

Cardiac remodelling following coronavirus disease 2019 infection?

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This editorial refers to ‘Progressive left and right heart dysfunction in coronavirus disease-19: prospective echocardiographic evaluation’, by H. Chaturvedi et al., pp. 319–325.

This article refers to ‘Progressive left and right heart dysfunction in coronavirus disease-19: prospective echocardiographic evaluation’ by H. Chaturvedi et al.,¹ published in this issue.

Cardiac involvement in acute coronavirus disease 2019 (COVID-19) has been studied extensively,^{2–5} and raises the question of potential long-term cardiac consequences. The possible correlation with ongoing cardiorespiratory symptoms in COVID-19 survivors, as part of the ‘long-COVID’ syndrome, emphasizes the clinical importance of this question. However, post-COVID-19 cardiac consequences still require elucidation.

A fundamental cardiac manifestation in acute COVID-19 is right ventricular (RV) dysfunction, thought to be secondary to increased RV afterload generated by parenchymal lung disease, hypoxia, positive-pressure ventilation, and pulmonary vascular thrombosis, with possible contribution of direct viral or inflammatory insult.² Left ventricular (LV) dysfunction is less common and usually more subtle during the acute disease and was mostly attributed to myocarditis, septic-induced cardiomyopathy, acute coronary syndromes, and stress-induced cardiomyopathy.⁶

Preliminary cardiac magnetic resonance-based reports showed persistence of subtle myocardial injury in recovered patients.^{7,8} Nonetheless, the lack of control group and baseline imaging, combined with a highly sensitive modality, limit the interpretation of these findings.

The first study to include both baseline and 3-month follow-up echocardiography of 79 patients recovered from COVID-19 showed that RV dysfunction was more common than LV dysfunction during the acute disease. Significant RV recovery was observed at follow-up, while LV function did not change significantly.⁹ However, the study was subjected to selection bias as the baseline exam was performed only in patients with clinical indication for echocardiography.

ECHOVID-19¹⁰ was a multicentre prospective cohort, including non-intubated patients with COVID-19 that underwent an echocardiography according to a pre-determined protocol. Speckle tracking echocardiography (STE) of the left and right ventricles were also assessed, and follow-up echocardiography was performed 2–3 months after recovery in surviving patients. The final cohort included 91 patients with baseline and follow-up echocardiography, matched with 91 control patients based on sex and age. RV parameters, including tricuspid annular plane systolic excursion (TAPSE) and RV longitudinal strain, significantly improved following the resolution of COVID-19. In contrast, LV ejection fraction (LVEF) decreased between the two echocardiographic examinations, and global longitudinal strain (GLS) did not improve. In fact, 20% had persistent LV systolic dysfunction (either abnormal LVEF or GLS) at follow-up. NT-pro BNP decreased significantly, C-reactive protein (CRP) was within normal range in most patients and none had elevated troponins at follow-up. Recovered COVID-19 patients had significantly lower GLS, TAPSE, and RV longitudinal strain (but not LVEF) compared to controls.

Similar results were presented in a prospective study of 80 COVID-19 survivors who were originally hospitalized with different degrees of acute disease severity, including patients requiring intensive care unit level-of-care.¹¹ Most RV-related haemodynamic parameters and STE markedly improved in a 3-month follow-up echocardiography. In contrast, 25% of patients still had LV systolic dysfunction based on STE, without significant improvement compared to baseline. A study evaluating cardiorespiratory abnormalities in 71 survivors of COVID-19 using cardiopulmonary exercise test combined with stress echocardiography, showed that abnormally low peak oxygen consumption was common 3 months after recovery and resulted mostly from a combination of attenuated stroke volume reserve and chronotropic incompetence.¹²

In the current study, Chaturvedi et al.¹ provide findings from a large prospective cohort of 1000 patients in India, where the burden of COVID-19 is amongst the highest in the world. Almost two-thirds of patients were available for follow-up evaluation. Findings from a

3-month follow-up in 632 patients showed a significant decrease in LV systolic and diastolic function, both when parameters were presented as continuous values, or as categorical cut-offs. Surprisingly, and in marked difference to the previously mentioned studies, they also showed a significant decrease in RV functional parameters, when presented as continuous values, albeit RV deterioration was less remarkable when addressing conventional cut-off values. Stratifying patients according to their acute disease severity showed that survivors of moderate–severe disease were more prone to long-term LV and RV deterioration than their counterparts who experienced mild acute disease. The study did not include STE, which could have delineated even more subtle differences between the two tests.

The surprising increase in RV size, and decrease in RV functional continuous parameters in the present study deserves special attention. Patients hospitalized with COVID-19 may present with hyperdynamic state because of the acute infection, fever and mental stress. This may result in relative hypovolaemia, decrease in RV size, and ‘improved’ parameters of RV function. In such patients, a decrease in TAPSE and increase in RV size several months post-recovery may be signs of recovery from acute disease, and not necessarily due to adverse remodelling, or RV functional deterioration. On the other side, unlike previous studies,^{9–11} baseline echocardiography of patients was obtained at the time of discharge from the hospital, hence after initial recovery from the acute disease. This is of importance, as baseline findings of LV and RV function were mostly within normal range, unlike previous publications that presented echocardiographic findings in the midst of the acute disease. Thus, it is possible that previous studies have missed subtle adverse long-term deterioration of RV (or LV) function, because they compared the follow-up exams to RV and LV at their worst state, under the extreme stress of acute infection.

As in previous studies, there is considerable selection bias in the present study, resulting from the fact that non-hospitalized patients were not included, as well as from the fact that one-third of patients did not undergo follow-up echocardiography. Another important limitation was the short-term follow-up. It will be important to demonstrate whether the LV and RV changes are permanent or reversible. Another limitation was the lack of laboratory information limiting the ability to ascribe a specific aetiology to the presented findings. On-going elevated CRP would have implied residual inflammatory process, while elevated troponin would have suggested an ongoing myocardial insult. Nevertheless, since all prior studies did not find elevated inflammatory or myocardial markers at follow-up, it is reasonable to postulate that the deteriorating cardiac function is a result of an on-going remodelling process.

Findings suggesting cardiac remodelling following pneumococcal pneumonia were presented in a non-human primate model that showed direct invasion of bacteria to the myocardium, as well as short-term collagen deposition secondary to TGF- β pathway activation.¹³ This was suggested as a potential aetiology for increased long-term cardiac risk in survivors of community-acquired pneumonia. Although still speculative at present, the fact that SARS-CoV-2 was found to infect the myocardium,¹⁴

combined with the aforementioned results from follow-up cardiac studies, raise the question of cardiac remodelling as a possible mechanism responsible for these findings.

The present study found a significant decrease in both systolic and diastolic LV function during follow-up. Whether this decline signifies clinically relevant change will require future clarification. However, even subclinical changes in LV function have been associated with poorer prognosis in other types of cardiac disease.¹⁵ Thus, it seems prudent to follow-up carefully on patients with even subclinical dysfunction. Lastly, data on the value of medical treatment is still lacking. It will be interesting to study the effects of treatments proved to counteract cardiac remodelling, such as beta-blockers and renin–angiotensin–aldosterone system inhibitors, in patients recovering from COVID-19 infection with persistent cardiac dysfunction.

Conflict of interest: None declared.

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