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Post-acute Cardiovascular Sequelae of COVID-19: an Overview of Functional and Imaging Insights

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Abstract

Purpose of Review To evaluate the potential role of advanced cardiac imaging and cardiopulmonary exercise testing in the diagnosis and evaluation of persistent cardiovascular conditions after SARS-CoV-2 infection.

Recent Findings SARS-COV-2 has shown an overwhelming capacity to attack multiple organs, with the respiratory system being the most frequently involved. However, various cardiovascular complications have been reported during the course of the disease, becoming one of the most important causes of morbidity and mortality. Many articles have addressed the acute cardiovascular complications of SARS-CoV-2; however, chronic cardiovascular conditions that persist beyond acute infection are less well studied. Echocardiography has a role during the initial approach, but advanced cardiac images such as cardiac magnetic resonance and cardiac CT can be required since a normal echo finding does not exclude cardiovascular involvement. Cardiopulmonary exercise testing has proven to be a highly valuable tool in cases where the symptoms persist besides normal advanced images.

Summary The present review includes the most relevant articles regarding the use of cardiac imaging and cardiopulmonary exercise testing in the evaluation of chronic cardiovascular manifestations of COVID-19.

Keywords Cardiac magnetic resonance · Transthoracic echocardiogram · Cardiopulmonary exercise testing · Cardiac tomography · Post-COVID sequelae · Post-COVID dysautonomia

Abbreviations

ACE	Angiotensin-converting enzyme
CAC	Coronary artery calcium
COVID-19	Coronavirus disease of 2019
PASC	Post-acute sequelae of COVID-19
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise testing
ECHO	Echocardiogram
WHO	World Health Organization
SARS-COV-2	Acute respiratory syndrome coronavirus-2
POTS	Postural orthostatic tachycardia
LV	Left ventricle
LVEF	Left ventricle ejection fraction
HF	Heart failure
CCT	Cardiac computed tomography
DE-CTPA	Dual-energy CT pulmonary angiography
NICE	United Kingdom National Institute for Health and Care Excellence
TAPSE	Tricuspid annular plane systolic excursion
ECV	Extracellular volume
HU	Hounsfield units

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Introduction

Since its appearance at the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has generated the biggest outbreak of the last century, and it is one of the most widely documented diseases in

all human history. As of February 2023, there have been 755,041,562 confirmed cases of COVID-19, including 6,830,867 deaths, reported by the WHO COVID-19 Dashboard [1]. Although the respiratory system is most often affected, cardiac involvement is present in a large number of patients. Up to 30% of patients report cardiovascular symptoms and a high percentage of deaths have been attributed to a cardiac origin throughout the course of the disease [2].

Viral-induced acute myocardial injury is a well-known condition and is widely variable. Findings observed to date in multiple case reports allow classifying myocardial damage manifestations into myocarditis, pericarditis, arrhythmias, acute coronary syndrome, intracavitary thrombi, and thromboembolism. Patients with cardiovascular complications usually have pre-existing comorbidities such as diabetes, hypertension, and dyslipidemia, although it may also occur in patients without such previous diseases [3–5].

The hypotheses about the pathophysiology of myocardial disease related to COVID-19 are still under debate. Some data points toward direct cytotoxic viral effect on cardiomyocytes mediated through SARS-CoV-2 angiotensin-converting enzyme 2 (ACE2) receptor activation; others suggest a combination of the aforementioned mechanism, plus induced cellular damage, caused by an exaggerated proinflammatory cytokine response to infection (cytokine storm). Hypoxia, stress cardiomyopathy, drug-induced toxicity, and microembolisms are also proposed as contributing agents in the acute phase [6].

