ESC European Society of Cardiology

Cardiovascular Research (2020) **0**, 1–5
doi:10.1093/cvr/cvaa093

REVIEW

The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease

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Received 13 March 2020; revised 23 March 2020; editorial decision 31 March 2020; accepted 1 April 2020

Abstract Angiotensin-converting enzyme 2 (ACE2) has emerged as a key regulator of the renin–angiotensin system in cardiovascular (CV) disease and plays a pivotal role in infections by coronaviruses and influenza viruses. The present review is primarily focused on the findings to indicate the role of ACE2 in the relationship of coronaviruses and influenza viruses to CV disease. It is postulated that the risk of coronavirus or influenza virus infection is high, at least partly due to high ACE2 expression in populations with a high CV risk. Coronavirus and influenza virus vaccine usage in high CV risk populations could be a potential strategy to prevent both CV disease and coronavirus/influenza virus infections.

Keywords Angiotensin-converting enzyme 2 • Cardiovascular disease • Coronaviruses • Influenza viruses

Background

The renin–angiotensin system (RAS) plays a critical role in maintaining normal cardiovascular (CV) functions and contributes to a spectrum of CV diseases, such as hypertension, coronary heart disease, myocarditis, and congestive heart failure.[1] Generally, the RAS is composed of angiotensinogen, renin, angiotensin II (Ang II), Ang II receptors (AT1 and AT2 receptors), and angiotensin-converting enzyme (ACE).[2,3] ACE is ubiquitously present in many cell types, tissues, and organs. ACE is an ectoenzyme that plays a role in the generation of Ang II by catalysing the extracellular conversion of the decapeptide Ang I.[4] In the past two decades, a new homologue of the enzyme, termed angiotensin-converting enzyme 2 (ACE2), was identified, and ACE2 can convert Ang II to Ang(1-7) or convert Ang I to Ang(1-9).[5,6] Although Ang II increases blood pressure (BP), Ang(1-7) is a vasodilator, and the ACE2/Ang(1-7) axis has been suggested to act as a natural damping mechanism for the activation of the classical RAS.[7]

Besides its crucial role in CV disease, ACE2 has also been considered as a functional potential coronavirus [including severe acute respiratory syndrome (SARS) coronavirus, human coronavirus NL63 (HCoV-NL63), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called 2019-nCoV] receptor that binds directly to the viral spike protein.[8–11] In addition, ACE2 plays an important role in acute lung injury induced by influenza viruses, such as H1N1, H5N1, and H7N9,[12–14] suggesting that ACE2 still has unexpected facets with clinical implications.

CV diseases are the most common non-communicable diseases globally.[15] In addition, emerging viral infections also represent a major global public health concern,[16–18] such as coronavirus disease 2019 (COVID-19,caused by SARS-CoV-2) in China[19] and 2009 H1N1 in the USA and Canada.[20] ACE2 could be a novel therapeutic target for CV diseases and a potential target for the treatment of coronaviruses and influenza viruses. The present review is primarily focused on the findings indicating the role of ACE2 in the relationship of coronaviruses and influenza viruses to CV disease (*Figure 1*).

Coronaviruses/influenza viruses and CV diseases

Both influenza viruses and coronaviruses are typically contagious viruses that cause respiratory disease. Coronaviruses are members of the subfamily Coronavirinae, in the Coronaviridae family and the Nidovirales order, including four genera—*Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.[21] Coronaviruses cause respiratory and intestinal infections in animals and humans. They were not considered to be highly pathogenic to humans until the outbreak of SARS in 2003. Six human-infecting types of coronaviruses were discovered before 2019. Two highly pathogenic viruses [SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)] cause severe respiratory syndromes in humans, and the other four human coronaviruses (HCoV-NL63,

