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Review

Beyond Acute COVID-19: A Review of Long-term Cardiovascular Outcomes

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ABSTRACT

Statistics Canada estimated that approximately 1.4 million Canadians suffer from long COVID. Although cardiovascular changes during acute SARS-CoV-2 infection are well documented, long-term cardiovascular sequelae are less understood. In this review, we sought to characterize adult cardiovascular outcomes in the months after acute COVID-19 illness. In our search we identified reports of outcomes including cardiac dysautonomia, myocarditis, ischemic injuries, and ventricular dysfunction. Even in patients without overt cardiac outcomes, subclinical changes have been observed. Cardiovascular sequelae after SARS-CoV-2 infection can stem from exacerbation of preexisting conditions, ongoing inflammation, or as a result of damage that occurred

RÉSUMÉ

Statistique Canada estime qu'environ 1,4 million de Canadiens souffrent de la COVID-19 de longue durée. Bien que les changements cardiovasculaires au cours de l'infection aiguë par le SRAS-CoV-2 soient bien connus, il en va autrement des séquelles cardiovasculaires à long terme. Dans cette synthèse, nous avons voulu caractériser les conséquences cardiovasculaires chez l'adulte dans les mois qui suivent la phase aiguë de la COVID-2019. Nous avons relevé des études portant sur des cas de dysautonomie cardiaque, de myocardite, de lésions ischémiques et de dysfonction ventriculaire. Même chez les patients sans troubles cardiaques manifestes, des changements subcliniques ont été observés. Les séquelles cardiovasculaires après une

It is well-documented that multiorgan symptoms of SARS-CoV-2 infection can persist after recovery from acute illness. The resulting post-COVID condition, often referred to as long COVID, has emerged as a "postpandemic pandemic." As of August 2022, it is estimated that nearly 15% of COVID-19 survivors, or approximately 1.4 million adult Canadians, are continuing to experience post-COVID symptoms at least 3 months after a confirmed or suspected infection.[1]

Several definitions for postacute sequelae of COVID-19 have been suggested, with long COVID often used as a general term. According to the World Health Organization, post-COVID condition is defined as the presence of post-COVID symptoms that persist past 3 months, last for at least 2 months, and cannot be explained by an alternative diagnosis.[2] The National Institute for Health and Care Excellence in the United Kingdom has divided the postacute COVID-19 period into ongoing symptomatic COVID-19 at 4-12 weeks, and post-COVID syndrome (> 12 weeks).[3] The Centers for Disease Control and Prevention in the United States uses "post-COVID conditions" as an umbrella term and a minimum 4-week post-COVID time frame.[4] Despite slight variation in terminology and definition, all groups recognize that common long COVID symptoms include fatigue, shortness of breath, and cognitive dysfunction. Long COVID can be debilitating, leading to exercise intolerance and inability to return to work,[5] school, and normal living.

To date, there has been no established link between SARS-CoV-2 infection and major long-term cardiovascular risk. However, some epidemiologic evidence suggests that COVID-19 might be associated with long-term increased risk of cardiovascular outcomes.[6,7] The Canadian Cardiovascular Society Rapid Response team suggests consultation with a cardiologist for patients who experience persistent chest pain, shortness of breath, frequent palpitations, or postural lightheadedness > 4 weeks after COVID-19 diagnosis.[8] Because these symptoms are nonspecific and might be related to other conditions, investigations are encouraged to differentiate

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during acute infection. For example, myocardial fibrosis has been reported months after hospital admission for COVID-19 illness, and might be a consequence of myocarditis and myocardial injury during acute disease. In turn, myocardial fibrosis can contribute to further outcomes including dysrhythmias and heart failure. Severity of acute infection might be a risk factor for long-term cardiovascular consequences, however, cardiovascular changes have also been reported in young, healthy individuals who had asymptomatic or mild acute disease. Although evolving evidence suggests that previous SARS-CoV-2 infection might be a risk factor for cardiovascular disease, there is heterogeneity in existing evidence, and some studies are marred by measured and unmeasured confounders. Many investigations have also been limited by relatively short follow-up. Future studies should focus on longer term outcomes (beyond 1 year) and identifying the prevalence of outcomes in different populations on the basis of acute and long COVID disease severity.

infection par le SRAS-CoV-2 peuvent résulter de l'exacerbation de maladies préexistantes, d'une inflammation persistante ou de lésions survenues pendant l'infection aiguë. Par exemple, des cas de fibrose myocardique ont été signalés des mois après l'admission à l'hôpital du fait de la COVID-19 et pourraient être une conséquence de la myocardite et des lésions myocardiques survenues pendant la phase aiguë de la maladie. La fibrose myocardique peut pour sa part entraîner d'autres conséquences, notamment la dysrythmie et l'insuffisance cardiaque. La gravité de l'infection aiguë pourrait être un facteur de risque de problèmes cardiovasculaires à long terme, mais des changements cardiovasculaires ont également été rapportés chez de jeunes individus en bonne santé qui présentaient une maladie aiguë asymptomatique ou bénigne. Bien que de plus en plus de données semblent indiquer qu'une infection antérieure par le SRAS-CoV-2 pourrait être un facteur de risque de maladie cardiovasculaire, il n'existe pas de consensus à cet égard et certaines études comportent des facteurs de confusion mesurés et non mesurés. De nombreuses études sont également limitées du fait d'un suivi relativement court. Les études ultérieures devraient donc se focaliser sur les issues à long terme (au-delà d'un an) et sur la prévalence des complications dans différentes populations sur la base de la gravité de la phase aiguë de l'infection et de la COVID-19 de longue durée.

between cardiac and other etiologies. The incidence and nature of the long-term cardiovascular consequences of COVID-19 have yet to be fully characterized.

In this review, we sought to summarize existing evidence on cardiovascular sequelae after SARS-CoV-2 infection (Fig. 1). Specifically, we focused on outcomes occurring longer than 1 month after acute COVID-19 illness. We also considered a breadth of possible outcomes, even those that are thought to be less often associated with viral respiratory infections. A summary of reports that fulfil the World Health Organization definition of long COVID (symptoms persisting for $\geq$ 3 months) are included in Table 1.

We conducted our literature search in Ovid MEDLINE with a focus on adult populations. To include the broad use of the term, "long COVID," we included studies focused on outcomes occurring at 4 weeks or longer postinfection. Please see Supplemental Appendix S1 for details on our search strategy. In this review we first examine evidence on clinical cardiovascular outcomes observed after acute COVID-19 infection followed by potential mechanisms.

Myocarditis and Pericarditis

Myocarditis

Myocarditis has been observed in the acute phases of COVID-19 illness,[9] raising concerns about long-term myocardial injury. Myocarditis, myocardial inflammation, and myocardial edema have previously been linked to viral infections, but most patients recover from myocardial inflammation within weeks of acute infection and do not suffer long-term consequences.[10] Similarly, myocarditis has been observed in the weeks after acute SARS-CoV-2 infection, with a limited number of studies focused on longer-term outcomes.