The number of asymptomatic or paucisymptomatic patients with COVID-19 myocardial injury is even higher and is not always detected (i.e., subclinical), with the risk of persisting infection, leading in the long-term to unpredictable consequences. There is ongoing debate regarding the potential infiltration of the virus into myocardial cells and subsequent damage. While some studies have not found evidence of viral activity, others have suggested a potential connection. Therefore, the relationship between viral infiltration and myocardial damage remains controversial (Fig. 1) [7].

Many patients will persist symptomatic during weeks or months after the initial infection, and these post-acute sequelae have been increasingly reported in the literature. Pulmonary, neurocognitive, metabolic, cardiovascular, gastrointestinal, and mental health disorders have been described, as well as malaise, fatigue, and peripheral neuropathy [8]. Proposed mechanisms involved in chronic or Long-COVID are chronic inflammatory response against persistent viral reservoirs, molecular mimicry leading to chronic autoimmune inflammation, and endothelial dysfunction [9].

Several nomenclatures have been proposed to define the symptoms experienced by patients after the acute phase. The

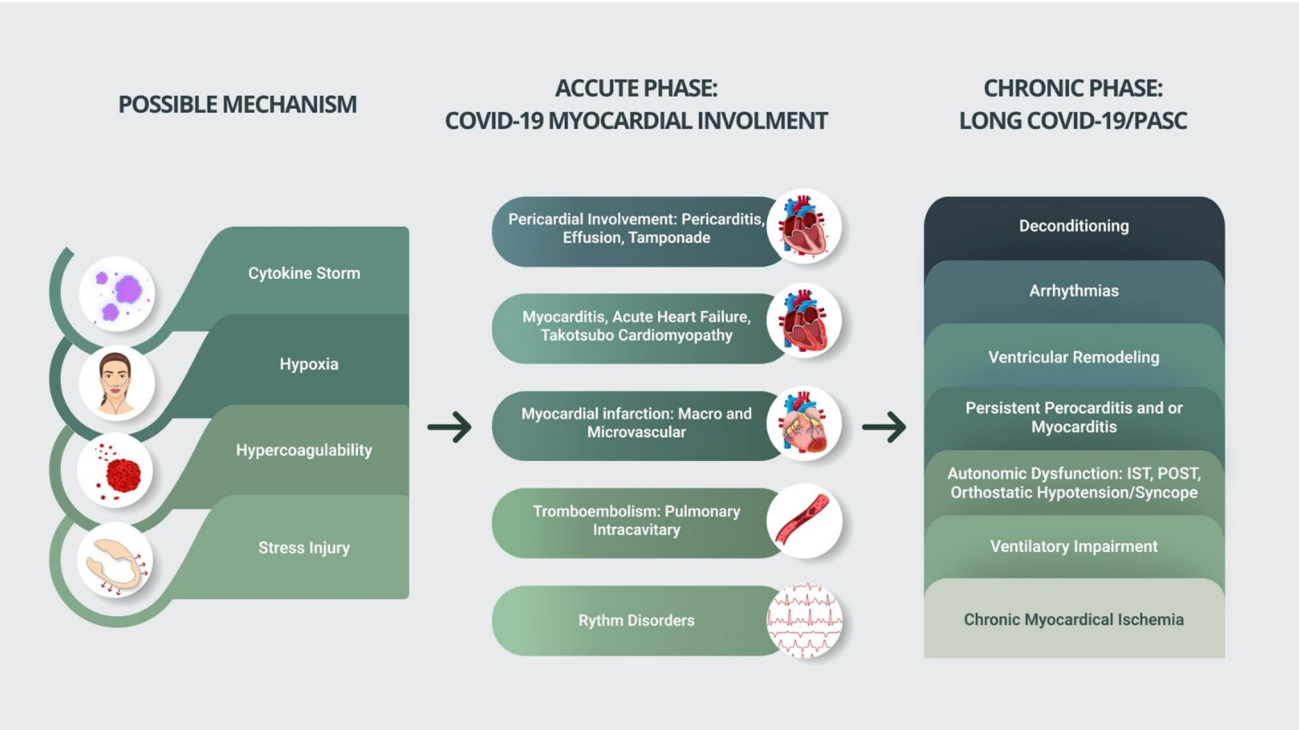

Fig. 1 Possible mechanism underlying the genesis of myocardial involvement during acute COVID-19 and its subsequent evolution to a chronic phase (PASC)

