Chest pain and coronary endothelial dysfunction after recovery from COVID-19: A case series

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Abstract
Endothelial cell damage related to coronavirus disease 2019 (COVID-19) has been described in multiple vascular beds, and many survivors of COVID-19 report chest pain. This case series describes two previously healthy middle-aged individuals who survived COVID-19 and were subsequently found to have symptomatic coronary endothelial dysfunction months after initial infection.

KEYWORDS
angina pectoris with normal coronary arteriogram, case study, coronary artery vasospasm, COVID-19 virus disease

1 INTRODUCTION
The novel coronavirus 2019 and the associated coronavirus-related respiratory distress syndrome (SARS-CoV2) have caused a worldwide pandemic with over 100,000,000 people infected.1 Acute cardiovascular manifestations of coronavirus disease 2019 (COVID-19) include myocarditis, ST-elevation myocardial infarction, arrhythmias, vascular endothelial dysfunction, and coronary vasospasm.2 Endothelial dysfunction or virus-related endotheliopathy has been proposed as a mechanism for these cardiovascular manifestations in COVID-19, and thrombotic events during acute illness have been attributed to endothelial damage.3 However, the role of coronary endothelial injury in long-term cardiac symptoms after resolution of acute infection is not well understood.

After recovery from the acute phase of illness, as many as 91% of patients experience persistent fatigue, gastrointestinal symptoms, body aches, or brain fog, and a significant portion (up to 35% at 6 months) experiences ongoing chest pain/burning or tightness in the chest.4 These patients have been termed “long haulers,” and cardiovascular diagnostic studies are often normal and do not reveal the mechanism of disease.5 This report describes the diagnostic evaluation of two patients who developed post-COVID-19 angina and were found to have myocardial ischemia with no obstructive coronary artery disease. Both patients were ultimately diagnosed with symptomatic...
coronary endothelial dysfunction with invasive coronary physiology testing (Data S1).

2 | CASE SERIES

2.1 | Patient 1

A 65-year-old previously healthy man was admitted to the hospital with fevers, chills, and left-sided chest pain. He was found to have left lung ground-glass opacities on a computed tomography (CT) scan of the chest and was diagnosed with COVID-19. He was started on hydroxychloroquine, atazanavir, vancomycin, and piperacillin-tazobactam, and was placed on supplemental oxygen. Ten days after diagnosis, his respiratory status deteriorated with progressive hypoxemia and he was intubated for mechanical ventilation. A transthoracic echocardiogram showed normal left ventricular function. Tocilizumab and doxycycline were added to his treatment regimen, and within 48 h, he was extubated. He improved and was discharged from the hospital 17 days after initial diagnosis.

Over the subsequent three months, he developed progressive chest discomfort and dyspnea on exertion without a clear cause. Coronary computed tomography (CT) angiography showed non-obstructive atherosclerosis, and cardiac magnetic resonance imaging (MRI) showed patchy transmural delayed enhancement possibly consistent with prior myocarditis. He was initiated on medical therapy with a beta-blocker and angiotensin-converting enzyme inhibitor. He underwent exercise single-photon emission computed tomography (SPECT) cardiac stress testing with technetium-99m Tetrofosmin, and he exercised for 10 minutes before stopping for chest discomfort and ischemic electrocardiographic changes (Figure 1C, compared to baseline in Figure 1B). Stress perfusion imaging showed a reversible perfusion defect in the apical anterior/septal segments concerning for ischemia (Figure 1A). He was referred for coronary angiography and an invasive assessment of coronary physiology, which showed minimal epicardial atherosclerosis (Figure 2A) with a fractional flow reserve (FFR) of 0.87, normal coronary flow reserve (CFR) of 3.6, and normal index of microcirculatory resistance (IMR) of 11 (complete protocol in Supplemental Appendix). Administration of 100µg intracoronary acetylcholine revealed diffuse >70% constriction of the mid to distal left anterior descending artery (LAD) and the patient reported malaise (Figure 2B, Video

FIGURE 1 Exercise Electrocardiographic and SPECT Findings in Patient 1. Panel A shows single-photon emission computerized tomography (SPECT) images obtained at baseline and after exercise. Note the marked diaphragmatic attenuation that resolves with attenuation correction and leaves a residual apical anterior and septal defect on stress images, consistent with ischemia. (arrows). Panel B shows the baseline electrocardiogram showing normal sinus rhythm. Panel C shows the electrocardiogram during treadmill exercise after 10 min, while the patient reported chest pain. Note the presence of 1.5 mm ST depressions in inferior leads that were not present at baseline (arrows)
There were no associated ischemic ECG changes (Figure 2C,2D). 200µg of intracoronary nitroglycerin was administered with resolution of the angiographic abnormalities. Based on these findings, the patient was diagnosed with severe coronary endothelial dysfunction and anti-anginal therapy was initiated. He reported modest relief of his angina with verapamil, sublingual nitroglycerin, and ranolazine. Notably, at the time of anginal symptoms, there was no significant elevation in the patient’s inflammatory markers or markers of endothelial cell activation (Tables 1 and 2).