Kotecha et al. studied 148 patients who presented with elevated troponin levels during hospitalization for acute SARS-CoV-2 infection. At a median of 68 days (interquartile range [IQR], 39-103) after COVID-19 diagnosis, there was a 27% rate of myocarditis-pattern late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (MRI) consistent with myocarditis. One-third of the patients with myocarditis-pattern LGE showed signs of ongoing active myocardial inflammation. However, regional wall motion and biventricular function remained normal.[10]

In a German study of 100 patients (33% required hospitalization for acute COVID-19 illness), cardiac MRI performed at a median of 71 (IQR, 64-92) days after COVID-19 diagnosis revealed abnormal findings in 78% of patients, including ongoing myocardial inflammation in 60% of patients. LGE was seen in 32% of patients and myocardial native T1 and T2 signals were increased in 73% and 60% of patients, respectively. Findings were independent of preexisting conditions, disease severity, and overall course of the acute illness.[11] Of note, increased native T2 signals are specifically indicative of myocardial edema, which is known to be closely linked to myocarditis.[12] Myocardial edema has also been seen in patients in another study within 1-2 months after recovery from acute SARS-CoV-2 infection.[13]

Post-COVID-19 myocarditis was also investigated in a case series of 14 patients hospitalized for new cardiac symptoms 1-5 months after acute COVID-19 illness. These patients had no history of myocarditis, valvular heart diseases, hypertensive heart disease, nor evidence of coronary artery stenoses $>$ 50%. Myocarditis in these patients was diagnosed in a myocardial biopsy conducted during hospitalization on average at 5.5 months after SARS-CoV-2 infection. Histological findings of lymphocytic myocarditis were observed in 12 patients, eosinophilic myocarditis in 2 patients, and endocarditis in 3 patients. Similar to previously cited studies, these results show that SARS-CoV-2 infection can lead to subacute/chronic myocarditis.[14]

In some cases, post-COVID-19 myocardial inflammation can remain subclinical. From a study of 16 patients

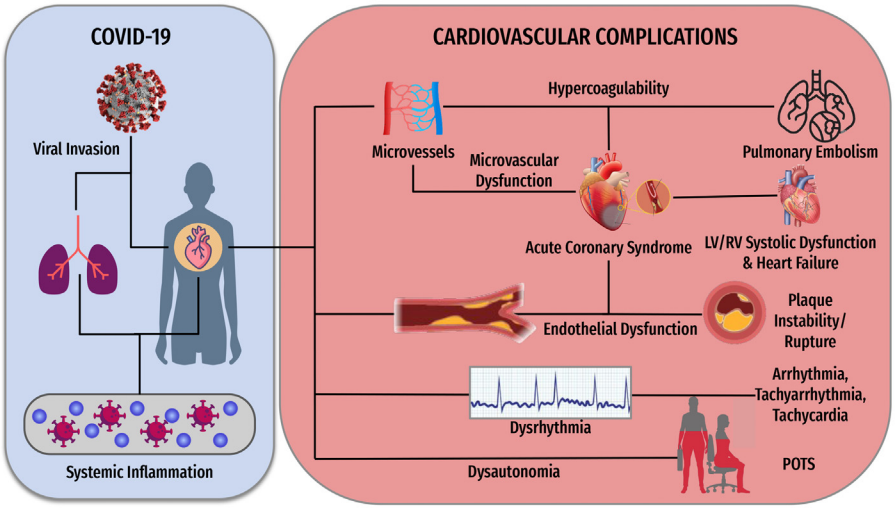

Figure 1. Long-term cardiovascular complications of COVID-19 illness. LV, left ventricle; POTS, postural orthostatic tachycardia syndrome; RV, right ventricle.

hospitalized for acute SARS-CoV-2 infection with raised troponin levels or electrocardiogram (ECG) abnormalities, 56% showed cardiac MRI abnormalities at a median 56 days postacute illness, but only 3 patients (19%) fulfilled Lake Louise Criteria for myocardial inflammation.[15] Of these 3 patients, 2 were asymptomatic, and only 1 showed elevated troponin levels at follow-up. Cardiac MRI can help with myocarditis identification and risk stratification in patients who show initial elevated cardiac biomarkers or ECG abnormalities in the acute phase.[10,16]

There is some evidence of myocarditis in otherwise low-risk individuals, particularly in the early convalescent period after mild acute disease. For example, in an investigation of 26 college athletes who experienced mild or asymptomatic acute COVID-19 illness, cardiac MRI revealed features of myocarditis in 15% of participants at 11-53 days post-infection.[16] In another study of 201 long COVID patients with a low rate of acute COVID-19 hospitalization and comorbidities, there was a 19% rate of myocarditis at a median of 141 (IQR, 110-162) days after infection. Yet, the rate did not reach statistical significance compared with healthy control participants (5.6%; $P = 0.053$). This study identified myocarditis as the presence of 3 or more segments with high T1 signals. Severe long COVID (defined as persistent breathlessness, Dyspnea-12 questionnaire score $\geq$ 10, or **E**uro**Q**ol **5**-**D**imension **5**-**L**evel [EQ-5D-5L] report of moderate or more severe problems with usual activities) was also associated with a significantly greater likelihood of myocarditis compared with moderate disease ($P = 0.027$).[17] However, in a long-term study of 149 health care workers at 6 months postinfection, cardiac MRI revealed no difference in myocarditis-like scarring among patients with previous mild SARS-CoV-2 infection and seronegative control participants.[18]

In addition to cardiac MRI and biopsy, cardiac positron emission tomography (PET) can also help identify cases of myocarditis.[19] In one study, 47 primarily nonhospitalized COVID-19 patients were tested using cardiac focal fluorodeoxyglucose uptake on PET at a mean of 67 $\pm$ 16 days after COVID-19 diagnosis.[20] Results consistent with myocardial inflammation were seen in 17% of patients (n = 8). Although evidence of inflammation was seen from cardiac MRI and blood biomarkers in most of these patients, only 3 individuals met Lake Louise Criteria for myocarditis. As measured during a later follow-up, PET/MRI and inflammatory blood markers resolved or improved after a mean (SD) of 52 (17) days postbaseline. Clark et al. also observed that in cases of myocarditis diagnosed with modified Lake Louise Criteria at a median of 71 days post SARS-CoV-2 detection, subsequent follow-up showed recovery and gradual LGE resolution in 2 of 4 patients; 1 at 119 days and 1 at 245 days.[21] This resolution in LGE suggests that cardiac inflammation present after acute COVID-19 illness might improve over time.