very popular "Long-COVID" name coined by a patient, has been formally defined in 2020 according to the National Institute for Health and Care Excellence (NICE) as "signs and symptoms that develop during or after the COVID-19 infection persisting for more than 4 weeks and could not be explained by any other diagnosis"; this definition was also endorsed by the 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults [10, 11].

Other authors have proposed alternative names such as "Long-Haul COVID" and "post-acute sequelae of SARS-CoV-2 infection (PASC)" in an attempt to encompass symptoms that appear during the course of acute infection, as well as those developed "de novo" after apparent resolution of the acute phase [12]. Indeed, one of the limitations of the available evidence is the lack of a universal definition of Long-COVID or PASC, leading to the heterogeneity of timing, evaluation methods, and huge results disparities.

Symptoms related to post-acute cardiovascular sequelae of SARS-CoV-2 have been reported in up to 13% of patients, as demonstrated by Xiong et al. in a 3-month follow-up study of 538 surviving COVID-19 patients. The most frequently reported symptom was inappropriate sinus tachycardia in 75% of cases, followed by postural orthostatic tachycardia syndrome (POTS), palpitations, and chest pain [13]. Some survey studies mention even much higher rates of cardiopulmonary symptoms in up to 86% of patients (reported by patients) [14].

Because symptoms experienced by the patient can arise from several causes, it is important to recognize when they come from a cardiac origin to determine the degree of involvement and eventually initiate appropriate treatment. At this point, multimodality cardiac imaging plays an important role in the diagnosis of cardiovascular PASC. In this paper, we pretend to carry out an analysis of the current evidence, regarding the use of cardiac imaging and other diagnostic techniques in patients with persistent cardiovascular symptoms after COVID-19.

Methodology

A literature review from well-known medical databases such as PubMed, PubMed Central, EMBASE, Cochrane Library, Google Scholar, and EuropePMC was performed. The following words were used as filters to refine the search: PASC, cardiovascular symptoms, cardiac imaging, CMR, echocardiography, and cardiopulmonary exercise testing. We included the following article types in English language: clinical studies, systematic reviews, randomized studies, and meta-analyses. Manuscripts including pediatric populations, acute COVID patients, or noncardiac PASC symptoms only were excluded.

Results

Electrocardiography

Inappropriate sinus tachycardia, atrial tachycardia, postural orthostatic tachycardia, premature ventricular and supraventricular contractions, and some other arrhythmias have been frequently described as post-COVID cardiac complications and can last beyond 6 months after initial infection. Several studies about electrocardiogram (ECG) and ambulatory monitoring by wearable devices have been described, but they are beyond the scope of this review regarding cardiac imaging and CPET [15].

Echocardiography

Echocardiography is an inexpensive and widely available tool with several advantages in diagnosing both acute and post-acute cardiovascular COVID manifestations. It has some security benefits for patients such as a lack of ionizing radiation or nephrotoxic contrast media. It has the ability to accurately evaluate the presence and severity of pericardial effusion and/or constriction. It can identify contractility defects, decrease in right or left ventricle function, evaluate chamber dilation, valvular regurgitation/stenosis, the likelihood of pulmonary hypertension, etc.

During the acute phase, bedside echocardiography is the first imaging tool during the initial evaluation. Right ventricle dilation and dysfunction are by far the most frequently found abnormalities probably secondary to hypoxic pulmonary vasoconstriction, direct myocardial injury, ventilator-induced lung injury, thromboembolism, etc. Other abnormalities including left ventricle dysfunction are also present but to a much lesser degree [15]. Nevertheless, after the acute phase (Long-COVID), some studies have shown normal echocardiography findings or slight ventricular remodeling even in patients with persistent symptoms [15]. Another retrospective study by Sechter et al. with a median of 142 days after the acute COVID infection showed abnormal echo findings in up to 32% of cases although most of them were classified as mild: minimal pericardial effusion was the most common finding in 19% followed by left ventricle dysfunction in just 4% [16].

