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EDITORIAL

What we (don't) know about myocardial injury after COVID-19

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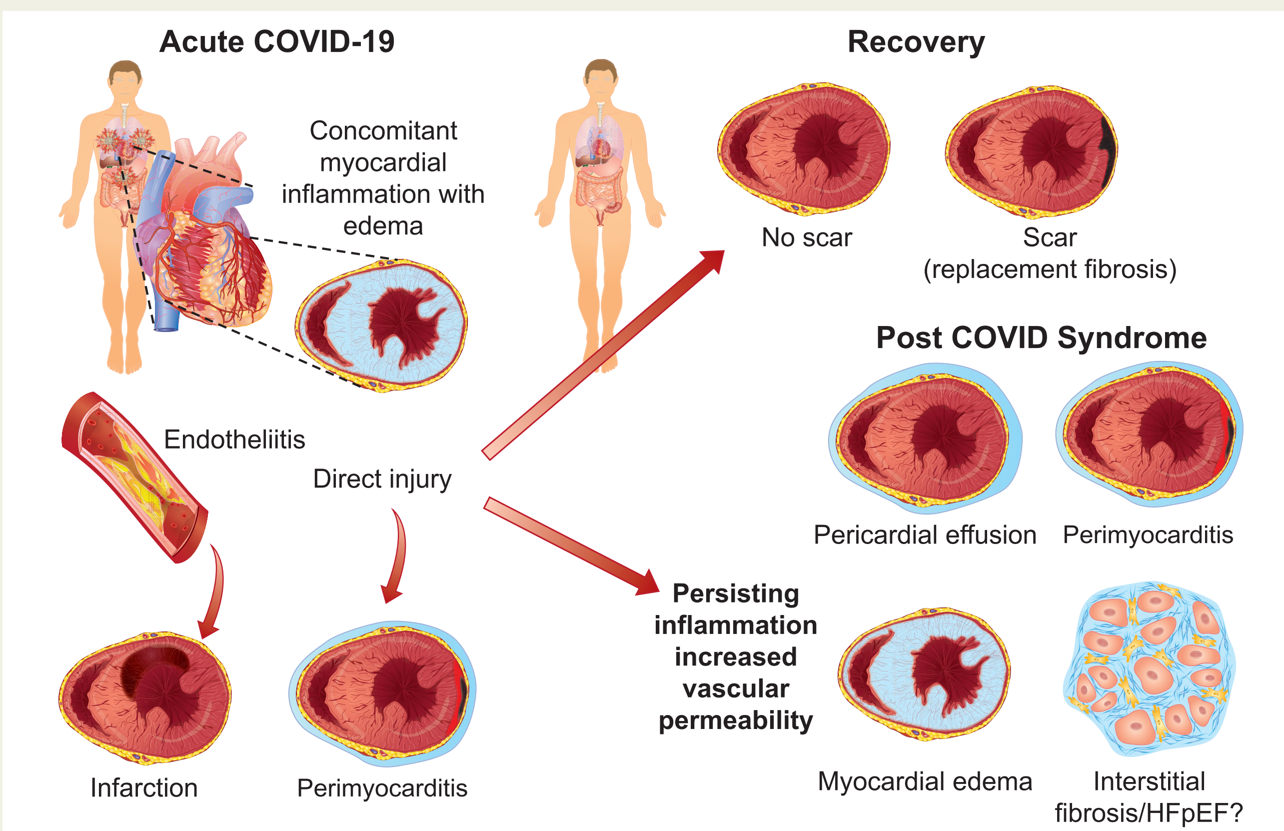
This editorial refers to 'Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance', by T. Kotecha *et al.*, doi:10.1093/eurheartj/ehab075.



Graphical Abstract Acute and chronic outcomes of symptomatic COVID-19 infection for the heart. HFpEF, heart failure with preserved ejection fraction.

