EDITORIAL COMMENT

Recovery of cardiac function following COVID-19

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This article refers to 'Recovery of cardiac function following COVID-19 – ECHOVID-19: a prospective longitudinal cohort study' by M.C.H. Lassen et al., published in this issue on pages 1903–1912.

There has been a large number of publications concerning cardiac complications in acute coronavirus disease 2019 (COVID-19) infection.[1–5] Myocardial injury during the acute phase of COVID-19 raises the question of potential long-term cardiac implications, however, less is known about these potential consequences. Preliminary magnetic resonance imaging (MRI) based reports described common persistence of subtle cardiac injury in recovered patients.[6,7] However, these studies used extremely sensitive MRI protocols and lacked baseline imaging and comparison to control healthy patients. In an early echocardiographic study on survivors of COVID-19 infection, even patients with prior detection of increased troponin did not have any evidence of persistent cardiac dysfunction.[8] However, the study included mostly patients at low risk for persistent cardiac injury, and lacked baseline imaging obtained during hospitalization. Furthermore, speckle tracking echocardiography (STE), that would detect more subtle cardiac changes, was not performed.

The first longitudinal echocardiographic study (including both baseline and follow-up echo exams) analysing the persistence of cardiac pathology following COVID-19 infection had different results.[9] Forty-one percent of patients had right ventricular (RV) remodelling or dysfunction during acute infection, but only ≈15% had either left ventricular (LV) alone, or biventricular involvement. At 3 months post-acute infection, there was reverse RV remodelling in the majority of patients with abnormal right ventricle at baseline, but no significant changes in LV parameters. However, the study was subjected to selection bias because baseline echo during hospitalization was performed only in patients with critical disease, or clinical deterioration.

In this issue of the Journal, Lassen et al.[10] used the ECHOVID-19 cohort, which is a large multicentre prospective cohort, including unselected patients with COVID-19 that underwent an echo examination according to a pre-determined research protocol, irrespective of severity of lung disease, or clinical indication. As part of the evaluation, they used both routine and STE assessment of the left and right ventricle. Follow-up echo exams were performed 2–3 months after recovery in surviving patients. Participants were matched 1:1 on age and gender, with control patients from the Copenhagen City Heart Study. The final cohort included 91 patients with baseline and follow-up echocardiography, matched with 91 control patients. Almost half of participants suffered from subclinical myocardial injury during hospitalization for COVID-19, using a broad definition including either abnormal tricuspid annular plane systolic-excursion (TAPSE), RV longitudinal strain, LV ejection fraction (LVEF), global longitudinal strain (GLS), or combination of the above. All measures of right circulation including RV functional parameters (TAPSE and RV longitudinal strain), right atrial area, or tricuspid annular area, significantly improved following the resolution of COVID-19. In contrast, LVEF decreased between the two echocardiographic examinations, and GLS did not improve. In fact, 18 (20%) continued to display LV systolic dysfunction (either abnormal LVEF or GLS) at follow-up. N-terminal pro-B-type natriuretic peptide decreased significantly between the two visits, C-reactive protein was within normal in most patients, and none of the participants 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.

Right ventricular function post-COVID-19

Numerous studies have shown that the most common cardiac pathology among hospitalized patients with acute COVID-19 infection is RV dilatation and/or dysfunction.[3,11] In the present study, most RV parameters improved (although did not normalize) 3 months after hospitalization. Similar results were presented in another recent prospective longitudinal study by Baruch et al.[12] In that study, non-invasive haemodynamic evaluation was

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performed concomitantly with routine and STE and showed that during the acute phase of COVID-19 infection RV remodelling or dysfunction are associated with elevated pulmonary vascular resistance.[4,12] Proposed mechanisms included either pulmonary embolism, hypoxic pulmonary vasoconstriction, elevated left atrial pressure, or combination of the above. The authors postulated that the increase in RV afterload during acute infection may decrease RV function, and may even decrease RV contractility by a reduction in coronary perfusion, or septal bowing towards the left ventricle. Irrespective of its cause, they showed improvement in most right circulatory haemodynamic parameters several months post-acute infection. They suggested that the reversal of the spiral of events described above, during recovery from acute infection, probably explains the almost universal improvement in RV function observed 3 months after hospitalization.