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HCoV-229E, HCoV-OC43, and HKU1) induce only mild upper respiratory tract diseases in immunocompetent hosts.[15,22,23] In 2019, a novel coronavirus (SARS-CoV-2) was identified in China and all over the world. It has infected >1 300 000 of the population and became a public health emergency declared by the World Health Organization (WHO). So far, the pathology of COVID-19 pneumonia is still not clear. Human influenza viruses are members of the *Orthomyxoviridae* family. Based on the matrix and nucleoprotein genes, influenza viruses have been classified as type A, B, C, and D. In humans, only influenza A and B viruses (influenza A and B) are of epidemiological and public interest,[24] although other related viruses (influenza C and D viruses) may also cause at least subclinical infections in humans.[15] Despite the production of annually designed vaccines and the many improvements in public health surveillance and infrastructure, each year, in the USA alone, seasonal influenza A and B viruses continue to evolve and take the lives of 3000–48 000 people.[25] Highly transmissible and pathogenic virus outbreaks cause a significant disease burden in terms of morbidity and associated complications, and have a huge economic impact.[11,26,27] Meanwhile, CV disease is also the leading cause of death and disease burden worldwide.[15]

Infection with the virus might be one of the pathogeneses of atherosclerosis and related CV disease. Atherosclerosis is a chronic inflammatory disease of the arteries associated with pro-inflammatory lipid abnormalities.[28] Infectious diseases are suggested to be a causative factor, and several viruses have been studied for their relationship to CV diseases.[15,29] Influenza can trigger heart attacks, and vaccination against influenza reduces the risk of CV events. For example, influenza infection has long been thought to directly contribute to CV morbidity and mortality.[30] Various influenza viruses are involved in the development and progression of atherosclerosis and related CV disease,[31,32] and influenza virus RNA has even been found in mouse and human atherosclerotic plaques.[33,34] Further, acute influenza infection has been shown to accentuate the progression of atherosclerosis and related CV disease.[35]

Epidemiological data on the coronavirus and CV disease are scant. However, it is shown that MERS-CoV patients have a high prevalence of hypertension and CV disease. In MERS-CoV patients, the prevalence of chronic heart disease and hypertension is 15% and 33%, respectively.[36] More recently, there are new pieces of evidence which show that the precondition of CV disease may increase the risk of SARS-CoV-2 infection. Among 41 admitted hospital patients infected with SARS-CoV-2 in Wuhan, 15% had hypertension, and 15% had CV disease.[15] Another study included 138 patients infected with SARS-CoV-2 in Wuhan and found that 31% of the patients had hypertension, and 15% had CV disease.[37] In another retrospective study of 99 patients with pneumonia, 40% had CV and cerebrovascular diseases.[38] The association between coronaviruses and CV disease still needs further study.

ACE2 and CV disease

ACE2 has emerged as a key regulator of the RAS.[39] Increasing evidence suggests that ACE2 plays a protective role in CV disease and other pathologies.[40] In atherosclerosis-prone apolipoprotein E knockout mice, ACE2 deficiency results in augmented vascular inflammation, and the inflammatory response contributes to increased atherosclerotic plaque formation.[41] In animal studies, Sarkissian *et al.* found that cardiac overexpression of ACE2 exerted a protective influence on the heart during myocardial infarction by preserving cardiac function, left ventricular wall motion, and contractility.[42] Yamamoto *et al.* reported that ACE2 gene knockdown resulted in severe cardiac dysfunction (i.e. reduced contractility, increased hypertrophy, and dilation).[43] In addition, ACE inhibitors and AT1 receptor antagonists, which have been proven to be beneficial for the treatment of myocardial infarction and heart failure, increase ACE2 gene expression, attenuate ACE2 gene down-regulation, and normalize AT1 receptor expression in the myocardium post-myocardial infarction.[44–46] Loss of ACE2 enhances adverse remodelling and susceptibility to pressure and volume overload.[47] Human recombinant ACE2 suppresses myocardial hypertrophy, fibrosis, inflammation, and BP.[47] Feng *et al.* reported that ACE2 overexpression reduced Ang II-induced cardiac hypertrophy partially through a decrease in sympathetic drive in syn-hACE2 transgenic mice.[48] Wysocki *et al.* found that, during Ang II infusion, recombinant human ACE2 effectively degraded Ang II and, in the process, normalized BP.[49] One of the ACE2 activators, xanthenone, has been demonstrated to decrease BP and improve cardiac function with inhibition of cardiac and renal fibrosis in spontaneously hypertensive rats.[50] The key role of ACE2 in the progressive deterioration of cardiac remodelling and systolic dysfunction has further been found in humans.[51] Circulating ACE2 activity increases with increasing vascular tone, which suggests that elevated ACE2 may be a compensatory response to hypertension.[15] Ohtsuki *et al.* reported that the up-regulation of the ACE2 gene in the left ventricular myocardium of patients with severe heart failure was associated with the degree of left ventricular dilatation and may thereby constitute an important adaptive mechanism to retard the progression of adverse left ventricular remodelling.[15] Studies with recombinant human ACE2 have shown beneficial cardiac effects.[49,50]