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Table 1 Cardiac magnetic resonance imaging findings after acute COVID-19: published data

Author	No. of patients	Mean age (years)	Severity of illness	Mean interval from diagnosis to CMR imaging	CMR findings	Dexamethasone treatment
Kotecha *et al.*[12]	148	64	Hospitalized; all with troponin elevation	68 days	54% total abnormal, 32% inflammatory pattern, 28% ischaemic pattern	Not reported
Raman *et al.*[6]	58	55	All hospitalized	2–3 months	26% increased native T1, 11.5% inflammatory LGE	28%
Puntmann *et al.*[10]	100	49	33% severe, 49% mild–moderate, 18% asymptomatic	71 days	78% total abnormal, 73% increased native T1, 60% increased native T2, 32% abnormal LGE	8%
Rajpal *et al.*[11]	26	20	College students with mild disease, no troponin	24 ± 10 days	46% abnormal LGE,15% abnormal T2 + LGE	0%
Huang *et al.*[13]	26	38	85% moderate, 15% severe	47	54% increased T231% abnormal LGE	50%

CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement.

The frequency of cardiac injury among hospitalized patients with acute coronavirus disease 2019 (COVID-19) is estimated at 13–41% as defined by elevated troponin levels.[1] Evidence of cardiac involvement in hospitalized COVID-19 patients is significant because cardiac injury is associated with higher mortality.[2,3] Multiple mechanisms can lead to cardiac damage, including demand ischaemia, systemic hypoxia, intravascular thrombosis and endotheliitis, and myocarditis. Myocardial inflammation can result from both a systemic inflammatory response[4] and, less commonly, direct viral injury. Because of a low rate of histological inflammation associated with the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the tissue on autopsy or endomyocardial biopsy, some have questioned whether COVID-19-related myocarditis exists. Cardiovascular injury from COVID-19 in children and adolescents is much less common than rates seen in cohorts of older patients and includes a multisystem inflammatory syndrome (termed MIS-C) with higher rates of myocarditis and arterial aneurysms.[5]

Following recovery from the acute COVID-19 illness, shortness of breath and fatigue may persist. In a recent study, 64% of patients 2–3 months after COVID-19 reported dyspnoea and fatigue, an incidence much higher than after other viral diseases.[6] The reasons for 'long COVID' are not well understood, but are associated with signs of ongoing inflammation as well as tissue abnormalities of the lungs, heart, and kidneys as identified by magnetic resonance imaging (MRI).[7]

Cardiovascular magnetic resonance (CMR) is the non-invasive gold standard for the assessment of myocardial tissue pathology, especially myocardial oedema, which is not possible by other imaging modalities. Specifically, CMR is highly accurate to diagnose acute myocarditis when published consensus criteria are used.[8] Myocardial oedema assessed with T2-weighted sequences provides a unique role for MRI in the non-invasive cardiac assessment of patients with suspected ongoing inflammation.[9]

Myocardial oedema, as defined by increased myocardial T2 signal, has been described in up to 60% of older patients with CMR evidence of myocardial involvement in COVID-19 (*Graphical Abstract*).[6,10] The frequency of increased T2 in previously healthy, young competitive athletes with mild or no symptoms was lower at 15% (4/26) in one report.[11] In acutely ill COVID-19 patients, cardiac MRI is not commonly performed because haemodynamic instability and respiratory distress make imaging infeasible.

In this issue of the *European Heart Journal*, Kotecha *et al.*[12] report 148 hospitalized patients with COVID-19, all of whom had acute cardiac injury defined by elevated troponin values. On average, ~2 months after recovery, the authors applied a standard CMR protocol [cine images, T1 and T2 mapping, late gadolinium enhancement (LGE); some patients also underwent a CMR first-pass perfusion protocol]. Fifty-four percent (80/148) of patients had cardiac abnormalities. The scar/injury pattern was inflammatory in 32% (48/148 patients) and ischaemic in 28% (41/148), including 9 patients showing both. Twelve patients (8%) had evidence for (possibly still ongoing) myocardial inflammation at this late time point. Patient symptoms were not reported.