### 2.2 | Patient 2

A 55-year-old perimenopausal woman with a history of diabetes mellitus and obstructive sleep apnea presented with cough and shortness of breath and was diagnosed with mild COVID-19 infection. A CTA of the chest was performed which ruled out pulmonary embolism and showed patchy opacities of the lung bases bilaterally. She was discharged home with supportive care. However, one month later she had repeated outpatient and emergency department presentations for chest pain radiating to her left arm without evidence of an acute coronary syndrome. A pharmacological SPECT myocardial perfusion imaging stress test showed normal perfusion and a fixed inferolateral attenuation artifact (Figure 3A). There were no ischemic ECG changes with administration of regadenoson (Figure 3B,3C). She was referred for invasive coronary angiography which showed a 70% stenosis in the mid-left circumflex artery (Figure 4A) with no other significant disease. Coronary physiological assessment showed that the circumflex stenosis was not hemodynamically significant with an FFR of 0.83, as well as a normal CFR of 2.9 and an IMR of 24, reflecting preserved non-endothelium-dependent microvascular vasodilation. Intracoronary acetylcholine provocation resulted in severe epicardial narrowing of the first diagonal and apical LAD (Figure 4B), with chest pain and ischemic ST-segment depression on the electrocardiogram at the higher dose (Figure 4D, compared to baseline in Figure 4C) as well as sluggish flow consistent with mixed epicardial and microvascular vasospasm (Video S3 and S4). There was no significant angiographic change in the appearance of the atherosclerotic stenosis in the left circumflex. A total of 400 µg of intracoronary nitroglycerin were administered and the coronary arteries appropriately vasodilated and the patient’s chest pain resolved. The patient noted that the chest pain during acetylcholine infusion exactly replicated her presenting symptoms. Based on these findings, she was diagnosed with severe epicardial and microvascular coronary endothelial dysfunction. She achieved significant improvement in her symptoms with the initiation of verapamil.

### 3 | DISCUSSION

Survivors of COVID-19 with persistent symptoms frequently report chest pain after recovery from acute illness. Chest discomfort has been attributed to residual viral pneumonia or COVID-19 myopericarditis, but symptomatic coronary endothelial dysfunction has not been reported. We describe two patients with persistent angina who were found to have non-obstructive atherosclerotic...
coronary artery disease but significant epicardial and microvascular endothelial dysfunction. Notably, these patients never had chest pain prior to COVID-19 infection and developed symptoms within several months of the infection, raising the possibility of a COVID-19-related coronary endotheliopathy. Vallejo et al. reported a similar case of microvascular-disease-related angina after COVID-19 which they diagnosed on first-pass stress perfusion CMR that showed circumferential subendocardial perfusion defect. However, to our knowledge, this is the first case series of COVID-19-related endothelial dysfunction that was diagnosed with invasive physiologic testing. In the first patient, we describe a vasospastic response of the left anterior descending artery in response to acetylcholine provocation but preserved endothelium-independent microvascular function in response to adenosine (IMR 11). The second patient was found to have epicardial and microvascular vasospasm as assessed by angiography but also with preserved endothelium-independent microvascular function (IMR 24). This suggests that in these patients, several months after the initial COVID-19 illness, there is lasting epicardial and/or coronary endothelial dysfunction that may be responsible for new-onset angina.

The mechanism for the observed findings cannot be ascertained from the available diagnostic findings but may include inflammation-related endothelial injury. In healthy arteries, acetylcholine binds to endothelial muscarinic acetylcholine receptors leading to nitric oxide-mediated vasodilation, but if the endothelium is injured or disrupted, administration of acetylcholine results in vasoconstriction via activation of muscarinic acetylcholine receptors on vascular smooth muscle as was observed in both of the reported patients. In both patients, the appropriate vasodilatory response to nitroglycerin rules out vascular smooth muscle hyperconstriction as the cause of vasospasm. In the second case, there was evidence of preserved endothelium-independent microvascular function but angiographic evidence of slow flow during acetylcholine provocation, suggesting disruption of endothelium-dependent microvascular function.

