Editorial

Myocardial involvement in post-COVID-19 condition: a note from the surgical approach

Mikołaj Seostianin[1,2]^, Paweł Burchardt[3,4]^

[1]Department of Anesthesiology and Intensive Therapy, Józef Struś Memorial Multidisciplinary Municipal Hospital, Poznań, Poland; [2]Department of Teaching Anesthesiology and Intensive Therapy, Poznań University of Medical Sciences, Poznań, Poland; [3]Department of Cardiology, Józef Struś Memorial Multidisciplinary Municipal Hospital, Poznań, Poland; [4]Department of Hypertension, Angiology, and Internal Medicine, Poznań University of Medical Sciences, Poznań, Poland

Correspondence to: Mikołaj Seostianin, MD. Department of Anesthesiology and Intensive Therapy, Józef Struś Memorial Multidisciplinary Municipal Hospital, ul. Szwajcarska 3, 61-285 Poznań, Poland; Department of Teaching Anesthesiology and Intensive Therapy, Poznań University of Medical Sciences, Poznań, Poland. Email: mseostianin@gmail.com.

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The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has exerted a widespread burden all over the world and affected every aspect of human life (1). The fallout of the pandemic is still evolving with over 7 million death toll and over 700 million infected individuals to date. Concerning problem is currently the post-COVID-19 condition [also known as a post-COVID syndrome or post-acute sequelae of SARS-CoV-2 infection (PASC)]. World Health Organization defines this phenomenon as symptoms occurring at least three months (new onset following recovery from acute SARS-CoV-2 infection or persist from the initial illness) after probable or confirmed SARS-CoV-2 infection which must last for at least two months and cannot be explained by an alternative diagnosis (2). However, the terminology has not been well-established yet. According to the clinical definition of the Centers for Disease Control and Prevention (CDC), PASC could be diagnosed when symptoms are present 4 or more weeks after initial infection (3).

Incidence of post-COVID-19 condition is estimated to be 10–35% of COVID-19 outpatient cases with the percentage increasing to even 80% in patients hospitalized for acute infection (4,5). Females, patients with co-existing comorbidities, and those with increased cardiovascular risk are more likely to develop post-COVID complications (with the last also being more likely to suffer from symptomatic PASC) (4,6-8). Symptomatology of post-COVID-19 condition consists of over 100 manifestations influencing all body systems including fatigue, cough, memory deficits, dyspnea, depression, anxiety, anosmia, sleep problems, joint pains, and more (3,5). Cardiovascular manifestations are of special concern and consist of palpitations, arterial hypertension, dyspnea, chest pain and tightness, autonomic dysfunction, tachycardia, and other arrhythmias, myocardial fibrosis, and scarring, myocarditis, pulmonary hypertension, reduced cardiac reserve, increased cardiometabolic demand and other (3,9). American College of Cardiology (ACC) 2022 Expert Consensus Decision Pathway on Cardiovascular sequelae of COVID-19 in adults distinguished two forms of cardiovascular manifestations in PASC: a known cardiovascular condition which is present

^ ORCID: Mikołaj Seostianin, 0000-0002-7754-3949; Paweł Burchardt, 0000-0003-0353-3470.

during the early post-acute phase of infection or chronic COVID-19 (PASC-CVD) and cardiovascular symptoms which cannot be explained by initial testing that extend beyond acute infection (PASC-CVS) (10). The pathogenesis of post-COVID syndrome is believed to be multifactorial. Available literature suggests direct viral involvement, immunological dysregulation, hyperinflammatory, thromboembolic events as well as metabolic and genetic factors that might contribute (3,9,11,12). As for viral persistence—many organs (including the heart, lungs, gastrointestinal tract, brain, and more) were found to be reservoirs for SARS-CoV-2 many months after the acute phase of infection (3,13). However, the evidence behind the association of PASC symptoms and viral presence in body-derived samples is scarce (due to heterogeneous results, a low number of studies, and testing limitations) (14). This might be indicative of complex pathological mechanisms behind post-COVID syndrome.