Although several studies have investigated myocarditis-like changes on cardiac MRI after resolution of acute SARS-CoV-2 infection, few studies have used the Lake Louise Criteria for diagnosis. Thus, observed rates of myocarditis in patients with long COVID should be interpreted with caution. Indeed, in studies that have referred to the guidelines, few cases fulfil the criteria even when some cardiac changes are present. In cases in which Lake Louise Criteria is not referenced, the association between myocarditis-like changes and cardiac outcomes is unclear. Specifically, in studies reported in this section that primarily did not reference Lake Louise Criteria, resolution of myocarditis or no mortality was reported. Granted, the follow-up periods in these studies were within 1 year. Despite no significant reductions in cardiac function in post-COVID-19 myocarditis, minor reductions in right ventricular (RV) ejection fraction have been observed in at least 3 studies.[10,13,21] Of these, only the study from Clark et al. reported Lake Louise Criteria.[21]

Pericarditis and pericardial effusion

Isolated pericardial involvement, including pericarditis and pericardial effusion, has not been commonly reported in studies of long-term cardiovascular outcomes after acute

Table 1. Summary of studies of cardiovascular outcomes at 3 months or longer after SARS-CoV-2 infection (reviews and database studies excluded)

Reference	Population	Acute COVID-19 illness severity	Follow-up time frame	Findings of interest	Section(s) with citation
Cohort studies					
Ingul et al.[33]	• n = 204 post-COVID • n = 204 controls • Mean (SD) age: 58.5 (13.6) years • 56% Male	Hospitalized and ICU	Cardiac function assessed at 3-4 months after hospital discharge for acute COVID illness	• Arrhythmias found in 27% of patients, of which 18% were premature ventricular contractions • Post-COVID patients had worse right ventricle free longitudinal strain, lower tricuspid annular plane systolic excursion, and cardiac index compared with controls	Arrhythmias RV dysfunction
Vallejo et al.[37]	• n = 10 who underwent CMR • Mean (SD) age: 44.6 (8.0) years • 20% Male • Patients evaluated in long-COVID unit	Mild to moderate severity	Stress perfusion CMR at mean of 8.2 months (IQR, 3.2-11.4) after infection	• 27% of patients evaluated in long-COVID unit had chest pain • Of 10 patients who underwent CMR, 5 (50%) showed significant circumferential subendocardial perfusion	Ischemic myocardial injuries and microvascular disease
Karagodin et al.[57]	• n = 153 • Median (range) age: 57 (49-66) years • 52% Male • Patients considered if they received a transthoracic echocardiogram during initial COVID-related hospitalization	Hospitalized (32% ICU)	Mean (SD) of 129 (60) days after acute COVID-19 illness	• Patients with hyperdynamic LVEF at baseline showed reduced LVEF at follow up (-8.8%; $P < 0.001$) • Patients with abnormally low LVEF values at baseline showed significant increase by follow-up (+6.7%; $P = 0.02$). • Patients with normal LVLS at baseline showed significant worsening at follow-up (1.2%; $P = 0.006$) • Patients with impaired LVLS at baseline showed significant improvement at follow up (-2.2%; $P < 0.001$) • Patients with abnormal RVLS at baseline had significant improvement by follow-up ($P = 0.004$)	LV and RV dysfunction
Fayol et al.[60]	• n = 48 • Mean (SD) age: 58 (13) years • 69% Male	Hospitalized for symptomatic COVID-19 pneumonia	Echocardiography evaluation 6 ± 1 month posthospitalization for SARS-CoV-2 infection	• E/e′ ratio after low-level exercise was increased in patients who experienced myocardial injury during acute COVID-19 illness compared with those without myocardial injury during acute illness (10.1 ± 4.3 vs 7.3 ± 11.5; $P = 0.01$) • Diastolic abnormalities seen without systolic involvement	LV dysfunction
Hanneman et al.[20]	• n = 47 • Mean (SD) age: 43 (13) years • 49% Male • Patients invited via mail after testing positive for COVID-19 at centre	85% recovered at home	• Baseline PET scan at a mean (SD) of 67 (16) days after COVID-19 diagnosis • Follow-up PET scan 52 (17) days later	• At baseline PET scan, 17% (n = 8) patients had focal FDG uptake, indicative of myocardial inflammation • At follow-up, these patients showed improvements in PET/MRI and blood biomarkers	Myocarditis

Continued

Table 1. Continued.

Reference	Population	Acute COVID-19 illness severity	Follow-up time frame	Findings of interest	Section(s) with citation
Moody et al.[64]	• n = 79 • Mean (SD) age: 57 (11) years • 74% Male • Invited patients who underwent TTE during hospitalization	Hospitalized for COVID-19 pneumonia	Repeat TTE at 3 months after hospitalization for acute COVID illness	Despite resolution of acute abnormalities in ventricular size and function, there was a 29% rate of ongoing adverse ventricular remodelling	RV dysfunction
Raafs et al.[45]	• n = 42 • Mean (SD) age: 64 (13) years • 69% male	ICU hospitalization for severe SARS-CoV-2 infection	6.4 (IQR, 6.1-6.7) months after hospital discharge for SARS-CoV-2 infection	• 8/42 (19%) Had new coronary artery disease diagnosis • Of 38 patients who underwent CMR, 8 (21%) had LGE indicative of myocardial fibrosis	Ischemic myocardial injuries and microvascular disease Myocardial fibrosis
Wu et al.[41]	• n = 13 with cardiac injury during hospitalization • n = 14 controls without cardiac injury during hospitalization • Median (range) age: 63 (58-70) years • 29.6% Male	Hospitalized	Up to 6 months after hospital discharge	Positive LGE from CMR in 29.6% of all patients	Ischemic myocardial injuries and microvascular disease
Ródenas-Alesina et al.[24]	• n = 109 (29 controls) • Median (IQR) age: 55.7 (46.2-66.1) years • 60% Male • Patients admitted to hospital with elevated cardiovascular biomarkers	Severe (hospitalized without mechanical ventilation)	Echocardiograph performed at 4.3 months (IQR, 3.5-5.3) after discharge for acute COVID illness	No pericardial effusion found in any patients with abnormal echocardiography	Pericarditis
Dennis et al.[17]	• n = 201 (36 controls) • Mean (range) age: 45 (21-71) years • 29% Male • Recruited participants with persistent post-COVID symptoms	81% nonhospitalized	Median 141 days (IQR 110-162) after initial COVID-19 symptoms	• Myocarditis seen in 19% of post-COVID patients (compared with 5.6% of healthy controls [note, $P = 0.053$]) • Report of severe post-COVID condition was associated with higher likelihood of myocarditis compared with moderate post-COVID condition (25.0% vs 11.7%; $P = 0.027$) • LVEF and LV end diastolic volume not significantly different for post-COVID patients and healthy controls • Systolic dysfunction was observed in 9% of post-COVID patients	Myocarditis LV dysfunction
Cross-sectional studies					
Durstenfeld et al.[22]	• n = 102 • Median age: 52 years • 59% male • Participants with confirmed SARS-CoV-2 infection were recruited from community	19% Hospitalized	Echocardiogram at a median of 7.2 months (IQR, 4.1-9.1) after SARS-CoV-2 infection	n = 4 patients (9%) with cardiopulmonary symptoms (dyspnea, chest pain, palpitations) had evidence of pericardial effusion, compared with 0 patients without symptoms (note, $P = 0.11$)	Pericarditis