Endothelial inflammation and injury during COVID-19 occur due to direct SARS-CoV2 viral infection of endothelial cells, possibly via the ACE-2 receptor, triggering a host inflammatory response. This phenomenon has been described in several distinct vascular beds, including the small arterioles/venules of the heart, pulmonary artery,
FIGURE 3  Regadenoson Electrocardiographic and SPECT Findings in Patient 2. Panel A shows single-photon emission computerized tomography (SPECT) images obtained at baseline and after regadenoson administration. Note a fixed inferolateral defect on non-attenuation corrected images that resolves with attenuation correction and is consistent with attenuation artifact. Note that attenuation correction creates anteroseptal artifact.

FIGURE 4  Angiography without and with Acetylcholine Administration and Accompanying Electrocardiographic Changes in Patient 2. Panel A shows the baseline coronary angiogram with a 70% stenosis in the mid-left circumflex (asterisk) and arrows indicating a diagonal branch and the distal left anterior descending artery. Panel B shows the vasoconstriction of the diagonal branch and the left anterior descending artery after intracoronary acetylcholine infusion with an unchanged stenosis in the left circumflex artery (asterisk). Panels C (baseline) and D (after acetylcholine) show electrocardiograms obtained at the time of cardiac catheterization. Note the ischemic ST-depression in leads II and V with acetylcholine administration seen in Panel D.
mesenteric vessels, glomerular capillary loops of the kidney, and portal triads of the liver.

Notably, autopsy studies of COVID-19 decedents have not reported clear evidence of inflammation involving the coronary arteries, but there are increased CD4+ and CD8+ lymphocytes in the pericytes which surround the cardiac vascular beds. Pericytes have previously been implicated as mediators of coronary flow and vasoconstriction, and are suspected to contribute to vascular dysfunction and thrombosis in COVID-19. Furthermore, a systemic inflammatory response may contribute to endothelial dysfunction. Elevated serum levels of interleukin-6 (IL-6) have been described as a hallmark of severe COVID-19 illness. One of our patients developed a significant increase in IL-6 during the acute illness and received tocilizumab, a monoclonal antibody against the IL-6 receptor. Plasma IL-6 levels are known to be associated with coronary endothelial dysfunction, but this specific association has not been described after COVID-19 infection. It is possible that in some “long haul” patients a persistent inflammatory state contributes to coronary endothelial dysfunction.

The primary limitation of this case series is the lack of acetylcholine provocation testing in the same patients prior to COVID-19 infection to prove that coronavirus infection was the inciting factor for the development of coronary endothelial dysfunction. We rely instead on the development of new-onset angina after COVID-19, and the lack of any prior patient-reported or documented evaluations for chest pain. While approximately ~30% of patients undergoing intracoronary acetylcholine provocation may show mild epicardial coronary artery luminal narrowing, the degree of lumen reduction observed in the reported cases was profound. Our diagnostic criteria for endothelial dysfunction included >70% epicardial narrowing, patient-reported chest pain, and evidence of electrocardiographic changes. Finally, we did not directly assess coronary flow velocity during acetylcholine provocation, and the diagnosis of microvascular spasm, while consistent with accepted criteria, was not based on Doppler wire assessment.

4 CONCLUSION

COVID-19 infection is associated with systemic inflammation and pathological evidence of vascular endothelial cell and pericyte disruption. We report two cases of new-onset angina due to symptomatic coronary endothelial dysfunction which occurred after recovery from COVID-19 infection. Survivors of COVID-19 should be carefully screened for the presence of angina, which may be mistaken for residual symptoms related to viral pneumonia. In patients with prior COVID-19 and suspected ischemia in the absence of obstructive coronary artery disease, there should be consideration of provocative testing for endothelial dysfunction. Future studies are necessary to investigate the mechanisms of coronary endothelial dysfunction and its prognostic implications in COVID-19 patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Samit Shah involved in conceptualization, investigation, writing—original draft, visualization, and supervision. Natalija Odanovic and Attila Feher involved in writing—review and editing, and visualization. Steffne Kunnirickal involved in investigation, and writing—review and editing. Stephen Pfau involved in writing—review and editing, and supervision. Erica Spatz involved in conceptualization, investigation, writing—review and editing, and supervision.

ETHICAL APPROVAL

This case report was deemed exempt from Institutional Review Board (IRB) review per the Yale Guidance on Patient Privacy and the Publication or Dissemination of Case Reports.

CONSENT

Informed consent was obtained from the patients to publish this report in accordance with the journal’s patient consent policy. One patient provided written consent and the other provided verbal consent via telephone.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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