

# Cardiac involvement in COVID-19: cause or consequence of severe manifestations?

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Since the inception of the COVID-19 pandemic, the identification of factors associated with unfavourable outcomes has been a topic of intense investigation. With limited disease-specific therapies, early stratification of those at highest risk of complications can guide who needs intensive clinical monitoring and supportive management. The large body of evidence in the early phases of the pandemic strongly suggested that cardiac involvement could potentially be one of these prognostic factors, and several hypotheses have been raised for the cardiovascular abnormalities observed, especially in severely ill patients. Markers of acute myocardial injury have been reported in up to one-fifth of patients with COVID-19,<sup>1</sup> and several mechanisms have been implicated: (a) direct myocardial injury due to viral invasion of cardiomyocytes; (b) systemic inflammatory response and cytokine storm; (c) increased cardiometabolic demand associated with acute hypoxic respiratory failure; (d) increased vascular shear stress precipitating plaque rupture in the setting of a prothrombotic state; (e) deleterious cardiovascular effects of empirical drug regimens; (f) critical electrolyte disturbances. These disease-related mechanisms may be exacerbated by underlying cardiac disease and increase risk of adverse outcomes.<sup>1</sup>

The present study by Singh *et al*<sup>2</sup> brings a significant contribution to this growing body of evidence. Fifty-two patients recovered from COVID-19 (one-third with intensive care admission and one-fifth requiring mechanical ventilation)

underwent a comprehensive imaging protocol with gadolinium and manganese-enhanced MRI, with 23 additionally undergoing CT coronary angiography for evaluation of underlying coronary artery disease. They were compared with 10 healthy controls and 26 volunteers propensity matched for cardiovascular morbidity. COVID-19-recovered patients demonstrated impaired left (LV) and right (RV) ventricular systolic function, elevated myocardial T1 values and extracellular volume fraction, and reduced myocardial manganese uptake compared with healthy controls. In contrast, when comparing with comorbidity-matched volunteers, patients with COVID-19 had preserved LV function but reduced RV systolic function with comparable MRI measurements: native T1 values, extracellular volume fraction, late gadolinium enhancement and manganese uptake. The observations were irrespective of a COVID-19 severity score, concomitant myocardial injury or symptoms. From these findings, the authors hypothesise that existing comorbidities may be a major driver in previous reports of COVID-19-associated LV involvement.

The utilisation of advanced imaging has helped the understanding of mechanisms of cardiac abnormalities associated with COVID-19. However, availability, limited practicality—especially for severe cases—and issues related to the decontamination of imaging environments are barriers to the widespread generation of CT and MRI data in this context. In a preliminary MRI study by Erdol *et al* that enrolled 100 patients without known chronic disease and diagnosis of COVID-19 in the post-quarantine period, 49% had cardiac involvement, 33% exclusive myocardial abnormalities.<sup>3</sup> In addition, individuals with cardiac disease were more symptomatic and had lower LV ejection fraction (LVEF) (61% vs 66%,  $p=0.001$ ), LV stroke volume and tricuspid annular plane systolic excursion (TAPSE) measured by MRI. Values, however, were within the normal range, and differences were not detected by transthoracic echocardiography.<sup>3</sup> The high proportion of individuals with MRI abnormalities in the absence

of significant comorbidities differs from the present study, but no control group was included. In a report of 26 patients recovered from COVID-19 (hypertension was the only comorbidity reported—eight cases), the observations of disease-related cardiac involvement were reinforced: abnormal findings in conventional MRI were found in 58% of patients; myocardial oedema in 54% and late gadolinium enhancement in 31%. Decreased RV function was also found in patients with MRI abnormalities, as well as elevated global native T1, T2 and extracellular volume.<sup>4</sup> Furthermore, to provide a broader overview of cardiac involvement in COVID-19 with MRI, a study by Ojha *et al* compiled findings from 34 preliminarily published reports (199 patients) and highlighted that only 21% had normal imaging with being diffuse myocarditis the most common diagnosis (40%), with a large proportion of T1 and T2 mapping abnormalities, myocardial oedema and subepicardial late gadolinium enhancement. LV function, on the other hand, was predominantly normal.<sup>5</sup> The patients' clinical profiles were heterogeneous, precluding causal and temporal inferences, or comparisons with the data by Singh *et al*, but suggesting exacerbated tissue inflammation as a significant driving factor.

