for vascular function remain uncertain.

Recently published data suggested that post-COVID-19 residual activation of the immune system might reflect persistent endothelial dysfunction and is partially responsible for long COVID-19 [6]. Moreover, some studies imply that long COVID-19 is directly associated with endothelial function status [7]. Therefore, the latest recommendations of the European Society of Cardiology [8] propose that endothelial function testing should be considered in the follow-up of convalescent COVID-19 patients.

Results of the study by Ambrosino et al. [9] indicate the presence of persistent endothelial dysfunction (ED) among COVID-19 patients assessed by alterations of endothelium-dependent flow-mediated dilation. Additionally, the authors noticed sex-dependent diversity in ED with lower prevalence in female subjects probably due to genetic and hormonal reasons. The mentioned impairment of ED can be reversible after rehabilitation. These positive changes are also correlated with improvement in pulmonary function [10].

Despite these initial encouraging data, it is still unclear whether complete restoration of endothelial function ensures reduction of the residual risk for cardiovascular and thrombotic events and decreases the likelihood of symptomatic long COVID-19.

There is no data on CMD assessment in patients with long COVID-19. Hence, our pilot study is the first focused on the evaluation of CMD in this population. Our data suggest that microvascular disorders are not the dominant finding. In our cohort, we observed it in 25% of subjects. However, our study did not assess the vasospastic component (microvascular and epicardial) of CMD. The prevalence of these disorders measured by an invasive provocation test (acetylcholine, ergonovine) may reach even up to 60% in patients with CMD [11]. Comparing these data with the fact that in patients with symptomatic non-obstructive CAD overall CMD prevalence reaches up to 66% [12], we may assume that long COVID-19 syndrome has a more comprehensive etiopathogenesis than CMD.

Recent publications suggest that long COVID-19 has multiple causes and may be related to a prolonged systematic inflammatory response involving interleukin 1 and 6, and tumor necrosis factor α, increasing the probability of myocardial fibrosis and remodeling [13]. Results of cardiac magnetic resonance (CMR) of COVID-19 convalescents seem to support this thesis. Around 80% of the post-COVID population showed cardiac injury on CMR and increased levels of troponin [14]. However, laboratory assays from our cohort study contradict these findings. Additionally, inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia syndrome (PoTS) related to previous SARS-CoV-2 infection may be responsible for observed symptoms [15].

Limitations

The study is a relatively small non-randomized observational registry without a control group. Due to safety concerns, spasm provocation testing including ergonovine or acetylcholine was omitted. Additionally, pulmonary function assessment was only limited to blood gas analysis without any information about spirometry.

Table 1. Characteristics of the study cohort

Variables	Study cohort (n = 24)
Baseline clinical data	
Age, mean (SD)	59.6 (11.5)
Male sex, n (%)	17 (70.8)
Previous hospitalization for COVID-19, n (%)	7 (29.2)
Advanced respiratory support[a] applied during the COVID-19, n (%)	6 (20.7)
Days of COVID-19 hospitalization, median (IQR)	11 (0-7.25)
COVID-19 vaccinated, n (%)	6 (25)
Diabetes mellitus, n (%)	6 (25)
Chronic heart failure, n (%)	2 (8.3)
Hypertension, n (%)	23 (95.8)
Hyperlipidemia, n (%)	22 (91.6)
Atrial fibrillation, n (%)	3 (12.5)
History of CAD, n (%)	10 (41.7)
COPD, n (%)	4 (16.7)
Active smoker, n (%)	8 (33.4)
Pharmacotherapy	
ACEI/ARBs, n (%)	20 (83.3)
ASA, n (%)	18 (75)
NOAC, n (%)	2 (8.3)
VKA, n (%)	1 (4.2)
Statin, n (%)	22 (91.7)
Calcium channel blocker, n (%)	11 (45.8)
β-blocker, n (%)	22 (91.7)
Diuretic, n (%)	14 (58.3)
Oral antidiabetic drugs, n (%)	11 (45.8)
Insulin, n (%)	1 (4.2)
MRAs, n (%)	9 (37.5)
Basic laboratory assay	
Leucocytes, $\times 10^9$/l, median (IQR)	6.9 (6–7.8)
RBC, mln/ul, median (IQR)	4.7 (4.5–5.2)
Hemoglobin, g/dl, mean (SD)	14.3 (1.8)
TnI, ng/l, median (IQR)	10 (7.4–11.5)
D-dimer, µg/l, mean (SD)	450.2 (228.8)
CRP, mg/l, median (IQR)	1.9 (0.6–4.4)
Creatinine, µmol/l, mean (SD)	82.6 (14.2)
TSH, mU/l, median (IQR)	1.5 (1.2–2.1)
HBA1C, %, mean (SD)	5.8 (0.7)
Post-COVID IgG antibodies, AU/ml, median (IQR)	86 (11.4–180)
Cholesterol, mmol/l, mean (SD)	4.5 (1.1)
LDL-cholesterol, mmol/l, mean (SD)	2.6 (1.1)
pH, mean (SD)	7.42 (0.01)
PaO_2, mm Hg, mean (SD)	64.5 (8.3)
$PaCO_2$, mm Hg, mean (SD)	33.8 (4.11)
Echocardiographic features	
LVEF, %, mean (SD)	54.6 (11.5)
TR max, m/s^2, median (IQR)	2.5 (2.4–2.5)
TAPSE, mm, (SD)	22.9 (3.6)
LA-diameter, mm, median (IQR)	40 (37–41.2)
LVEDD, mm, mean (SD)	52.2 (7.6)
IVS, mm, mean (SD)	11.2 (2)
Moderate diseases, n (%)	1 (4.2)
Microcirculation measurements	
FFR-LAD, mean (SD)	0.91 (0.04)
RFR, mean (SD)	0.94 (0.03)
CFR, median (IQR)	3.15 (2.20–5.23)
CFR norm, median (IQR)	4.33 (2.69)
IMR, median (IQR)	16.33 (12.44)
CFR <2, n (%)	4 (16.7)
IMR >25, n (%)	4 (16.7)
CFR <2 and IMR >25, n (%)	2 (8.3)

[a]High-flow nasal cannula, mechanical ventilation

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid; CAD, coronary artery diseases; CFR, coronary flow reserve; COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; CRP, C-reactive protein; FFR, fractional flow reserve; HBA1C, glycated hemoglobin; IMR, index microcirculation resistance; IVS, intraventricular septum; LA, left atrium; LAD, left anterior descending artery; LDL, low-density lipoprotein; LMWH, low molecular weight heparin; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NIV, non-invasive ventilation; NOAC, non-vitamin K antagonist oral anticoagulants; RBC, red blood cells; RFR, resting full-cycle ratio; SD, standard deviation; TAPSE, tricuspid annular pulmonary systolic excursion; TR, tricuspid regurgitation; TSH, thyroid-stimulating hormone; VKA, vitamin K antagonists

In conclusion, the prevalence of CMD in long-COVID--19 subjects is similar to that observed in patients with symptomatic non-obstructive CAD [11, 12]. Future studies are necessary to fully understand the etiopathogenesis of long COVID-19.

Article information

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