Petersen et al.[34]	• n = 443 post-COVID cases • n = 1328 matched controls • Median (IQR) age of cases: 55 (51-60) years • 47.4% Male • Post-COVID patients were invited after identification in clinical information system	Mild to moderate severity (nonhospitalized)	Median 9.6 months after a positive SARS-CoV-2 test	Compared with controls, post-COVID patients showed: - Longer QT intervals but not other ECG abnormalities - Trend of increased focal myocardial fibrosis, but comparable diffuse myocardial fibrosis - Lower LV and RV function higher hs-cTnI, NT-proBNP	Arrhythmias Myocardial fibrosis LV dysfunction
Akkaya et al.[62]	• n = 105 post-COVID cases • n = 105 controls • Mean (SD) age: 43.5 (12.5) years • 60.9% Male • Previously treated COVID-19 outpatients	Mild (outpatient, nonhospitalized, with fever, muscle and/or joint pain, cough, sore throat, no respiratory distress)	Echocardiography at 3 months after COVID-19 diagnosis	Decrease in RV GLS, RV FWLS, and TAPSE negatively correlated with levels of C-reactive protein, neutrophil to lymphocyte ratio, d-dimer, ferritin, and platelet to lymphocyte ratio during acute phase of SARS-CoV-2 infection	RV dysfunction
Case-control studies					
Joy et al.[18]	• n = 74 seropositive • n = 75 matched controls • Median (range) age: 37 (18-63) years • 42% male • Participants recruited from prospective study on health care workers	Mild (ranging from asymptomatic to symptoms of fever, dry cough, anosmia, ageusia, dysgeusia)	Cardiovascular phenotyping at 6 months 9 days (IQR, 5 months 26 days to 6 months 20 days) after SARS-CoV-2 infection	No difference for seropositive patients and controls in: - Late gadolinium enhancement - T1 and T2 signals - Myocarditis-like scarring	Myocarditis
Clark et al.[21]	• n = 50 cases with cardiopulmonary symptoms • n = 50 controls • Median (IQR) age of cases: 26.5 (23-31) years • 98% Male • Soldiers referred for CMR for cardiopulmonary symptoms after COVID-19 (eg, abnormal ECG, chest pain)	• 4% Mild • 86% Moderate • 10% Hospitalized	Initial CMR conducted at a median of 71 days post SARS-CoV-2 detection Myocarditis cases from initial CMR underwent first follow-up CMR at a range of 82-122 days, and second follow-up CMR at a range of 119- 271 days	At first CMR: - 11 cases (22%) had myocardial LGE - 4 cases (8%) diagnosed with myocarditis At follow-up CMR: - 2/4 myocarditis cases had complete resolution (119 and 245 days post-SARS-CoV-2 detection)	Myocarditis
Case series					
Blagova et al.[14]	• n = 14 (2 patients postvaccine) • Mean (SD) age: 50.1 (10.2) years • 64% Male • Patients admitted for new cardiac symptoms after COVID-19 infection	Unreported	Cardiac symptoms appeared 1-5 months after SARS-CoV-2 infection	• Lymphocytic myocarditis in 12 (86%) patients • Eosinophilic myocarditis in 2 (14%) patients • Endocarditis in 3 (21%) patients	Myocarditis
Blitshteyn and Whitelaw[5]	• n = 20 • 70% female • Median (range) age: 40 (25-65) years • Chart review of patients referred to dysautonomia clinic (had no previous orthostatic intolerance)	Mild or nonhospitalized	Residual autonomic symptoms 6-8 months after SARS-CoV-2 infection	• 85% had residual self-reported autonomic symptoms 6-8 months after COVID-19 infection • 12 (60%) unable to return to work because of symptoms • 15 (75%) had POTS diagnosed after COVID-19 infection	POTS

CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; E/e′, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; FDG, fluorodeoxyglucose; FWLS, free wall longitudinal strain; GLS, global longitudinal strain; hs-cTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVLS, left ventricular longitudinal strain; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; PET, positron emission tomography; POTS, postural orthostatic tachycardia syndrome; RV, right ventricular; RVLS, right ventricular longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.

COVID-19 illness. Durstenfeld et al. showed that 9% of patients with cardiopulmonary symptoms including dyspnea, chest pain, and palpitation 7.2 months after initial SARS-CoV-2 infection had trace pericardial effusion measured using echocardiography. None of these patients had comorbidities that would increase the risk of pericardial effusion development. However, no echocardiographic signs of significant hemodynamic changes were observed among these cases.[22] Other studies have shown no evidence of pericardial effusion in any participants during follow-up for acute COVID-19 illness.[23,24]

Cardiac Dysautonomia and Arrhythmias

Inappropriate sinus tachycardia and bradycardia

Tachycardia is one of the more commonly observed cardiovascular symptoms after acute COVID-19 illness. Indeed, post-COVID tachycardia syndrome has been proposed as a subsyndrome of long COVID, and might present as inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia syndrome (POTS) after acute illness.[25] Aranyó et al. reported that 20% of 200 long COVID patients met the diagnostic criteria for IST (83% had mild acute infection).[26] Decreased heart rate variability (HRV) parameters were seen in patients with IST. Decreased HRV might be associated with other long-term cardiovascular complications including coronary insufficiency and coronary heart disease.[27] IST and decreased HRV can be attributed to an autonomic nervous system imbalance and decreased parasympathetic nervous system activity, compensated by increased sympathetic nervous system activation.[26] In a similar study of long COVID patients using 24-hour Holter monitoring, the low frequency to high frequency ratio, which reflects the sympathovagal balance, was higher in COVID-19 patients with decreased HRV and therefore higher sympathetic activity due to dysautonomia.[28]

Multiple studies have suggested that prevalence of sinus tachycardia and bradycardia are increased after acute COVID-19 illness. These changes can be transient or sustained,[29] with resolution observed in long-term follow-up. For example, a study from Hong Kong showed significant bradycardia (heart rate $<$ 50 beats per minute) in 7.2% of 97 patients at 1-4 weeks postdischarge, but changes resolved several weeks later.[30]

POTS

Evidence suggests that even healthy patients with relatively mild or asymptomatic infection might develop POTS months after COVID-19 diagnosis. In a case series of 20 patients who presented with autonomic symptoms after acute COVID-19 illness, 15 were diagnosed with POTS.[5] At 6-8 months after SARS-CoV-2 infection, 85% of all patients self-reported residual autonomic symptoms such as dizziness, syncope, and palpitations, with 60% unable to return to work. Some long COVID patients also present with POTS alongside orthostatic intolerance, and experience overlapping symptoms such as tachycardia, dizziness, and cognitive dysfunction.[31]

In 2021, Nalbandian et al. showed that autonomic dysfunction and POTS after viral illness are associated with irregular adrenergic modulation.[32] This in turn might disrupt normal blood pressure regulation and lead to the symptoms associated with these syndromes.