The study by Singh *et al* used an elucidative comparative approach to go deeper into inferences about the cause/effect relation between cardiac involvement by COVID-19 and the presence of underlying cardiac risk factors, suggesting that cardiac abnormalities may reflect existing morbidities. The topic remains debatable without a definitive conclusion in sight. In a similar design applied by Puntmann *et al*, 100 patients (71 with detectable troponin T leak) recently recovered from COVID-19 (median 71 days) were enrolled for a systematic cardiac MRI protocol.<sup>6</sup> Cardiac involvement was detected in a high proportion (78 patients), ongoing myocardial inflammation in 60 and ischaemic late enhancement in 12, independently of pre-existing conditions and disease severity. In the comparative analysis with 50 healthy and 57 risk factor-matched controls, the findings differed from the current study: patients post-COVID-19 had lower LV ejection fraction, higher LV volumes, and elevated native T1 and T2.<sup>6</sup> Also in its early phases, COVID-19 myocarditis differed from other patterns of cardiac inflammation when compared with acute non-COVID-19 myocarditis and healthy individuals.<sup>7</sup> Diffuse myocardial oedema impacting LV function with lower LVEF was present in eight patients with signs of

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acute myocardial injury and no history of structural abnormalities. Conversely, late gadolinium enhancement (as an indirect sign of necrosis) was lower in COVID-19 myocarditis, suggesting that the pathophysiology of SARS-CoV-2 involves a unique interplay of inflammatory pathways, irrespective of underlying structural disease.<sup>7</sup>

The differences between cardiac MRI studies in COVID-19 are multifactorial and the timing of image acquisition may partially explain the contrasts between previous publications and this study. Patients were enrolled by Singh *et al* in the late post-discharge period, with a median 116 days since symptom onset. Thus, tissue healing over time, and regression of systemic inflammation may explain to similarities with control subjects especially for findings associated with the acute phase, such as tissue oedema and active myocarditis leading to ventricular dysfunction. And, as previously reported, extensive necrosis and subsequent fibrosis do not seem to be particularly frequent post-COVID-19, and in this study the prevalence of ischaemic late enhancement was similar to that observed in risk-factor matched controls. Wu *et al* compared 6-month follow-up MRI findings of patients with COVID-19 cardiac injury (13 with elevated markers of myocardial necrosis) with individuals post-COVID-19 without cardiac injury (N=14). Morphological and functional parameters (LVEF, cardiac output, cardiac index and ventricular volumes) and native T1 measurements were similar, but a higher proportion of late gadolinium enhancement (7 of 13 vs 1 of 14) was observed in those with myocardial injury, especially in the LV septum and RV insertion points.<sup>8</sup> However, a direct analogy with the present study is not possible, in the absence of a risk-factor matched group.

Interestingly, in the study by Singh *et al*, RV function (contrasting with LV function) was reduced in patients post-COVID-19 when compared with risk-factor matched volunteers, reinforcing a distinct disease pattern. This is of particular interest, since RV involvement has been proposed as an independent predictor of adverse outcomes in COVID-19 in echocardiographic studies. Even when the LV is spared, variables such as TAPSE, RV ejection fraction, RV strain and pulmonary artery pressure are associated with lab markers (D-dimer, troponin) and clinical outcomes.<sup>9</sup> Although this may result from

pulmonary vascular and parenchymal involvement and ventilatory support, the exact mechanisms are yet to be elucidated. Importantly, given the hyperdynamic state of patients with COVID-19 (especially in severe forms with exposure to vasopressors), LV and RV variables must be cautiously interpreted, as they may predict unfavourable outcomes even within a 'normal' range for other populations.<sup>9</sup> Thus, MRI may add to prognostic scores, given its high sensitivity for subtle abnormalities.

The present study has limitations, addressed by the authors. The main one—common to other MRI studies—is sample size, what is explainable by the relatively complex logistics to perform advanced imaging in COVID-19. Second, inclusion was independent of signs of myocardial injury or myocarditis, and a proportion (50%) of eligible patients—presumably the most severity ill—died, what may limit more definitive conclusions about causality and comparison with the matched controls. Thus, detectable cardiac involvement following COVID-19 may lie beyond pre-existing comorbidities or underlying cardiovascular disease and may be linked to a myriad of host conditions, as individual predisposition, immune response, inflammatory burden/cytokine modulation and systemic pathological conditions. Although further investigations are warranted for many of these points, the study by Singh *et al* is a valuable contribution to the field, pointing towards the insightful role of advanced imaging modalities to elucidate the mechanisms of cardiac involvement by COVID-19, the importance of RV performance, predisposing factors, causality and the extent of the hypothetical influence of comorbidities and underlying cardiovascular disease.

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