

## EBM opinion and debate

## SARS-CoV-2 myocarditis: what physicians need to know

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## Introduction

Myocarditis is one of the complications seen with viral infections like parvovirus B19, human herpes virus, Epstein-Barr virus, cytomegalovirus, adenovirus and enteroviruses. Recent data suggest that SARS-CoV-2 could be a possible aetiological agent for myocarditis in the current pandemic.<sup>1</sup> Although we have some understanding of its respiratory manifestations, limited data are available regarding the involvement of the heart with this virus.

Myocarditis secondary to SARS-CoV-2 has been reported as one of the causes of increased mortality.<sup>1</sup> The European Society of Cardiology (ESC) states 'in the absence of vaccines or curative medical treatment, SARS-CoV-2 exerts an unprecedented global impact on public health and healthcare delivery'.<sup>2</sup>

In this article, we outline the pathophysiology, clinical manifestations, investigations and some of the treatment modalities that have been used so far for the management of SARS-CoV-2-related myocarditis. We also suggest areas for further research.

## What do we know so far?

Multiple case reports have described SARS-CoV-2-related myocarditis.<sup>3-5</sup> However; there are no randomised controlled trials or meta-analysis on this subject.

Proposed mechanisms for injury to the myocardium include binding of SARS-CoV-2 spike protein to ACE 2 which facilitates virus entry into the target cells,<sup>6</sup> immune-related myocardial inflammation and direct injury to the myocardium caused by hypoxemia.<sup>7</sup> Furthermore, it has also been suggested that IL-6 plays an integral role in activation of helper T cells, which in turn release inflammatory cytokines ultimately resulting in myocardial inflammation and damage.<sup>8</sup>

Age distribution and clinical presentation of SARS-CoV-2-related myocarditis is variable. Clinical manifestations can be as mild as fatigue and shortness of breath to devastating complications such as life-threatening arrhythmias, acute-onset heart failure with cardiogenic shock, pericardial effusion with cardiac tamponade and residual chronic heart failure.<sup>3-5</sup>

Electrocardiography changes are non-specific including intraventricular conduction delays, premature ventricular complexes, left ventricular hypertrophy and diffuse T wave inversion.<sup>3-5</sup> Moreover, changes pertaining to pericarditis may also be evident.<sup>9</sup> Furthermore, patients can present with

different tachyarrhythmias and bradyarrhythmias including high-degree atrioventricular conduction blocks.<sup>2</sup> Laboratory investigations usually reveal raised inflammatory markers including C reactive protein, erythrocyte sedimentation rate, procalcitonin, NT-proBNP and troponin.

ESC recommends imaging such as transthoracic echocardiography or cardiac magnetic resonance (CMR) in suspected myocarditis.<sup>2</sup> Focused cardiac ultrasound study is another effective option to screen for cardiovascular complications of SARS-CoV-2 infection.<sup>2</sup> Echocardiographic findings can vary from biventricular hypertrophy with preserved ejection fraction to severe left ventricular systolic dysfunction and regional wall motion abnormalities.<sup>3-5,9</sup> Furthermore, patterns of regional wall motion abnormalities consistent with reverse takotsubo cardiomyopathy have been described in the literature.<sup>10</sup> Pericardial effusion and cardiac tamponade have also been reported with SARS-CoV-2.<sup>9</sup> Myocardial wall oedema can be found on CMR.<sup>3,10</sup> T1/T2 mapping and late gadolinium enhancement can be useful in the diagnosis.<sup>11</sup> Coronary angiogram can be considered to rule out ischaemic cardiomyopathy in patients who are haemodynamically stable.<sup>4</sup> However, CT coronary angiogram has been recommended by ESC as a preferred modality to rule out concomitant coronary artery disease.<sup>2</sup> Endomyocardial biopsy can be used in cases where there is diagnostic uncertainty. But it has significant limitations, is not readily available in most centres and often not feasible in the context of current pandemic.

Numerous treatment options are being reviewed for SARS-CoV-2 infection. Currently, UK's National RECOVERY Trial is investigating the role of various antivirals, antibiotics, immunosuppressive therapies and convalescent plasma in patients with SARS-CoV-2. However, so far there are no clear recommendations on the management of myocarditis related to SARS-CoV-2. Multiple treatment approaches have been used with variable success.

Position statement of the ESC from 2013 discourages the routine use of corticosteroids or other immunosuppressive therapies in patients with any form of active viral myocarditis due to risk of overwhelming infection.<sup>12</sup> The routine use of corticosteroids in SARS-CoV-2-related myocarditis has not yet been established either. However, there are few available case reports describing the use of corticosteroids. Dennis Doyen *et al* described



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a case where they used corticosteroids in the management of SARS-CoV-2 myocarditis.<sup>4</sup> Individual case of corticosteroid use in combination with IL-6 receptor antagonist, tocilizumab, has also been reported.<sup>13</sup> However, given that there is no randomised control study on corticosteroid use in SARS-CoV-2 myocarditis, we do not advocate its routine use.

It is important to consider other causes of myocarditis, which are unrelated to SARS-CoV-2, as a concomitant infection with the virus may be an incidental finding. More importantly, the treatment would be guided by the underlying aetiology.

Kociol *et al* have suggested the use of inotropes and vasopressors in acute heart failure and cardiogenic shock secondary to fulminant myocarditis.<sup>14</sup> Ventilatory support has been used in few cases with progressive acute respiratory distress syndrome. Salamanca *et al* described a case of successful early use of temporary mechanical circulatory support for cardiogenic shock caused by fulminant myocarditis.<sup>15</sup> ESC also advocates the use of mechanical circulatory support such as extracorporeal membrane oxygenation in cardiogenic shock secondary to SARS-CoV-2 myocarditis.<sup>2</sup>

### What needs to be done?

Myocarditis secondary to SARS-CoV-2 is being increasingly recognised. We described common presentations that have been reported in the literature along with the possible laboratory and imaging findings. SARS-CoV-2 myocarditis has a high morbidity and mortality and an early recognition is crucial for the prompt initiation of treatment and prevention of complications in the phases to come. Knowledge gained so far can be used to improve the clinical practices before the next wave of pandemic.

Educational and promotional events can help to increase the awareness of myocarditis related to SARS-CoV-2. Clear distinction between cardiogenic pulmonary oedema secondary to SARS-CoV-2-related myocarditis and non-cardiogenic pulmonary oedema caused by lung inflammation is crucial. Echocardiography can be used as a tool for this distinction, since it is quick, reliable and readily available at the bedside. This can later be confirmed with further imaging modalities, like CMR, in more detail.

There is an opportunity to conduct further research and to identify the effective treatment options that would offer a prognostic benefit. A range of potential treatments have been suggested and trialled for SARS-CoV-2 in the national RECOVERY trial.<sup>16</sup> Results, so far, have demonstrated that there is no clinical benefit of hydroxychloroquine or lopinavir-ritonavir in hospitalised patients with SARS-CoV-2.<sup>16</sup> Dexamethasone has shown reduction in mortality by one-third in hospitalised patients with severe respiratory complications.<sup>16</sup> However, whether corticosteroids are effective for the management of SARS-CoV-2-related myocarditis; this is still not known.

There are many questions that need to be answered including the possible advantages and disadvantages of giving immunosuppressive therapy in this patient subset with myocarditis. Moreover, the role of different inotropic agents (sympathomimetics vs phosphodiesterase 3 inhibitors vs calcium channel sensitizers) needs to be evaluated in patients developing cardiogenic shock secondary to myocarditis. Whether they offer any prognostic benefit or is their role just limited to the management of acute haemodynamic instability is also not clear.

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