Arrhythmias

Patients with a wide range of demographic characteristics and severity of acute COVID-19 disease have shown increased incidence of arrhythmias in the months after infection. A database study of $>$ 150,000 COVID-19 patients showed that postinfection patients had a higher incidence of dysrhythmias 12 months after a positive COVID-19 test than healthy control participants. Increased risks included sinus tachycardia (hazard ratio [HR], 1.84 [95% confidence interval (CI), 1.74-1.95]), atrial fibrillation (HR, 1.71 [95% CI, 1.64-1.79]), atrial flutter (HR, 1.80 [95% CI, 1.66-1.96]), ventricular arrhythmias (HR, 1.84 [95% CI, 1.72-1.98]), and sinus bradycardia (HR, 1.53 [95% CI, 1.45-1.62]).[7] In a study of 204 patients hospitalized for severe acute COVID-19 illness, arrhythmias were found in 27% of patients at 3-4 months postdischarge, with premature ventricular contractions (18%) being the most common.[33]

Although patients with severe acute infection might be predisposed to a risk of arrhythmias, reports have shown that relatively mild acute COVID-19 disease can also be associated with rate and rhythm abnormalities after acute COVID-19 illness.[30,34] A screening of 97 patients after nonsevere acute COVID-19 illness showed rhythm abnormalities in one-third of patients at 3-4 months postinfection, including sinus bradycardia (29.9%), and new onset atrial fibrillation (1%).[30] An investigation of 443 primarily nonhospitalized patients showed longer corrected QT intervals but no difference in other rhythm abnormalities compared with control participants at a median of 9.6 months after acute illness.[34]

Promisingly, risk of post-COVID arrhythmias decreases over time after initial infection. One matched cohort study of $>$ 400,000 COVID-19 patients without cardiovascular diseases showed increased incidence of atrial arrhythmias in the acute phase (1-4 weeks) after infection (adjusted rate ratio [RR], 6.44 [95% CI, 4.17-9.96]), but incidence decreased between 5 and 12 weeks (RR, 1.58 [95% CI,1.10-2.27]), and further by 13 weeks and onward (RR, 0.85 [95% CI, 0.68-1.05]).[35] This suggests that patients are most at risk of developing arrhythmias shortly after SARS-CoV-2 infection.

With regard to mechanisms of action, myocardial fibrosis and resultant cardiomyopathy from infection have been suggested to lead to reentrant arrhythmias. It is also suggested that cytokine release (interleukin [IL]-6, IL-1, tumour necrosis factor α) can increase catecholaminergic states. This might worsen existing arrhythmias by changing cardiomyocyte ion channel expression and thus extending ventricular action potentials.[32]

Ischemic Myocardial Injuries and Microvascular Disease

Approximately 20%-30% of patients experience chest pain, including angina-like chest discomfort, as a post-COVID-19 symptom.[36-38] Although post-COVID-19 chest pain might be explained in part by noncardiac causes including anxiety, musculoskeletal, and pulmonary factors, myocardial injuries might also be present. Although

myocardial infarction has been observed in the acute phase of COVID-19 illness,[39] fewer studies have focused on cardiac ischemic disease in the postacute period.[40]

Possible mechanisms for myocardial injury and microvascular dysfunction in COVID-19 illness include direct damage by SARS-COV-2 on the myocardium, general inflammation and cytokine storm, and a hypercoagulable state.[41] The hypercoagulable state induced by SARS-CoV-2 promotes endothelial damage and plaque rupture, increasing the risk of myocardial infarction and coronary thrombosis.[39]

Predictors of myocardial injury after SARS-CoV-2 infection have been examined. Troponin T level during acute illness has been shown to be a predictor for recovery and long-term cardiac sequelae in patients who had an episode of acute cardiac injury during hospitalization for acute COVID-19.[42,43] Additionally, the association between SARS-CoV-2 infection and myocardial injury corresponds to the severity of acute COVID-19 illness.[44] This association might also be relevant in the context of long COVID.

Indeed, cardiac ischemic findings have been observed after hospitalization for severe COVID-19 illness. In a study of patients admitted to the intensive care unit (ICU) who received mechanical ventilation during their acute COVID-19 illness, 19% had newly diagnosed coronary artery disease 6 months after ICU admission.[45] In another study of patients who were hospitalized with severe SARS-CoV-2 infection and presented with elevated troponin levels on admission, 26% showed ischemic-pattern findings on a follow-up cardiac MRI 2 months after hospitalization.[10] Of these patients, 95% had at least 1 cardiovascular risk factor, but 66% had no history of ischemic heart disease and this was their first presentation of coronary artery disease. Nevertheless, because most patients had risk factors, it is possible that tachycardia, fever, and hypoxia during acute COVID-19 illness unmasked preexisting, previously compensated, coronary artery disease and resulted in ischemic injuries.[10]

Other studies have not shown overt ischemic changes after acute COVID-19 illness. For example, Ródenas-Alesina and colleagues investigated myocardial infarction and mortality outcomes in COVID-19 patients with no previous cardiovascular disease at 7 months posthospitalization.[24] The authors showed no difference in outcomes among those who were initially admitted with elevated high-sensitivity troponin (> 45 ng/L) compared with those without.

However, even when overt ischemic changes are not observed, other underlying changes might be present. In one study patients with no history of cardiovascular disease who experienced chest pain and were referred to a long COVID outpatient clinic were examined.[37] Despite the absence of any ischemic patterns and myocardial T1 and T2 mapping changes, adenosine stress perfusion cardiac MRI showed significant circumferential subendocardial perfusion defect in 50% of cases over 8 months after SARS-CoV-2 infection. This is highly suggestive of microvascular dysfunction. Similarly, Wu et al. investigated patients without a history of coronary heart disease who suffered from cardiac injury during the acute phase of COVID-19 illness.[41] Patients returned to normal cardiac function within a 6-month follow-up. However, cardiac MRI revealed a significantly higher proportion in positive LGE in the cardiac injury group compared with control participants, suggestive of myocardial fibrosis. Fibrosis after SARS-CoV-2 infection can result from myocardial damage during acute illness,[41] but previous studies on SARS-CoV-1 also show fibrosis might be associated with changing transforming growth factor β signalling.[46]

Myocardial Fibrosis

Acute myocardial injury, including ischemic myocardial involvement and myocarditis, can lead to myocardial fibrosis after recovery from acute SARS-CoV-2 infection.[47] Indeed, several studies have reported that approximately 20%-30% of their patient populations experience myocardial fibrosis after recovery from acute SARS-CoV-2 infection.[47,48] For example, in a prospective study of 159 patients hospitalized with COVID-19, Morrow et al. reported that 1 in 5 patients had evidence of myocardial fibrosis 28-60 days postdischarge.[47] Similarly, 21% of patients in another investigation were observed to have LGE indicative of myocardial fibrosis 6 months after ICU admission.[45] Interestingly, a third study showed a trend of increased focal myocardial fibrosis among primarily nonhospitalized COVID-19 survivors, yet findings of diffuse myocardial fibrosis were comparable with the control group.[34]