A multicenter, prospective, observational, cohort study carried out by Moody et al. including 79 post-severe-COVID patients 3 months after hospital discharge found abnormal right ventricle systolic function (TAPSE < 17 mm or FAC < 35%) in 14%, whereas left ventricle dysfunction (EF less than 50%) was found in just 9%. Among those with RV dysfunction, 44% had pulmonary embolism previously diagnosed on computed tomography angiography during admission. Almost one-third of patients (29%) had persistent right

ventricle involvement (dilation or dysfunction) at 3-month follow-up [17].

On the other hand, several works have failed to show abnormal cardiac findings on echocardiography 3–6 months after COVID-19 besides persistent cardiovascular symptoms and, therefore, lack sufficient evidence supporting echocardiographic parameters and their relationship with symptoms, even in patients with positive biochemical biomarkers (troponins). This finding should not be taken as discouraging with regard to echo use but rather suggest that other more advanced techniques may be needed to rule out whether or not there is underlying cardiac damage that explains the patient's symptoms [18–20].

Cardiac CT

Cardiac CT offers a better image quality than echocardiography which is especially useful in cases with poor acoustic windows and requires less exposure time between healthcare workers and patients. It has also the advantage of being able to evaluate surrounding structures such as lungs and pulmonary vessels, identifying in many cases potential life-threatening conditions during acute COVID: pulmonary embolism, coronary artery disease, parenchyma lung disease (fibrosis, edema, and pleural effusion) and myocardial dysfunction.

Also, in hospitalized COVID patients with no known coronary artery disease, a coronary calcium score (CAC) > 400 HU can identify patients at risk of adverse cardiovascular outcomes such as hospital mortality and ICU admission [21]. Another study identified a positive CAC in 50.7% of patients hospitalized for COVID-19. Of those, 50% experienced noninvasive or invasive mechanical ventilation, ECMO, or death within 30 days after admission compared with 17.5% in patients with negative CAC [22]. These findings suggest that the CAC score could be a useful test for coronary artery disease stratification in this population.

Nevertheless, in both acute COVID-19 and PASC, the main role of cardiac CT is to noninvasively confirm or rule out the presence of cardiovascular disease by using coronary CT angiography which has a negative predictive value of 90.9%, positive predictive value of 87.9%, sensitivity 96.5%, and specificity of 72.4% for detection of coronary artery disease [23].

Cardiac CT can not only confirm the presence of significant coronary obstruction but also characterize such lesions determining if they pose high-risk features for rupture such as the napkin-ring sign, spotty calcifications, and eccentric remodeling [24]. An increased epicardial adipose tissue attenuation in patients with severe COVID as demonstrated by Iacobellis et al. could play a potential role as an inflammatory marker associated with plaque vulnerability [25].

Furthermore, with the implementation of technologies such as dual source CT, it is possible to identify myocardial scar and quantify extracellular volume fraction (ECV) through late iodine enhancement (quadruple rule-out) [26]. However, this technique has still some limitations such as a low contrast-to-noise ratio, the need for highly trained observers, and requires more contrast volume than a normal CT. In consequence, tissue characterization by CT is not widely available yet, and CMR remains the gold standard for the noninvasive characterization of myocardial tissue [27]. In addition, a dual-energy CT (DECT) angiographic study can aid in detecting pulmonary perfusion defects (proximal and distal thrombosis) usually overlooked during acute infection [28].