The predilection of SARS-CoV-2 to the human heart has been associated with ACE2 receptors (as virus binding sites) early in the pandemic (15). As shown by autopsy studies, majority of deceased COVID-19 patients had the virus found in heart tissue. Histopathologically this involves direct damage of cardiomyocyte and its death, followed by fibrosis and scarring (but might slightly differ in presentation when compared to other viral myocarditis) (9,10,16). Indirect damage should also be considered as a dysregulated inflammatory response, aberrant antibody activity or even autoimmunological factors could play a crucial role in prolonged myocardial infection. Interleukin-6 (IL-6) is thought to mediate indirect myocardial injury through lymphocyte-T activation (17). Moreover, in a study among 14 patients with post-COVID biopsy-confirmed myocarditis in one patient, the virus was absent in the heart specimen whereas antiheart antibodies (AHA) were present in all subjects (with high AHA titers in 93%) (18). Myocardial infiltration could be focal or diffuse and diverse in presentation—from mild asymptomatic inflammation to severe or critical disease such as cardiogenic shock (10,19). Myocarditis could also be divided into active, chronic, and fulminant depending on its course (16). In opposition to other PASC symptoms males and younger individuals are more likely to develop post-COVID myocarditis (16). Endomyocardial biopsy and cardiac magnetic resonance imaging (MRI) are considered the gold standard for diagnosing viral myocarditis. However, myocarditis in PASC might not necessarily meet the 2018 Lake Louise Criteria for active myocarditis in MRI (6,19,20). Furthermore, the multifactorial pathogenesis of PASC-related myocarditis implements that unimpaired cardiac MRI cannot exclude the late onset of the disease (16). Diagnostic methods such as electrocardiography, echocardiography, and biochemical markers (troponin, natriuretic peptides etc.) are encouraged for more detailed clinical testing (21). Interestingly, chronic myocarditis in PASC is believed to provoke a proarrhythmic state by altering cardiomyocyte membrane conductivity (16). This should be taken into special consideration as tachycardia is one of the most commonly reported symptoms by COVID-19 survivors (12).

The study by Sanjiu *et al.* investigated myocardial involvement of SARS-CoV-2 in patients who tested negative for COVID-19 and were scheduled for open-heart surgery six months after acute infection (22). The testing for virus colonization was performed in the material which is normally discarded with special regard to inflammatory markers such as IL-6 and interleukin-1β (IL-1β). In four patients who tested negative for systemic infection, the virus was present in atrial specimens, and in some of this group expression of cytokines (such as IL-6 and IL-1β) was raised in sampled tissue due to persistent myocardial inflammation. The surgical procedure also caused (however statistically insignificant) greater increase of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) in the SARS-CoV-2 positive group when compared to the control group. Serum IL-6 and IL-1β levels were also measured perioperatively. The findings from this study (however based on a small group) might have clinical implications in the population of patients with PASC (especially those who undergo surgery). It is still to be explored if patients with asymptomatic persistent myocardial involvement are more susceptible to complications in the perioperative setting. Moreover, whether underlying post-COVID-19 inflammation of the myocardium might be exacerbated by surgical stimulus is unclear. The vast majority of patients who suffer from chronic diseases (including heart diseases) should be taken into special consideration regarding their COVID-19 status and post-COVID complications which could undermine the treatment. These patients require exceptional attention in the clinical environment many months after acute infection. Thus, past medical history of COVID-19, its course, timing, and complications (including reported cardiovascular complaints) should be a firm part of anamnesis and clinical examination. Updated literature on PASC myocarditis epidemiology and detailed duration, definite (preferably non-invasive) diagnostic pathway, specified pathophysiology, possible treatment options, and prognosis could be highly desired in the current post-COVID era.

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