More than 10 years before the COVID-19 pandemic, viral genomes were found in endocardial biopsies from patients with idiopathic chronic cardiomyopathy. These findings demonstrated that viral infections are deeply involved in the pathogenesis of heart diseases. In this study, the Japanese authors used a three-dimensional human heart tissue model to investigate the risk of cardiac dysfunction and heart failure progression in persistent heart infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

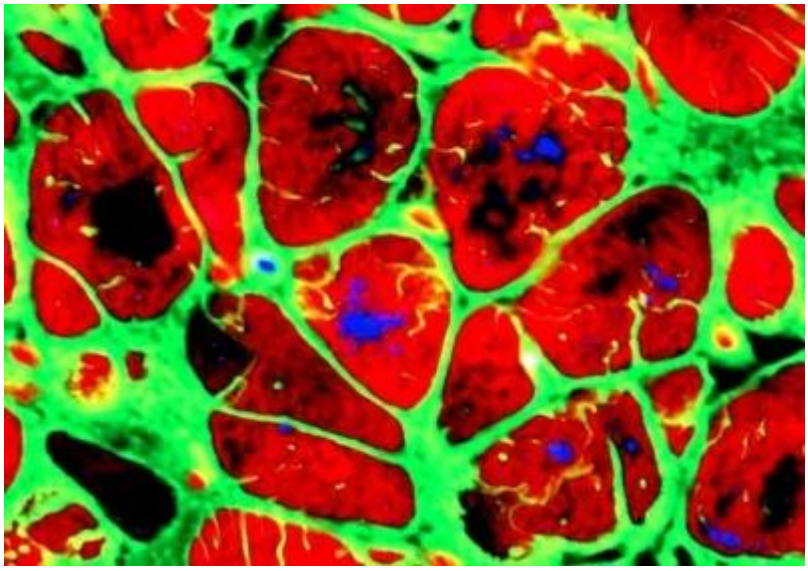
SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. Two host-cell factors are important for SARS-CoV-2 viral entry into many cell types: angiotensin-converting enzyme 2 (ACE2), which is bound by S protein, and transmembrane serine protease 2 (TMPRSS2), which cleaves S protein, allowing this binding to take place.

As previous studies reported highly expressed ACE2 receptors in the heart and cardiomyocytes of patients with heart failure, the authors hypothesized that some patients with chronic cardiomyopathy may have a persistent heart infection with SARS-CoV-2 and that conditions like heart failure may influence the infection severity.

About the study

The authors used a model of human cardiac microtissues (CMTs), differentiated from human iPS cells. The CMT model was composed of cardiomyocytes and other cardiac component cells (vascular endothelial cells and vascular mural cells) with a structure that morphologically and functionally mimics the human heart.