Cardiac Magnetic Resonance Imaging

When evaluating cardiovascular involvement after COVID-19, cardiac magnetic resonance stands as the most studied imaging tool. It has several advantages over other techniques as it is not undermined by a poor acoustic window, does not require ionizing radiation, and has a high signal-to-noise ratio, which is very useful in detecting subtle changes of the myocardial parenchyma associated with persistent inflammation or scarring. Multiple studies have shown features associated with myocardial injury; some of these trials are summarized in Table 1 [29–33, 36, 38, 40–43].

Early in 2020, a prospective observational cohort study evaluated 100 patients who recently recovered from COVID-19 (33% previously hospitalized) with a mean of 71 days after diagnosis. Among them, 78% had abnormal CMR findings, increased T1 in 73%, and T2 in 60% (indicating edema and ongoing myocardial inflammation). Endomyocardial biopsy in severe cases showed active lymphocytic inflammation. In addition, COVID patients showed higher ventricular volumes and lower ejection fractions than matched controls. T1 and T2 had the best discriminatory power for the detection of COVID-19-related involvement, against age, sex-matched healthy controls, and risk factors matched patient controls [30].

More recent studies also support the ability of CMR in detecting myocardial damage during the first 3–6 months after COVID-19 infection. A prospective study involving 148 post-severe COVID-19 patients with a mean time of 68 days after infection showed decreased EF in 11%, the persistence of LGE in 54%, myocardial infarction scars in 19%, and criteria compatible with ongoing myocarditis in 30% [31]. Myopericarditis was also identified as probable (41%) or very likely (13%) in 159 previously hospitalized post-COVID patients between 28 and 60 days post-discharge [32]. In 2022, Eiros et al. reported high rates of CMR abnormalities in up to 75% of healthcare workers at 10.4 weeks

Table 1 Summary of the most important CMR trials carried out in post-COVID patients [29–33, 36, 38, 40–43]

Study	Year	Number of patients	Duration	Inclusion criteria	Results
Knight et al	2020	29 patients	64 (± 15) days after initial symptoms, 27 (± 11) days after discharge	Post. hosp. PCR-confirmed COVID with unexplained high troponins	7% pericardial effusion. 69% any myocardial injury: 38% nonischemic, 17% ischemic, mixed pattern 14%
Puntman et al	2020	100 patients and 107 controls	71 (64–92) days	> 2 weeks after severe PCR confirmed COVID	Cardiac involvement in 78%, ongoing myocardial inflammation in 60%. LGE in 32%, pericardial enhancement in 22%. lower left ventricular ejection fraction, higher left ventricle volumes, and raised native T1 and T2
Rajpal et al	2020	26 competitive athletes	11–53 days after COVID diagnosis	Low-risk COVID, no hosp.	Myocarditis criteria in 15%. Pericardial effusion in 7.5%. LGE of any extension in 46%
Huang et al	2020	26 patients	47 (36–58) days after COVID onset	Patients with PCR confirmed COVID who reported symptoms after recovery	Myocardial edema in 54%, LGE in 31%. Decreased RVEF
Kotecha et al	2021	148 patients and 80 controls	68 days	Post-severe COVID and elevated troponins	Dec. EF in 11%. LGE in 54% (nonischemic in 26%) 30% of nonischemic with ongoing myocarditis. MI in 19%. Nl T1 and T2
Eiros et al	2021	139 health care workers	10.4 weeks	Past COVID, 16% previously hospitalized	Abnormal CMR in 75%: myocarditis 26%, myopericarditis 11%, pericardial effusion 30%, edema 4%, increased T1 (37%) and ECV (7%)
Dennis et al	2021	201 patients	141 (110–162) days after infection	Low-risk mortality COVID patients, 19% prev. hosp.	Cardiac impairment in 26% (9% syst. dysfunction. 19% myocarditis)
Raman et al	2021	58 patients and 30 controls	2–3 months from moderate-severe PCR confirmed COVID onset	PASC > 3 months after PCR confirmed COVID	nl. EF. Increased T1 (26%). nl T2 and ECV. Decreased VO2 peak in 55%. Earlier AT1, steeper VE/VCO2 slope
Myhre et al	2021	58 patients	175 (105–217) days after COVID	Past COVID. Previously hospitalized	Abnormal CMR (dec. LVEF or LGE) in 21%: 5.25% with major myocardial injury (Dec. LVEF, > 6.5% scar volume) and 15.75% minor myocardial injury (nl EF an < 6.5% scar volume on LGE)
Morrow et al	2022	159 patients and 29 controls	28–60 days post-discharge after COVID hosp.	Past COVID. Previously hospitalized	Myopericarditis criteria: probable in 41% and very likely in 13%
Durstenfeld et al	2022	120 patients (46 with advanced cardiac testing: CMR and/or CPET)	17 months following initial SARS-CoV-2 infection	PASC > 3 months after PCR confirmed COVID	Peak VO2 reduced in 57%. Chronotropic incompetence in 60% Normal T1, T2, EF, LGE Increased ECV