Cardiomyopathy

Increased risk of cardiomyopathy has been reported after acute COVID-19 illness, notably in large database studies.[7,49] Among > 150,000 individuals, the risk of ischemic and nonischemic cardiomyopathy was higher in SARS-CoV-2-positive individuals (30 days after positive test) than in noninfected control participants (HR, 1.75 [95% CI, 1.44-2.13] and HR, 1.62 [95% CI, 1.52-1.73], respectively.[7] A similar conclusion was reached in a study of > 690,000 nonvaccinated individuals who tested positive for COVID-19, with an increased risk of ischemic cardiomyopathy (HR, 2.81 [95% CI, 2.48-3.19]) 1-12 months after a positive COVID-19 test.[49] Ischemic cardiomyopathy was ranked within the top 2 cardiovascular risks (HR, 2.81 [95% CI, 2.48-3.19]) after COVID-19 illness for all age categories, and was more pronounced in women.[49]

It is difficult to disentangle the effect of direct viral infection from pandemic-related stress when examining cardiovascular effects after acute COVID-19 illness. Notably, a retrospective study of 1914 patients showed that among those who presented with acute coronary syndrome, there was a greater incidence of cardiomyopathy during the pandemic (March to April 2020) than before the pandemic (rate ratio, 4.58 [95% CI, 4.11-5.11]). There is speculation that this finding relates to pandemic-associated anxiety, because all patients diagnosed with cardiomyopathy tested negative for COVID-19 on admission.[50] This finding raises an important consideration regarding the etiology of many cardiovascular sequelae of acute COVID-19 infection, including stress cardiomyopathy.

Cardiac Dysfunction and Heart Failure

There is some evidence suggestive of an increased risk of heart failure beyond the first 30 days after SARS-CoV-2

infection.[7] Although the risk is not limited to hospitalized patients, patients admitted to ICUs have the greatest risk, followed by hospitalized non-ICU patients and nonhospitalized patients.[7] The effect of COVID-19 disease on heart failure might be due to the long-term effects of SARS-CoV-2 on cardiac function, residual adverse effects of cardiac involvement in the acute COVID-phase, or the worsening of previous cardiovascular disease postinfection.

Patients with underlying conditions might be particularly at risk of cardiovascular complications after acute COVID-19 illness. In patients with a history of ST-elevation myocardial infarction, there were higher rates of major cardiovascular and cerebrovascular events and hospitalization with heart failure among those who tested positive for COVID-19 vs those who did not. However, there was no difference in long-term mortality in ST-elevation myocardial infarction patients with or without a COVID-19 infection.[51]

Some studies have not shown evidence of cardiac dysfunction after acute COVID-19 illness. In a cross-sectional study of 105 patients who were hospitalized for COVID-19, structural and functional cardiac characteristics on echocardiography were similar to matched control participants at a median of 41 days from COVID-19 diagnosis.[52] Findings were also similar in patients who experienced severe and mild acute COVID-19 illness. In another short-term study, normal left ventricular (LV) and RV function on echocardiography was reported in most patients 6 weeks after discharge from hospital because of SARS-CoV-2 infection.[53] The normal findings in these studies might be because of the short duration of follow-up (< 2 months). Indeed, although subclinical myocardial injury might appear early on, later changes in cardiac function like diastolic dysfunction can present. It has been reported that although cardiac MRI and ECG changes are often observed within the first 3 months after SARS-CoV-2 infection, echocardiography changes often present in 3-6 months.[54]

LV dysfunction

LV dysfunction has been observed after acute COVID-19 illness. Indeed, several studies have observed statistically significant reductions in LV ejection fraction (LVEF) compared with controls 2-9 months after acute COVID-19 illness, including patients with acute disease ranging from asymptomatic to severe.[11,34] Moreover, congestive heart failure and a prominent reduction in LVEF (mean LVEF 28%) has been observed in patients with biopsy-proven post-COVID-19 myocarditis at an average of 5.5 months after COVID-19 infection.[14] There are also reports of subclinical LV dysfunction after COVID-19 diagnosis among patients at low cardiac risk who reported their SARS-CoV-2 infection as asymptomatic and recovered from acute symptoms at home.[55]

In other cases, echocardiography testing has not shown changes in ejection fraction after acute SARS-CoV-2 infection. For example, in a study of COVID-19 patients with no previous cardiovascular disease who presented with elevated cardiovascular biomarkers on admission, there was no difference in LVEF, LV diameters, LV mass, or left atrial volumes on echocardiograms performed at a median of 4.3 months after discharge compared with those without elevated markers.[24] None of the patients died or were admitted because of heart failure at their median 7-month follow-up. In their study of 201 long COVID patients with a low rate of acute COVID-19 hospitalization and comorbidities, Dennis et al. reported LVEF and LV end diastolic volume were not significantly different among long COVID patients and healthy control participants.[17] Similarly, although Lassen et al. showed a reduction in LVEF 2 months after hospitalization for acute COVID-19 illness, it was not significantly different from the control group.[56]

A possible explanation for null LVEF findings is that LVEF testing might not be sensitive enough to detect cases of minor LV impairments. Studies show that measurement of LV longitudinal strain (LVLS) has a greater sensitivity for detecting minor LV myocardial function impairment compared with measurement of LVEF.[57-59] This difference can be explained by the fact that LVEF is dependent on myocardial function and volume load, whereas LVLS is affected mostly by myocardial function.[57] In a cohort of 153 hospitalized patients who received an echocardiogram at baseline and at a mean follow-up of 129 days, a pattern of normalization and regression to mean in LVEF was shown.[57] LVEF decreased in those with an elevated baseline LVEF (which could be due to an adaptive physiological response to stress during acute COVID-19 illness), those with reduced baseline LVEF improved at follow-up, whereas those with normal baseline LVEF remained normal. However, results from LVLS showed a reduction in those with normal baseline measures, potentially revealing a higher sensitivity of LVLS measurement to LV impairment.[57]

In addition to LV systolic dysfunction, LV diastolic dysfunction has also been reported. One study among patients who experienced myocardial injury during the acute COVID-19 illness showed significant cardiac diastolic abnormalities without systolic involvement 6 months after hospitalization.[60] Resting echocardiographic results were similar among those who had myocardial injury and elevated cardiac markers in the acute phase vs those who did not. However, exercise induced an increased E/e′ ratio (the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; an indicator of LV filling pressure) and systolic pulmonary artery pressure in the patients who had myocardial injury during acute COVID-19 illness, compared with those without myocardial injury. The changes in LV diastolic markers were not associated with cardiovascular risk factors, leaving COVID-19 illness as a potential cause. It is suggested that the increased E/e′ ratio post-COVID is due to the myocardial inflammation that can initiate tissue fibrosis and stiffness. This change can affect cardiac relaxation and diastolic function in the long term.[60]

