SARS-CoV-2 receptor ACE2 expression in the human heart: cause of a post-pandemic wave of heart failure?

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This editorial refers to ‘Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts’, by L. Nicin et al., on page 1804.

The current ongoing pandemic COVID-19 (coronavirus disease outbreak at the end of 2019) is based on a positive-sense single-stranded RNA virus associated with a nucleoprotein within a capsid comprised of matrix proteins. Together with SARS-CoV and MERS-CoV, SARS-CoV-2 belongs to human betacoronaviruses. Although those viruses show many similarities, there are differences in their genomic and phenotypic structure resulting in huge consequences for their pathogenesis. Whereas fatality rates with previous SARS-CoV and MERS-CoV outbreaks were much higher, SARS-CoV-2 shows several unique features. There is a much higher contagiousity with a high prevalence for asymptomatic disease spreaders. The prolonged incubation period additionally helps the virus spreading towards a worldwide pandemic.

In infected patients, a high rate of asymptomatic and mild courses have been reported, with leading symptoms such as fatigue, coughing, shortness of breath, and fever. However, in quite a number of cases, there is a rapid spread of the virus in various organs including the lungs, neurological system, and most probably also the heart. The notion that pre-existing cardiovascular diseases (CVDs) strongly increase COVID-19 fatality rates is important and is due to at least two causes. In general, underlying diseases such as CVD, cancer, or immunocompromising diseases probably increase fatality rates in many infectious diseases including general flu or SARS-CoV-2. A number of pre-clinical studies have shown various organ systems to express the primary SARS-CoV-2 entry receptor, angiotensin-converting enzyme 2 (ACE2). Importantly, pre-clinical studies in rats indicated increased expression of ACE2 after renin-angiotensin-aldosterone system (RAAS) inhibitor medication. While ACE inhibitor therapy increased cardiac ACE2 mRNA but not cardiac ACE2 activity in rats, an angiotensin II type 1 receptor blocker (ARB) increased both cardiac ACE2 mRNA and activity.

A study published in the current issue of the European Heart Journal has now investigated expression of ACE2 in human hearts. Nicin et al. employed single nuclei RNA sequencing to analyse the expression of ACE and ACE2 in the different cell types of the human heart in five patients with aortic stenosis (AS), two patients with heart failure with reduced ejection fraction (HFrEF), and two samples from one healthy donor heart. They found ACE2 to be expressed in cardiomyocytes and pericytes, and at a lower level in fibroblasts, endothelial cells, and leucocytes. ACE2 was elevated in cardiomyocytes of patients with heart disease compared with healthy controls and also slightly, but not significantly, increased in endothelial cells and to a lower extent in fibroblasts. Immunostainings suggest increased expression of ACE2 in cardiomyocytes of patients with AS also at the protein level. In line with previous pre-clinical data, cardiomyocytes of patients who were treated with ACE inhibitors showed a significantly higher ACE2 expression (Figure 1). In contrast to pre-clinical data, they found less ACE2 activation in ARB-treated patients. Although preliminary, these data provide novel insights into the cell type-specific expression and regulation of ACE2 in the human heart.

This is an important hypothesis-generating observation with profound implications for basic and translational science, as well as another piece of the puzzle in the ongoing discussion of the optimal pharmacotherapy of SARS-CoV-2-infected cardiovascular patients.

There are several points I wish to discuss in light of those findings. In general, and as mentioned also by the authors, this study is clearly underpowered and any conclusions should be drawn very carefully. This especially includes the observation of less ACE2 activation in cardiomyocytes in patients treated with an ARB. Previous pre-clinical studies in rats had shown partly different results. However, there might be species differences as well as drug class-specific effects that need to be investigated in more detail in future studies, e.g. by...
employing human induced pluripotent stem cell (iPSC)-derived cardiomyocytes. Any clinical speculations on the ‘optimal’ pharmacotherapy of cardiovascular diseases, especially for heart failure patients, should at least currently not result in a change of guideline-directed therapies. This also includes antihypertensive treatments that should not be discontinued as doing so may be a greater risk factor for severe complications. In the future, the effects of current and future SARS-CoV2 antiviral medications or of co-morbidities such as diabetes on ACE2 expression should also be explored.

Although several organ systems seem to be affected, we currently do not exactly know about the organ-specific invasiveness of SARS-CoV2 in humans. Interestingly, a previous pathological study obtained from autopsies of fatal cases of SARS-CoV (not SARS-CoV2) found that with the exception of the lungs and gut, there was no viral detection in the heart, liver, spleen, kidney, lymph nodes, bone marrow, or muscles. The observations of elevated markers of cardiac damage, inflammatory reactions, and higher rate of rhythmological problems, however, may also suggest a direct cardiac infection by SARS-CoV-2.1,7,8

Another important finding of the study by Nicin et al. is the observation of a cell type-specific expression pattern of ACE2 in the human heart. This will also lead to follow-up studies investigating the cell type-specific role of ACE2 and potential functional implications. Importantly, another recent study also used single cell nuclei RNA sequencing in 15 healthy donor hearts and 40 failing explanted hearts obtained from the heart transplantation centre of Fuwai Hospital.9 In contrast to the observation of Nicin et al., these investigators found only low ACE2 expression in cardiomyocytes, but again high expression in pericytes. They conclude that SARS-CoV-2 infection in the human heart might attack primarily pericytes, and subsequently cause capillary endothelial cell dysfunction, thus inducing microcirculation disorders, explaining the observed elevation in markers of cardiac damage. Mechanistic follow-up studies in both cardiomyocytes and vascular cells, including pericytes and endothelial cells, are clearly warranted. This may also lead to intriguing insights and potential consequences for patients with heart failure of ischaemic vascular origin as well as for heart failure patients with preserved ejection fraction and impaired microvascular function.

Finally, we should not become ‘blinded’ by the COVID-19 pandemic for correct diagnosis and therapy of our patients with CVD. Some of the COVID-19 symptoms such as shortness of breath and coughing are typical problems of patients with heart failure. Whether these initial findings can be extrapolated to European or US hospitals is likely, but remains to be

**Figure 1** Cell type-specific expression of the putative SARS-CoV2 receptor ACE2 in cardiovascular cells and its infection consequences. Direct cardiac harm, fear of cardiac-diseased patient to go to a physician/hospital and the suboptimal treatment in selected hospitals with heavy COVID-19 overload may result in a post-pandemic wave of new cases of CVD patients, especially those with heart failure. ACEi, angiotensin converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
determined. Potentially, the COVID-19 outbreak will also lead to an increase of long-term complications of patients with CVD such as heart failure in both patients infected with SARS-CoV-2 and those that are not infected but that were treated suboptimally during the ongoing pandemic (Figure 1).

In conclusion, Nicin and co-workers report here an important observation with future implications in both research and, potentially, treatment of SARS-CoV-2-infected cardiovascular patients. These novel data at least suggest that it will be important to monitor SARS-CoV-2-infected patients for cardiovascular complications and assess the impact of ARB/ACE inhibitor therapy in more detail.

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