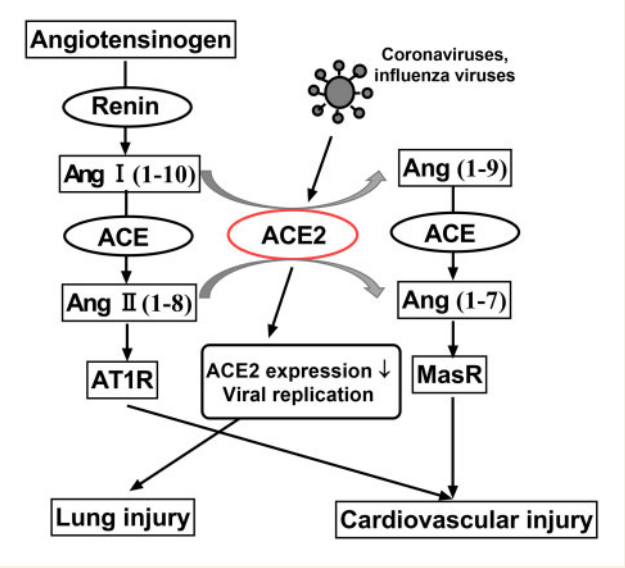

Figure 1 The role of ACE2 in coronavirus/influenza virus-induced cardiovascular and lung injury.

Coronaviruses/influenza viruses and ACE2

Human ACE2 is an endothelium-bound carboxymonopeptidase with a single active site catalytic region whose expression is limited mainly to endothelial cells of the arteries, arterioles, and venules in various organs including the heart, lungs, and kidneys.[52] Loss of ACE2 leads to age-

dependent cardiomyopathy and kidney disease, while also enhancing pulmonary, cardiac, and renal injuries.[53] On the other hand, ACE2 was identified as a functional SARS coronavirus receptor.[8] ACE2 and the AT2 receptor protect mice from SARS coronavirus-induced acute respiratory distress syndrome, whereas ACE, Ang II, and the AT1a receptor promote the impairment of lung function in mouse models.[9,54] Kuba *et al.* provided the genetic proof that ACE2 is a crucial SARS-CoV receptor *in vivo*, and SARS-CoV infections and the spike protein of SARS-CoV reduce ACE2 expression.[9] This study also found that blocking the renin–angiotensin pathway can attenuate the worsened acute lung failure induced by the injection of SARS-CoV spike protein in mice. Furthermore, antibodies directed against ACE2 and soluble ACE2 molecules and derivatives were demonstrated to be capable of blocking SARS-CoV infection.[55] Like SARS-CoV, HCoV-NL63 also employs ACE2 as a receptor for cellular entry.[56] Wevers and Hoek found that HCoV-NL63 infection induced a reduction of cellular ACE2 expression.[57] Tseng *et al.* demonstrated that transgenic mice expressing hACE2 were highly susceptible to SARS-CoV infection, resulting in a wide spectrum of clinical manifestations, including death, depending upon the transgenic lineages.[58] Letko and Munster first demonstrated that SARS-CoV-2 used the same cell entry receptor, ACE2, as SARS-CoV,[10] and subsequent studies also confirmed this result.[15,59–61]

In experimental mouse models, Zou *et al.* found that infection with highly pathogenic avian influenza A H5N1 virus results in a down-regulation of ACE2 expression in the lung and increased serum Ang II levels.[12] Genetic inactivation of ACE2 causes severe lung injury in H5N1-challenged mice, confirming the role of ACE2 in H5N1-induced lung pathologies.[12] Yang *et al.* reported that ACE2 could mediate the severe acute lung injury induced by influenza A (H7N9) virus infection in an experimental mouse model. Moreover, ACE2 deficiency worsened the disease pathogenesis markedly, mainly by targeting the AT1 receptor.[13] This result is consistent with a study by Huang *et al.*, who found that plasma Ang II levels were linked to H7N9-induced disease severity and predicted a fatal outcome in H7N9 patients.[62]