RV dysfunction

There is evidence suggesting particular susceptibility to RV dysfunction after acute COVID-19 illness.[57,61] This might be explained by the effect of virus-induced lung injury and pulmonary vascular resistance on the right ventricle.[56,57] Indeed, multiple studies have shown evidence of RV dysfunction 3-9 months after recovery from acute SARS-CoV-2 infection.[33,34,62] Dysfunction has been shown with reduction in RV global longitudinal strain, RV free wall longitudinal strain, and tricuspid annular plane systolic excursion.[33,34,62]

Additionally, Maestre-Muñiz et al. observed 2.7% right heart failure in a study of patients 1 year posthospitalization for SARS-CoV-2 infection. This finding was not associated with previous cardiac risk factors, with new onset hypertension, nor with left heart failure.[63] Meanwhile, other studies have shown that echocardiographic measures of RV function such as tricuspid annular plane systolic excursion and RV longitudinal strain improve after the resolution of acute COVID-19 illness.[56,57] Despite resolution of acute abnormalities in ventricular size or function, a 29% rate of persistent adverse ventricular remodelling has been observed at 3 months after hospitalization.[64]

Different explanations have been proposed for the development of RV dysfunction after acute COVID-19 illness. Akkaya et al. reported a decrease in RV global longitudinal strain and RV free wall longitudinal strain at 3 months was negatively correlated with acute-phase levels of C-reactive protein, neutrophil to lymphocyte ratio, d-dimer, ferritin, and platelet to lymphocyte ratio. These markers are indicators of inflammation and thrombosis, and point to the possible pathology behind RV dysfunction, including a combination of reduced contractility due to myocardial damage and increased RV afterload. This study also showed an increase in RV diameter and systolic pulmonary artery pressure at 3 months after COVID infection, suggesting the same mechanism.[62]

However, RV dysfunction has also been shown in cases without increased afterload. In an Italian study of hospitalized patients with no history of cardiovascular or lung disease who recovered from severe acute COVID-19 illness, subclinical RV dysfunction by abnormal RV longitudinal strain was found without any evidence of pulmonary hypertension (PH) or increased RV afterload in 42% of patients 2-3 months post COVID infection.[65] The incidence of RV dysfunction without increased afterload might point to reduced contractility as the main potential mechanism.

New Onset Hypertension

New onset hypertension has been observed after acute COVID-19 illness. For example, of 543 patients who were hospitalized or discharged from an emergency department for COVID-19, 12 (2.2%) had onset of high blood pressure in the following year.[63] However, because no control group was included, it is unclear whether this incidence exceeds expected levels. Further, this finding might relate to pandemic stress rather than SARS-CoV-2 infection. Another study showed that 1.3% of patients (n = 538) developed hypertension by approximately 3 months after hospital discharge for COVID-19.[66] Although comparison with control participants did not reach statistical significance ($P = 0.2$), none of the patients in the control group (n = 184) developed hypertension in the same time frame. Neither study formally evaluated new onset hypertension through repetitive blood pressure measurements, and instead relied primarily on medical records and patient report.

It is concerning that new onset hypertension has been observed even among young and previously healthy patients. One study of young adults (mean age: 21 [SD, 20-22] years) showed a prolonged effect on systolic and mean arterial blood pressure after acute COVID-19 illness, with gradual improvements 6 months postinfection (eg, mean systolic pressure at 1 month postinfection: 112 [± 7] mm Hg vs at 6 months: 101 [± 8] mm Hg; $P = 0.008$).[67] New onset hypertension has also been diagnosed in healthy adolescents in the months after mild COVID-19 illness.[68]

Of interest, an observational study of blood pressure 12 months or more after SARS-CoV-2 infection is currently under way (**Lo**nger-term Effects of SARS-**C**oV-2 **In**fection on Blood **V**essels **a**nd Blood P**r**essure [LOCHINVAR; NCT05087290].[69,70] This investigation extends a pilot study that showed patients hospitalized for COVID-19 had an average 8.6-mm Hg increase in blood pressure after SARS-CoV-2 infection compared with control participants 12 or more weeks after discharge (NCT04409847).[70]

Pulmonary Hypertension

Although evidence remains limited, some recent studies have reported PH after acute COVID-19 illness. Tudoran and colleagues reported that of 91 patients hospitalized for moderate COVID-19, 7 patients (7.69%) were diagnosed with PH 2 months after discharge.[71] Notably, all patients were younger than 55 years of age, had no history of cardiovascular pathology, and did not require mechanical ventilation during hospitalization. Development of PH in the 6-12 weeks after relatively severe COVID-19 illness has also been described in case reports.[72-74]

Several pathologies might explain predisposition to PH after recovery from acute SARS-CoV-2 infection. Thickening of pulmonary arterial walls has been observed histologically in patients who died of COVID-19,[75] revealing potential susceptibility of COVID-19 patients to future pulmonary arterial hypertension. Development of PH after acute COVID-19 illness has also been linked to increased inflammatory markers during hospitalization,[71] with endothelin upregulation proposed as a promoter of PH development.[76] Post-COVID PH has also been linked to pulmonary damage and vascular remodelling.[77,78] COVID-19 illness and PH share similar molecular features including endothelial and mitochondrial dysfunction.[78]

Potential Mechanisms

There are several proposed mechanisms regarding the development of cardiovascular outcomes after acute COVID-19 illness. Regarding acute SARS-CoV-2 infection, one of the main proposed mechanisms for development of cardiovascular complications is the angiotensin converting enzyme 2 (ACE2) and its interactions with the renin-aldosterone system (RAAS) and kinin-kallikrein system (KKS). The ACE2 receptor is expressed throughout the body, and is present in approximately 7.55% of myocytes.[79] It is expressed in the heart,[80] lungs, endothelium of blood vessels,[81,82] and neurons.[32] The S1 subunit of the SARS-CoV-2 spike protein binds the ACE2 receptor on the cell surface and allows the virus to enter the cell membrane. This results in a downregulation of the ACE2 receptor.[83-85]

Typically, the RAAS pathway begins with renin and produces angiotensin II. Angiotensin II functions with angiotensin type-1 receptor to induce vasoconstriction, fibrosis, and apoptosis, as well as to elevate blood pressure, facilitate cardiac hypertrophy, and increase heart rate.[86] ACE2 converts

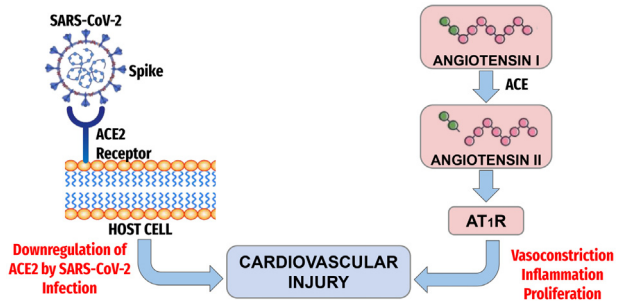

Figure 2. Schematic of a possible mechanisms for downregulation of angiotensin-converting enzyme II (ACE2) by SARS-CoV-2 infection and its downstream consequences. AT_1R, angiotensin type-1 receptor.

