Lingering cardiac involvement in previously well people after mild COVID-19

Serial heart MRI scans conducted in previously well people with mild initial COVID-19 illness suggest that lingering cardiac symptoms may be explained, at least in part, by ongoing mild cardiac inflammation.

This is a summary of:
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The problem

Lingering cardiac symptoms, including exercise intolerance, tachycardia and chest pain, are increasingly recognized as post-acute COVID-19 sequelae[1]. In patients with a severe course of initial illness, accrued cardiac injury and pre-existing conditions readily explain cardiac symptoms. However, signs of cardiac injury such as elevated troponin levels and structural heart disease are rare in previously well people with mild initial illness, despite often profound cardiac symptoms. Previous studies in populations of mainly young, athletic people have shown subtle non-ischemic cardiac inflammatory changes shortly after initial COVID-19 illness. However, it remains unclear whether these early observations are related to symptoms or persist with time.

The observation

Serial blood tests, heart MRIs and standardized symptom questionnaires were conducted in previously well people with no known heart disease and mild, acute COVID-19 illness. Baseline assessments were performed after a minimum of 4 weeks from the diagnosis of COVID-19 infection, and follow-ups were performed at least 4 months later. We used sensitive MRI measurements directed to detect subtle changes in function and strain. Diffuse myocardial involvement was assessed by tissue mapping, specifically native T1 mapping — a nonspecific measure of abnormal myocardium — and native T2 mapping, which relates to myocardial water content indicative of inflammatory edema. Late gadolinium enhancement was used to visualize expansions of extracellular space in the myocardium and within the pericardial layers. We also assessed the presence of pericardial fluid. Together, these readouts allowed assessment of the presence and severity of inflammatory cardiac involvement.

Whereas 73% of participants reported cardiac symptoms at baseline assessment, 57% of participants continued to experience cardiac symptoms at follow-up (n = 346). We found signs of inflammatory cardiac involvement that persisted for several months after acute COVID-19 illness (Fig. 1). These findings were more pronounced in participants with symptoms than in those with no symptoms or uninfected control participants. The magnitude of these changes was generally mild, and they were not associated with structural heart disease or an increase in biomarkers. Although there was an improvement in imaging markers at follow-up, native T2 remained higher in the subgroup with persistent cardiac symptoms. These findings suggest that inflammatory cardiac involvement after COVID-19 may be a pathophysiological commonality shared by all patients that is more pronounced in those with persistent cardiac symptoms. At baseline, female sex and abnormal myocardial measurements by native T1 were predictive of persistent symptoms at follow-up.

The interpretation

The mild but persistent non-ischemic cardiac inflammation that we describe in this study was not associated with overt structural heart disease or troponin release. Although it is triggered by a viral infection, profound myocardial injury or functional impairment is not typical, contrary to the classical definition of viral myocarditis[2]. Its pathophysiology is more reminiscent of findings in other chronic diffuse inflammatory syndromes that occur post-virally (for example, human immunodeficiency virus–associated cardiomyopathy)[3] or as a result of autoimmunity (for example, systemic lupus erythematosus[4,5]). In these cases, persistent subclinical cardiovascular inflammation seems to predispose people to a poor prognosis and the development of heart failure. Non-ischemic cardiac inflammatory involvement is therefore emerging as an important risk factor, and the long-term prognostic relevance of post-acute COVID-19 cardiac involvement in previously healthy people with mild initial COVID-19 illness requires further investigation.

There are some limitations to our study. Although mapping techniques provide valuable pathophysiological insights, transferability of these findings is limited by a lack of standardization and methodological variations. Furthermore, we note that these results are based on a selected population of people who had recovered from COVID-19, and thus an extrapolation of prevalence of symptoms or findings onto the general population is not possible. Although it was most likely driven by an autoimmune process, the underlying pathophysiology remains only partially understood.

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FROM THE EDITOR

"The long-term effects of SARS-CoV-2 infection on the heart is an area of intense current interest. Through cardiac MRI and heart injury biomarker measurements, this study takes an important first step in probing the underlying cardiac pathology of patients with COVID-19 who have cardiac symptoms that linger over many months, such as shortness of breath, heart palpitations, and chest pain." **Editorial Team**, ***Nature Medicine.***

FIGURE

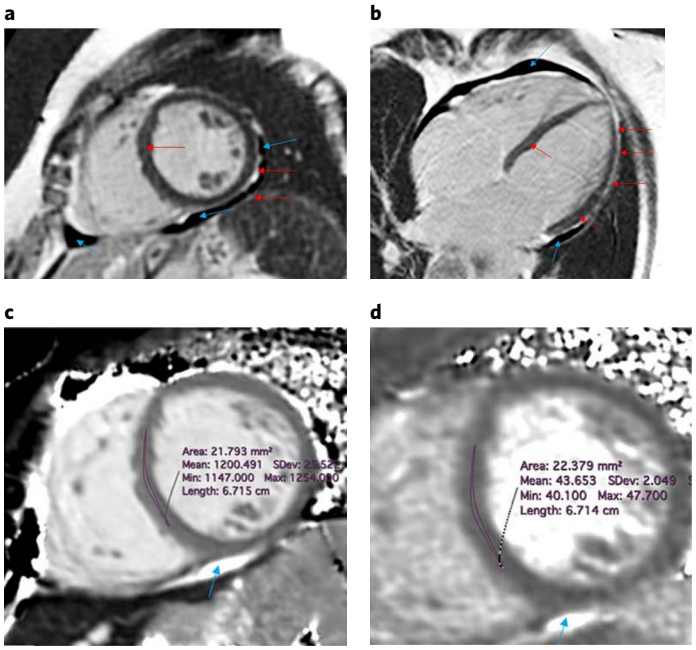

Fig. 1 | Representative imaging findings in a previously well person with persistent symptoms evaluated 201 days after COVID-19. Late gadolinium enhancement (**a**,**b**) allows visualization of regional accumulation of the gadolinium-based contrast agent, typically along the outer rim of the myocardial free wall (red arrows), as well as within the thickened pericardial layers, separated by small amounts of pericardial effusion (blue arrows). Increased native T1 (**c**) and T2 (**d**) measurements indicate diffuse myocardial edema.

BEHIND THE PAPER

We have been researching cardiac involvement in post-viral syndromes and rheumatological conditions for decades. We developed validated imaging tools that allow the detection of subtle changes related to chronic cardiovascular inflammation. In addition, by listening closely to patients, we learned about life-changing long COVID symptoms — and specifically cardiac symptoms — early and first-hand. The build-up of uncertainty around the persistent and often debilitating symptoms turned on the pressure for systematic research to provide answers and reassurance. As one of the few groups focusing mainly on previously well people, we recognized our duty of care and were honored by the commitment of our patient collective in return. We were lucky that our small team remained healthy throughout the pandemic and dedicated itself to this project. This research was made possible by flexible funding from the German Center for Cardiovascular Research, the German Heart Foundation and Bayer. **V.P. and E.N.**

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EXPERT OPINION

"In this article, the authors report a novel association between heart inflammation and prolonged shortness of breath, palpitations and chest pain, which are common after mild COVID-19. Elevated SARS-CoV-2 spike protein immunoglobulin has previously been linked to a spectrum of delayed symptoms after COVID-19. The identification of heart-specific inflammation by MRI advances the search for novel mechanisms to explain prolonged cardiac symptoms." **Leslie T. Cooper, Mayo Clinic, Jacksonville, FL, USA.**