Myocardial injury has been observed during coronavirus infection.[63,64] Pulmonary infection with human SARS-CoV in mice led to an ACE2-dependent myocardial infection, and myocardial damage was found in patients who had SARS-CoV in their hearts.[53] Thus, the use of cardioprotective medications is essential. The effect of ACE inhibitor (ACEI) treatment during coronaviruses/influenza virus infections in humans is unclear. Lei *et al.* reported that fusion proteins (ACE2–Ig) exhibit potent inhibitory activity against SARS-CoV and SARS-CoV-2 *in vitro*.[65] Huentelman *et al.* identified *N*-(2-aminoethyl)-1 aziridine-ethanamine as a novel ACE2 inhibitor that was effective in blocking the SARS coronavirus spike protein-mediated cell fusion.[66] A case study found that treatment with an ACEI together with plasma exchange improved the condition of a patient with scleroderma renal crisis complicated with thrombotic microangiopathy triggered by influenza B virus infection.[67] Another case study of a woman positive for H1N1 and with severe acute left ventricular failure found that aggressive initial therapy followed by beta-blockers and ACEIs led to restoration of the patient's left ventricular function and an associated marked improvement in symptoms.[68] Angiotensin II receptor blockers (ARBs), a first-line therapy of hypertension, could inhibit the actions of Ang II through selective binding of AT1 receptors in vascular smooth muscle,[69] and are effective in lowering BP and preventing major CV outcomes.[70] Previous studies suggest that ARBs could up-regulate ACE2 in both rats and humans.[71,72] A recent commentary suggested that ARB could be used as a therapy for reducing the aggressiveness and mortality from coronavirus infections.[73] There is now an urgent need to study the effect of ACEI and ARB treatment during coronavirus/influenza virus infections in humans.

Coronavirus/influenza virus vaccines and CV disease prevention

Vaccination constitutes the primary approach for controlling influenza. In recent decades, numerous advances have been made in the development of vaccines against influenza viruses, such as the replacement of inactivated whole-virus vaccines with split or subunit vaccines, which comprise less reactogenic alternatives.[74] The majority of available annual trivalent influenza vaccines contain two influenza A strains (H1N1 and H3N2) and only one influenza B virus.[75] More recently, inactivated quadrivalent vaccines containing both Victoria and Yamagata lineages of type B IV have become available.[76,77] Several epidemiological and clinical studies have demonstrated the beneficial effects of the influenza vaccine in patients with CV disease.[35,78,79] In a meta-analysis of randomized clinical trials, Udell *et al.* reported that the use of the influenza vaccine was associated with a lower risk of major adverse CV events.[80] In another meta-analysis including eight trials with 12 029 participants, Clar *et al.* reported that influenza vaccination may reduce CV mortality and combined CV events in patients with CV disease.[81] Furthermore, a recent meta-analysis including six cohort studies and 179 158 participants also confirmed that influenza vaccination was associated with a significant decrease in all-cause mortality in patients with heart failure.[82]

To date, no vaccine has been developed to prevent SARS-CoV-2 or other coronavirus infections. Scientists across the world are racing to develop a vaccine, which is also a promising tool to prevent CV disease, for the coronavirus to tackle the outbreak of COVID-19.

Conclusions and future prospects

A role for ACE2 in involvement in vascular protective actions has been postulated. We therefore hypothesize that the risk of coronavirus or influenza virus infection is high among the CV disease-susceptible population, at least partly due to high ACE2 expression in this population, which needs to be confirmed in the future. Our hypotheses suggest that more protection should be employed for patients with CV disease. Coronavirus or influenza virus vaccine usage in the high CV risk population could be a potential strategy to prevent both CV disease and coronavirus/influenza virus infections. Furthermore, there is an urgent need to develop a vaccine for coronavirus prevention and control, and it will be important to evaluate the effect of coronavirus vaccines on CV protection.

Conflict of interest: none declared.

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