post-infection: myocarditis 26%, myopericarditis 11%, and pericardial effusion 30% [33].

Beyond the first 3 months after infection, abnormal CMR features tend to be observed in a lesser number of patients and even absent at all after 6 months in some studies [33–35]. In other studies, however, pathological findings such as decreased LVEF, LGE, or persistently elevated T1 and T2 mapping were observed several months after infection suggesting that ongoing myocardial inflammation could contribute to the pathophysiological mechanisms underlying persistent cardiac symptoms [36, 37].

A prospective, observational cohort study showed cardiac impairment in 26% of 201 patients with a median of 141 days following SARS-CoV-2 infection, notwithstanding most patients (60%) persisted with severe post-COVID symptoms [38]. Another study showed that 19% of Long-COVID patients had abnormal CMR at baseline, including decreased LVEF, increased LV volumes, and increased T1. After a 1-year follow-up, up to 58% of these patients still had these findings [39].

Despite a trend to normalize pathologic CMR findings, many persons still complain of dyspnea, exercise intolerance, chest pain, palpitations, and a myriad of cardiovascular-related conditions. At this point, clinicians should avoid the temptation to assume a psychosomatic cause and keep pursuing the mechanisms responsible for these persistent conditions. Notably, a physiologic evaluation of a patient's response to exercise by a cardiopulmonary exercise testing can help identify potential mechanisms underlying symptoms.

Cardiopulmonary Exercise Testing

Some possible PASC mechanisms such as myocardial injury, lung injury, vascular abnormalities, muscular dysfunction, and dysautonomia can be evaluated by cardiopulmonary exercise testing as a complement to imaging, allowing a more physiological approach in these patients, since most of the symptoms reported are related to poor exercise capacity. Continuous monitoring of parameters helps to orientate if such symptoms are associated with ventilatory, circulatory, or gas exchange impairments.

Perhaps the most consistent finding among PASC patients is a reduced peak oxygen uptake ($V\dot{O}_2$). In a study involving 41 patients with PASC (approx. 8.9 months after infection) and previously normal pulmonary function tests and cardiac CT, 58.5% had a reduced peak $V\dot{O}_2$ (< 80% predicted) with circulatory limitation to exercise. Despite normal pulmonary function tests, ventilatory impairment was present in 88% of patients, with dysfunctional breathing in 63%; hypocapnia ($PetCO_2 < 35$) in 61%; and/or increased $V\dot{E}/V\dot{C}O_2$ slope in 41%, which can be interpreted as a manifestation of autonomic dysfunction [44]. Similarly, Ladlow et al. studied 205 patients and identified dysautonomia in 25%, defined in this study as a resting HR > 75 bpm, HR increase with exercise < 89 bpm, and HR recovery < 25 bpm within 1 min after exercise. Patients with this condition also showed decreased workload, lower peak $V\dot{O}_2$, and a steeper $V\dot{E}/V\dot{C}O_2$ slope [45].