angiotensin II to Ang 1-7 and Ang 1-9 which further interact with G-protein coupled receptors to have the opposite effect of angiotensin II. This allows for a balanced activation and deactivation response. SARS-CoV-2 infection leads to negative regulation of the ACE2 receptor, causing angiotensin II accumulation and hemostatic imbalance through activation of the coagulation cascade, impaired fibrinolysis, and thrombin generation (Fig. 2).[87]

Another downstream product of inflammatory pathways is the bradykinin storm of KKS, which normally causes vasodilation and regulates tissue repair, inflammation, cell proliferation, and platelet aggregation. Kallikreins serine proteases cleave kininogens to release bradykinin and kallidin. Downstream, they activate bradykinin-1 and bradykinin-2 receptors to increase blood flow and have antithrombogenic effects. ACE2 mediates the conversions in this pathway as well, meaning downregulation of ACE2 during SARS-CoV-2 infection prevents the counterbalancing action of the KKS system.[88] The RAAS and KKS pathways affect blood pressure, fluid and electrolyte balance, and cardiac function.[88,89] Excessive pressure increase and constriction of blood vessels can increase the risk of chronic hypertension and thrombosis. In the peripheral blood vessels, pressure and constriction causes an afterload on the heart.[90] Furthermore, the potential of the RAAS and KKS pathways to induce a cytokine or bradykinin storm has been proposed as a mechanism for the development of cardiovascular consequences of long COVID.[88]

Activation of $CD4^+$ T cells by viral infection can also cause the release of proinflammatory cytokines and interferon. Particularly, IL-6 and tumour necrosis factor α induce the cytokine storm. Hyperinflammation creates a feedback cycle of tissue damage, stimulating greater inflammatory response.[88] The response might also involve the toll-like receptor 4 (TLR4) cell surface immune receptor. The SARS-CoV-2 spike glycoprotein has been shown to have high protein-protein affinity to TLR4.[81] TLR4 activation can cause myocarditis and multiple organ injury through overactivation and hyperinflammation.[81] A prolonged version of this reaction is a proposed mechanism for long COVID. TLR4 receptors are also present on activated $CD4^+$ and $CD8^+$ T cells and can induce inflammatory cytokines. A dysregulation of the adaptive immune system, particularly involving $CD4^+$ and $CD8^+$ T-cell exhaustion or upregulation, could cause long COVID symptoms,[91,92] and increased risk of blood clots.[93] Evidence of this was shown among 25 convalescent COVID-19 survivors during longitudinal follow-up.[94] Their $CD8^+$ T lymphocytes returned to normal 4 months after symptom onset whereas $CD4^+$ lymphocytes remained low in half of the patients.

Lingering vasculopathy after acute SARS-CoV-2 infection can also lead to long-term cardiovascular complications. The endothelium of tissues serves as a barrier, has antithrombotic properties, and contributes to vascular tone. Inflammation of the endothelium (endotheliopathy) can negatively affect these functions. In the heart, this can induce thrombosis and myocardial injury leading to reduced functionality.[95] Endothelial dysfunction begins during the acute infection but has been observed at 6 months postinfection.[96] In a study of 80 individuals with long COVID symptoms, all participants had micro clots in their samples, suggestive of endotheliopathy and a disrupted clotting state.[97] Circulating endothelial cells have also been measured in post-COVID patients, indicating that vessel injury is persistent in those recovering from viral infection.[98]

Mitochondrial stress response is another proposed mechanism to explain long COVID symptoms. Significantly altered levels of proteins originating from the mitochondria have been observed at 40 days after SARS-CoV-2 infection, suggestive of continued mitochondrial stress.[99] When under stress, impaired mitochondrial function reduces metabolism and increases cardiomyocyte fatigue. Consequently, cardiac systolic and isovolumic times increase, reducing cardiac performance.[19]

Viral load might also be associated with development of long COVID. In the acute phase, high viral loads have been shown in the myocardium, and have been associated with increased cytokine levels.[100] Persistence of viral reservoirs might lead to chronic inflammation and has been proposed as a potential explanation for ongoing cardiac symptoms after acute illness.[29] Resultant chemokines might cause damage via reactive oxidative species and lead to prolonged long COVID pathology.

Some studies have also shown an association of higher antibody levels against SARS-CoV-2 and cardiopulmonary symptoms in long COVID patients. Cardiopulmonary symptoms have been more closely associated with antibody levels rather than with myocardial dysfunction and injury, because troponin levels were low or undetectable at a median of 7.2 months after SARS-CoV-2 infection.[22] Another proposed mechanism suggests that autoantibodies alongside localized inflammation might be involved in microvascular thrombosis leading to exacerbated long COVID symptoms.[101]

Many sequelae of postacute COVID-19 illness can also be considered as associated with the cardiometabolic syndrome, yet the exact nature of the association is unclear. Prolonged inflammation and tissue damage from acute infection have been suggested as promoters of cardiometabolic syndrome-associated diseases that occur after COVID-19 illness, including diabetes and heart failure.[102] For example, the long-established link of inflammation and expansion of atherosclerotic plaque might explain development of atherosclerosis among patients who have recovered from acute SARS-CoV-2 infection.[103] Although there is a lack of evidence on hyperlipidemia in the post-COVID period, evidence of abnormal

lipid levels has been observed in patients more than a decade after the emergence of SARS-CoV-1 in 2002.[104] This evidence, combined with findings of lipid dysregulation during the acute phase of SARS-CoV-2 infection,[105] raise concerns about the potential long-term effects of COVID-19 on lipid metabolism. Further research is needed to elucidate the connection of cardiometabolic syndrome-associated diseases after acute COVID-19 disease.

Conclusion

This review highlights evolving evidence on the potential cardiovascular complications after recovery from acute COVID-19 illness, as well as proposed underlying mechanisms. Cardiovascular complications might arise from damage during acute infection, outcomes resulting from ongoing inflammation, and exacerbation of preexisting conditions. Commonly reported outcomes include ischemic and non-ischemia myocardial injury, cardiac dysfunction, arrhythmias, and dysautonomia. Of concern, long-term outcomes including myocarditis and POTS have been observed in otherwise low-risk patients who experienced mild disease, highlighting the need for vigilance even in young, healthy populations. Although some studies show improvement over time, continued follow-up with long COVID patients will be needed to better characterize long-term outcomes.

This review adds to the growing body of literature summarizing postacute cardiovascular outcomes of COVID-19, with a focus on outcomes occurring more than 1 month after acute illness. In organizing our review according to specific outcomes, we draw attention to the breadth of potential cardiovascular complications. Although current evidence remains limited in quantity and quality, we hope this review will encourage clinicians to be mindful of potential cardiovascular risks and can serve as a starting point for future investigations.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2023.01.031.