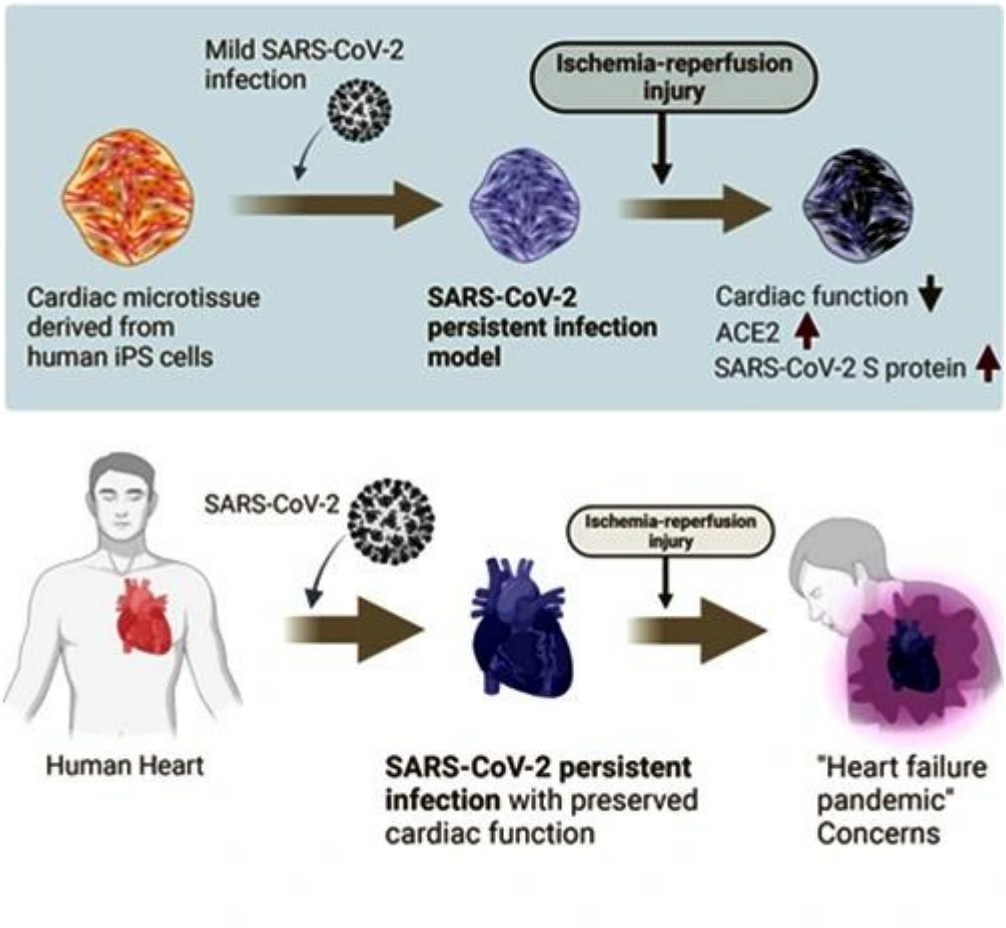
A model of human CMT was infected with mild, moderate, or high titers of SARS-CoV-2. The cardiac function was evaluated through tissue contractility measured by a video-based method.



Results

Seven days after the SARS-CoV-2 infection, the cardiac function deteriorated in the CMT model infected with mild, moderate, or high viral titers, compared to those in the non-infected CMT model. The cardiac function exhibited a recovery trend in the CMT model infected with mild or moderate titers, whereas in the CMT model infected with high viral titers a sustained decrease in contractility without a recovery was observed. These results confirm a possibility of cardiac function deterioration during the acute phase of COVID-19.

28 days after the SARS-CoV-2 infection, the histological and immunofluorescence analysis revealed that the vascular network was only slightly disrupted and that SARS-CoV-2 S proteins were intensely co-localized with CD31, a marker for cardiac endothelial cells in the CMT model infected with mild viral titers.



Original illustration from the study of Murata K. et al , 2023

As cardiac dysfunction and eventually heart failure may develop under additional cardiac stress, both CMT models, with and without persistent SARS-CoV-2 infection, were exposed to hypoxic stress mimicking ischemic heart disease.

In the CMT model infected with SARS-CoV-2, hypoxic stress for 18 hours and a subsequent normoxic condition for 48 hours led to a further deterioration of the contractile function. In addition, hypoxic conditions mimicking ischemic heart disease and reperfusion globally fragmented the vascular network formation and upregulated the ACE2 expression in cardiomyocytes. This was not seen in the non-infected CMT model which showed increased

pulsating frequency and recovery of contractile function.

The authors then explored whether the upregulation of inflammatory cytokines has a role in the deterioration of cardiac function under additional hypoxic stress. The expression of interleukin (IL)-1b, IL-6, tumor necrosis factor-α, and interferon-γ did not increase under hypoxic stress in the context of persistent SARS-CoV-2 infection, suggesting that cytokines involved in inflammatory response did not cause a deterioration of cardiac function.

Conclusion

This study which utilized a model of human cardiac microtissue demonstrated a high risk of cardiac dysfunction in heart tissues with persistent SARS-CoV-2 infection. Hypoxic conditions mimicking ischemic heart disease further deteriorated cardiac function and disrupted vascular network formation in a heart tissue model infected with SARS-CoV-2.

The authors emphasized that an explosive increase in the number of patients infected with SARS-CoV-2 may result in an enormously increased number of patients at potential risk for heart failure. They also noted that the model used in this study could be useful to investigate the development and progression of SARS-CoV-2 cardiomyopathy and possible therapeutic options.

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Murata K, Makino A, Tomonaga K, Masumoto H. Predicted risk of heart failure pandemic due to persistent SARS-CoV-2 infection using a three-dimensional cardiac model. iScience (2023), in press. https://www.sciencedirect.com/science/article/pii/S2589004223027189