Another possible explanation for reduced peak $V\dot{O}_2$ could be a diminished oxygen extraction (muscular deconditioning) secondary to muscle damage in patients suffering from cytokine storm, prolonged hospital stay, direct viral damage, etc. [46]. It is associated with an earlier anaerobic threshold, accelerated heart rate response, lower workload achieved, lower peak O_2-pulse, slow $V\dot{O}_2$ on-kinetics during unloaded cycling, and wider breathing reserve.

Additionally, chronotropic incompetence is one of the most frequently observed abnormalities among patients with reduced peak $V\dot{O}_2$ after COVID-19 being present in up to 60%. Consequently, chronotropic incompetence is associated as a potential cause or contributor to reduced exercise capacity observed in PASC patients [41].

Discussion

Integrative Physiologic and Imaging Approach

While approaching a patient with persistent symptoms after COVID-19, focus should be placed on determining whether his/her chief complaint derives from (1) a potentially fatal condition, (2) a condition that will carry adverse cardiovascular effects in the future, or (3) sequelae related to dysautonomia or deconditioning that can cause important limitations on the patient's quality of life.

As previously stated, results from clinical trials using echocardiography have shown scarce pathological findings on patients with PASC, as opposed to acute COVID-19. Nonetheless, it continues to be a useful tool, readily accessible to most cardiology departments and can be performed during initial clinical evaluation. On the other hand, CMR, cardiac CT, or cardiopulmonary exercise testing are not as easy to access; therefore, we suggest getting transthoracic echocardiography as the first imaging modality accompanying physical examination. It is mandatory to emphasize that a normal echocardiogram does not exclude cardiovascular conditions, and moving to a more advanced image technique is highly advisable when feasible [47, 48].

A pathological finding on transthoracic echocardiography or the persistence of cardiovascular symptoms dictates the necessity of pursuing further study of the patient through more advanced imaging techniques. As has been exposed in this paper, CMR is postulated as the ideal imaging modality to approach PASC; it can diagnose pericarditis and/or acute myocarditis allowing a timely administration of