Left ventricular function post-COVID-19

In marked contrast to the impressive recovery of RV function, LV dysfunction observed during acute COVID-19 rarely improved 3 months post-COVID-19. In fact, LVEF even decreased compared to exams performed during the acute phase. Furthermore, compared to the matched controls, GLS remained lower in recovered patients. Nevertheless, it is important to note that the reduction in LV functional parameters rarely reached the abnormal range. Because this study, and the recent study published by Baruch et al.,[12] showing a similar prevalence of 25% abnormal LV STE, were done on consecutive hospitalized patients, with all grades of clinical disease, they probably represent a more accurate picture of the level of persisting cardiac pathology in survivors of patients hospitalized for COVID-19 compared to preliminary reports.[6,9] Another important advantage of the present study was the routine use of STE. Recent data in patients with other types of myocarditis demonstrated that ejection fraction did not correlate with the amount of LV myocardial oedema or fibrosis by MRI, in contrast to STE.[13,14] Thus, it is clear that for optimal follow-up of patients with subtle myocardial injury after COVID-19 infection, STE is superior to conventional echocardiography. The mechanism of persisting LV dysfunction 3 months post-acute infection is still unclear. Possible mechanisms include continued adverse remodelling after acute myocardial injury, an 'adult type' multisystem inflammatory syndrome,[15] persisting cardiac inflammation, or chronic viral infection. However, at the time of the follow-up visit, C-reactive protein had dropped to zero, and troponin was normal in almost all participants, which makes the presence of systemic inflammation, or persisting myocardial damage by viral disease unlikely to be the sole explanation. It should be emphasized that the discussed mechanisms remain speculative at present.

Limitations, clinical implications, and future perspectives

A significant limitation was that the main analyses were performed for continuous values (LVEF and GLS) and not for the prevalence of abnormal categorical cut-offs at the acute state compared to recovery phase. In patients at the acute phase, LVEF and GLS may be hyper-dynamic because of the severe infection, fever and hyper-adrenergic state. In such patients, a decrease in LVEF (or GLS) may be just a sign of clinical improvement and recovery from acute illness and not necessarily of LV functional deterioration. In other words, the decrease in LVEF (or the persistence of LV GLS) as a continuous parameter may represent a mixture of some patients improving from the hyper-dynamic state, with others that indeed have deterioration in LV function. All things considered, it is important to note that similar results, concerning persistence of subtle LV dysfunction in almost a quarter of hospitalized patients months post-acute COVID-19 infection, were observed by other research groups as well.[9,12] The sample size was relatively small, and not all participants agreed to participate in the follow-up examination creating significant bias. Even more important, although the study included patients with milder forms of acute disease, it included only hospitalized patients. Thus, it does not represent the true spectrum of COVID-19 infection, because the majority of patients are asymptomatic or mildly symptomatic and do not need hospitalization. Another important limitation was the short-term follow-up. It will be important to demonstrate whether the subtle LV changes are permanent or reversible within several months. Therefore, a larger study, including non-hospitalized patients, with a longer follow-up will be crucial to assess the clinical relevance, and the prevalence of LV dysfunction, post-COVID-19 infection. Clinically meaningful decrease in LV function to the abnormal range was rare. However, such subclinical changes in LV function have been associated with poorer prognosis in other types of cardiac disease.[16] Thus, it seems prudent to follow up carefully on patients with such subclinical dysfunction, preferably using STE. Lastly, because LV systolic abnormalities were mostly subclinical, data on the value of medical treatment are still lacking. It will be interesting to study the effects of beta-blockers, or angiotensin-converting enzyme inhibitors, in patients recovering from COVID-19 infection and persisting sub-clinical LV dysfunction.

Conclusions

The study demonstrates persistence of subtle LV dysfunction in a significant proportion of hospitalized patients recovering from COVID-19 infection. Improvement in RV dysfunction is almost universal due to improved pulmonary haemodynamics. It will be important to demonstrate whether subtle LV changes are permanent or reversible with or without treatment.

Conflict of interest: none declared.

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