Kotecha *et al.*'s report adds further evidence that cardiac injury is common ~2 months following COVID-19. Their results apparently contrast with the higher rates reported by Puntmann *et al.*, where the proportion of patients with abnormalities was 73% with increased T1, 60% with increased T2, and 32% with LGE, despite 18% of these patients being initially asymptomatic (*Table 1*).[6,10–13] Raman *et al.* reported lower rates, with only 26% with abnormal T1 and 11.5% with an inflammatory LGE pattern.[6] While the proportion is much lower than in the study by Puntmann *et al.*,[10] it should be kept in mind that an incidence of 11.5% could still have significant consequences on a societal level, given the large number of hospitalized patients with symptomatic COVID-19.

A comparison of these studies reveals methodological differences that may confound systematic analysis, including selection of patients and control subjects, varying definitions of inflammation and injury using several CMR parameters individually or in combination, and differing intervals between the acute disease and the MRI scan. Apparent discrepancies of CMR results between some reports may in part be related to a lack of adherence of CMR protocols to published recommendations such as the Lake Louise Criteria for CMR in suspected myocardial inflammation[8] and the societal recommendations for CMR mapping of the myocardium.[14] Further, an abnormal myocardial T1 is not specific for acute myocardial inflammation or oedema, but is also found in diffuse fibrosis or infiltration. LGE reflects previous myocardial injury of any age; the observation of ischaemic or non-ischaemic LGE in higher risk patient populations may well reflect unrelated events prior to their COVID-19. Therefore, if used as standalone markers for acute or chronic inflammation, T1 and LGE may lead to overestimation of the prevalence of myocardial inflammation in COVID-19, unless combined with a tissue marker for myocardial oedema (T2 mapping or T2-weighted images). Moreover, myocardial oedema itself is specific neither for viral myocarditis nor even inflammation in general. The damage to endothelial angiotensin-converting enzyme 2 (ACE2) receptors by SARS-CoV-2 may increase vascular permeability[15] and thus cause the extravasation of fluid, even in the absence of a strong inflammatory response.

Pre-existing cardiovascular disease was reported in 56% of patients hospitalized with coronavirus in the USA in 2016–17.[16] The populations reported in the studies of Puntmann *et al.* and Kotecha *et al.* probably also had high rates of pre-existing cardiovascular disease not attributable to COVID-19. Histopathological studies from autopsy series also suggest that acute myocarditis is infrequent in patients who succumbed to COVID-19.[17]

Taken together these studies suggest that up to 64% of patients with acute, symptomatic COVID-19 may have suffered from prolonged symptoms including fatigue and shortness of breath despite a very low rate of systolic heart failure. Abnormalities of myocardial tissue characterized by MRI are common during COVID-19 recovery, but causal relationships of these tissue changes to symptoms and future cardiac events are not yet known. Unfortunately, the study does not report on symptoms or their relationship with abnormal imaging findings, and thus does not inform our understanding on the correlates of patients with ongoing symptoms.

Furthermore, the rates of impaired ventricular relaxation and altered cardiopulmonary reserve capacity should be carefully defined as possible contributing factors. For studies with larger populations, longer term follow-up and detailed imaging and functional assessments are required to understand the mid- and long-term clinical impact of COVID-19 on the heart. The mechanisms of injury and rates and types of clinical sequalae may differ by age and gender. In older, hospitalized patients, myocarditis defined by cellular infiltrates and myocyte necrosis is uncommon. Nonetheless, a minority of patients may experience longer term, mild inflammation that may delay recovery and prolong symptoms. The rates of diffuse myocardial oedema and the association with fibrosis, clinical heart failure, and arrhythmia risk over a meaningful span of several years need to be studied in diverse groups to develop a predictive risk model to impact the management of chronic COVID-19 cardiac injury. Several studies are ongoing and will deliver answers: COVID-HEART (NIHR 285147), PHOSP-COVID (NIHR 285439), MOIST (NCT04525404), MYOCOVID (NCT04375748), MIIC-MI (NCT04412369), CARDOVID (NCT04455347), and CISCO-19 (NCT04403607).

Conflict of interest: none declared.

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