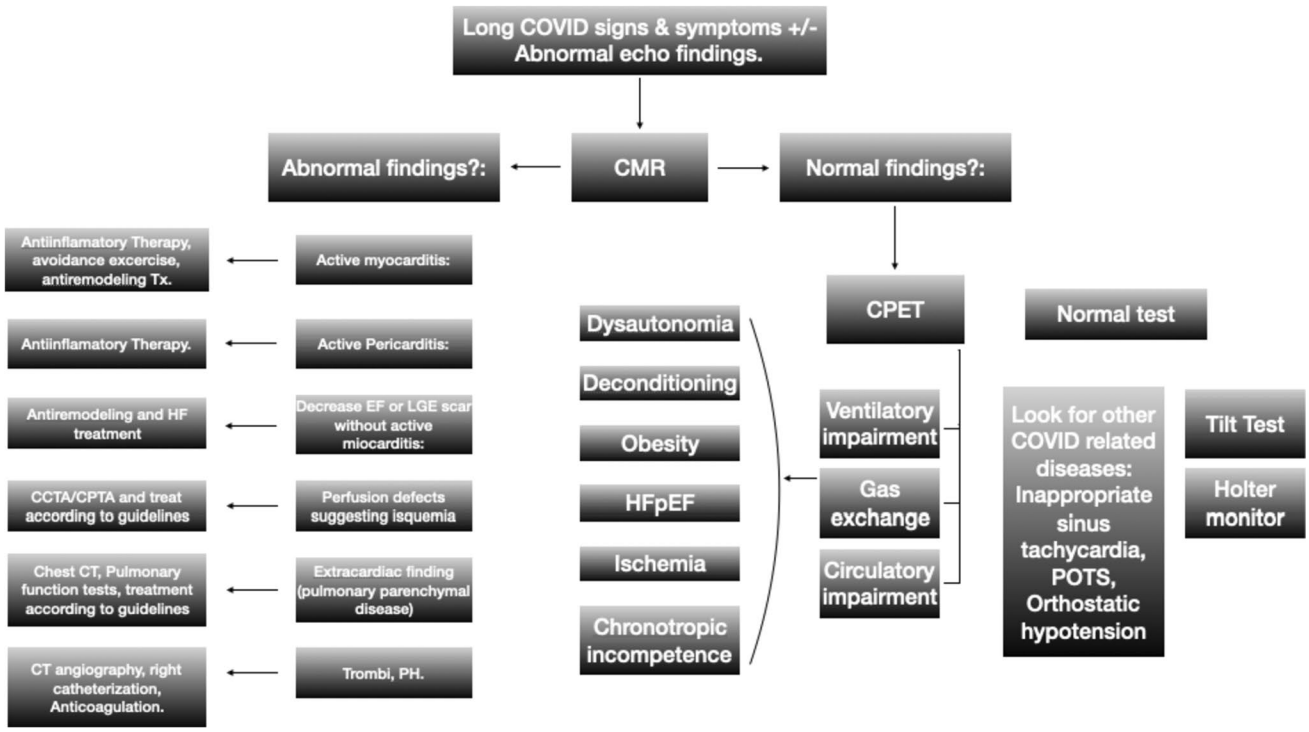

Fig. 2 Proposed algorithm for approaching cardiac symptoms in PASC. Echo is included as part of the initial evaluation because of its easy and widely available access. CMR remains the most studied and robust technique in evaluating cardiovascular injury after COVID-19. CPET is a useful tool in the presence of normal cardiac imaging findings or if a deeper physiological evaluation is required. Additional tests such as tilt test, Holter monitor, CTA, or CPTA can be required according to findings and clinical suspicion

anti-inflammatory drugs and therefore decreasing the risk of fibrosis and posterior cardiac remodeling. According to ESC guidelines, CMR can also help to diagnose significant ischemia through perfusion studies, guiding coronary revascularization, and optimizing anti-ischemic therapy [49].

In cases where images do not show any damage or the findings are not severe enough to explain the patient's symptoms, we suggest performing an additional test to identify underlying mechanisms behind them. As shown before, CPET seems to be an excellent tool to be used in combination with CMR, due to its ability to give a more physiological approach to the evaluation of PASC through a ventilatory, circulatory, and metabolic analysis of patients under exercise. Accordingly, relevant limitations such as deconditioning, chronotropic incompetence, or ventilatory inefficiency can be identified. In some cases, additional exams like tilt-testing and ambulatory ECG-monitor can be employed for the detection of POTS, inappropriate sinus tachycardia, etc. (Fig. 2) [50, 51].

Conclusion

In summary, as many patients overcome acute SARS-CoV-2 infection, we must keep in mind that up to 30% of them could experience persistent cardiovascular symptoms as part of PASC lasting for various months following infection. Our understanding of this condition is under investigation and is not yet fully understood. Cardiac imaging is one of the most valuable tools when evaluating this disease and should be used in conjunction with CPET and other additional tests aiming to promptly identify and treat potential severe cardiovascular complications which is paramount to prevent further and permanent damage.

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Declarations

Conflict of Interest VP and EN have received speaker fees from Bayer AG and Siemens AG, as well as educational grants from Bayer AG. Other authors declare no conflicts of interest. SM reported receiving personal fees from Bristol-Myers Squibb (consulting services) outside the submitted work. MH reported receiving personal fees from Abbott, Amgen, Bristol-Myers Squibb, Daiichi-Sankyo, and Medi and Medical Park (consulting fees and honoraria for lectures) and being the past-president of the European Association of Preventive Cardiology (2020–2022).

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