



## Angiotensin converting enzyme 2 (ACE2), COVID-19 and cardiac injury: what cardiologist should know

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### ABSTRACT

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Coronavirus disease 2019 (COVID-19) has already stated as a pandemic by the World Health Organization (WHO). Until now, Indonesia has also infected with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. All medical staffs join hand by hand to overcome this pandemic, not only pulmonologist but also cardiologist. Early reports from China showed that cardiovascular comorbidities add more mortality than without comorbid. Cardiac implication of this infection is cardiac injury. Viral pathology and pathophysiology that induced cardiac injury is still debatable and not well understood. Angiotensin-converting enzyme 2 (ACE2) has emerged as a key regulator of renin-angiotensin system in cardiovascular disease. ACE2 has been postulated as one of the pathophysiology of COVID-19 and cardiac injury.

### ABSTRAK

#### Keywords:

COVID-19;  
SARS-CoV-2;  
cardiac injury;  
pathophysiology;  
ACE2

*Coronavirus disease 2019*(COVID-19) telah dinyatakan sebagai pandemi oleh Organisasi Kesehatan Dunia (WHO). Saat ini, Indonesia juga telah terinfeksi dengan infeksi coronavirus 2 (SARS-CoV-2) yang parah. Semua staf medis bergandengan tangan untuk mengatasi pandemi ini, tidak hanya dokter paru tetapi juga ahli jantung. Laporan awal dari Cina menunjukkan bahwa komorbiditas kardiovaskular menambah lebih banyak kematian daripada tanpa komorbiditas. Implikasi jantung dari infeksi ini adalah cedera jantung. Patologi virus dan patofisiologi yang menyebabkan cedera jantung masih bisa diperdebatkan dan tidak dipahami dengan baik. Angiotensin-converting enzyme 2 (ACE2) telah muncul sebagai pengatur utama sistem renin-angiotensin pada penyakit kardiovaskular. ACE2 telah disimpulkan sebagai salah satu patofisiologi COVID-19 dan cedera jantung.

### INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a newly recognized viral infectious disease that has spread rapidly throughout Wuhan, Hubei, China, and several countries around the world, including Indonesia.<sup>1</sup> Studies from China have described the clinical characteristics and findings of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>2</sup> Patient of

COVID-19 showed respiratory symptoms but often has cardiovascular-related symptoms.<sup>3</sup>

The COVID-19 can cause cardiac injury and chronic damage to the cardiovascular system.<sup>3,4</sup> The mechanism of myocardial injury caused by SARS-CoV-2 infection might be related to angiotensin converting enzyme 2 (ACE2).<sup>3</sup> Chronic cardiovascular disease may become unstable because of this viral infection due to cytokine storm.<sup>3-5</sup>

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Most of cardiac markers are high due to acute inflammation of COVID-19.<sup>6</sup> The present review is focused on the role of ACE2 to cardiac injury in COVID-19.

### **COVID-19, ACE2 AND CARDIAC INJURY**

Currently, our knowledge about SARS-CoV-2 as novel enveloped single-stranded RNA beta-coronavirus(+ssRNA) is lacking, but it has phylogenetic similarity with severe acute respiratory syndrome corona virus (SARS-CoV) and middle east respiratory syndrome corona virus (MERS-CoV).<sup>7</sup> Coronavirus are positive-single-stranded RNA that classified into four categories; alpha coronavirus(alphaCov), beta coronavirus (betaCoV), delta coronavirus (deltaCoV), and gamma coronavirus (gammaCoV).<sup>8</sup> RNA virus is a highly mutated, but exploring and defining their biological characters are less important than detection, contamination, treatment and analysis of viruses that are pathogenic to human succeeding their discovery.<sup>9</sup> Even-though SARS-CoV-2 is not a descendent of the SARS-CoV, but genetically both of them have 82% similarity in nucleotide identity.<sup>10</sup> For that reason, the evolutionary history and characteristics of both viruses are conjointly informative in management of the current COVID-19 pandemic situation.

Based on previous insight about SARS and MERS, SARS-CoV-2 pathogenicity is determined by combination of viruses' replication and host immune response. They have unique coding strategy by translated into two large polyproteins from viral RNA and exoribonuclease (ExonN) function which allow them to maintain a large RNA genome without the accumulation of lethal mutation.<sup>11</sup> The SARS-CoV's envelope spike glycoprotein binds with its cellular receptor, ACE2, and the MERS-CoV with dipeptidyl peptidase 4 (DPP4).<sup>10,11</sup> Since spike structure of SARS-CoV-2 more likely similar to SARS-

CoV, their spike hypotheses bind with ACE2 in human cellular, instead of with DPP4. SARS-CoV-2 is able to use all ACE2 proteins to enter cells, but not cells that did not express ACE2, indicating that ACE2 is probably the cell receptor.<sup>12</sup>

Down regulation of the ACE2 is caused by attachment to SARS-CoV-2's protein spike. Contrary, ACE2 also has a protective effect on heart and lung organs. During COVID-19 infection, the reduction of ACE2 means an increase in viral infection and deteriorating cardiac protective condition.<sup>11,13</sup> Those condition makes angiotensin II (Ang II) increase and bind to angiotensin II type 1 receptor (AT1R) which responsible in heart pathologic condition<sup>13</sup>. ACE2 will change Ang II into angiotensin1-7 (Ang1-7) which responsible for opposing the proliferative and pro-fibrotic action of Ang II and acting via its own receptor. Binding of Ang1-7 and MasR will oppose the molecular and cellular effects of Ang II, such as anti-atrophy, antifibrosis, antiinflammation, antioxidant and vasodilation.<sup>14,15</sup>

Secondly, like ACE2, immune response is important for resolution process especially in viral infection but at some point, it can be immunopathogenic condition. There is a possibility of recurrent symptoms after COVID-19 patient fully recovered despite the diminution of the viral load. The Immunopathologic condition might responsible for exacerbation of clinical condition within 3 weeks after recovered and threaten cardiovascular system independently with viral load.<sup>16,17</sup> Retrospective longitudinal study shows fully recovered patient tends to develop an adaptive immune response and it suggests recurrent symptom might happen because failure to switch between innate to adaptive immune response.<sup>18</sup> COVID-19-induced myocardial inflammation is mediated predominantly by macrophages and the resultant production of chemokines.<sup>19</sup>

SARS-CoV-2 binds to ACE2 and involves cell surface associated trans-membrane protein serine 2 (TMPRSS2)<sup>20</sup> in endothelial cell and presumably activates disintegrin and metalloprotease-17 (ADAM17)<sup>21</sup> or tumor necrosis factor alpha converting enzyme (TACE) by its protein spike and subsequent intracellular degradation of ACE2 or soluble ACE2 (sACE2). ADAM17/TACE is a membrane-anchored protein responsible for ectodomain shedding of various trans-membrane proteins and it can initiate/inhibition of signal cascade and cellular responses. TACE substrates are responsible for endothelial wall inflammation, atherosclerosis, and

plaque formation and/or progression. The increasing local TACE activation correlates with macrophage infiltration and arterial remodeling. TACE, through up-regulation of tumor necrosis factor alpha (TNF $\alpha$ ), promotes premature endothelial cell senescence and takes part in coronary artery aging process.<sup>22</sup> Degradation of ACE2 in endothelial cell worsening the situation and it can lead to endothelial dysfunction, vascular vasoconstriction, inflammatory response until promoting atherosclerotic evolution.<sup>23</sup> FIGURE 1 explains the pathomechanism of COVID-19, ACE2, and cardiac injury.

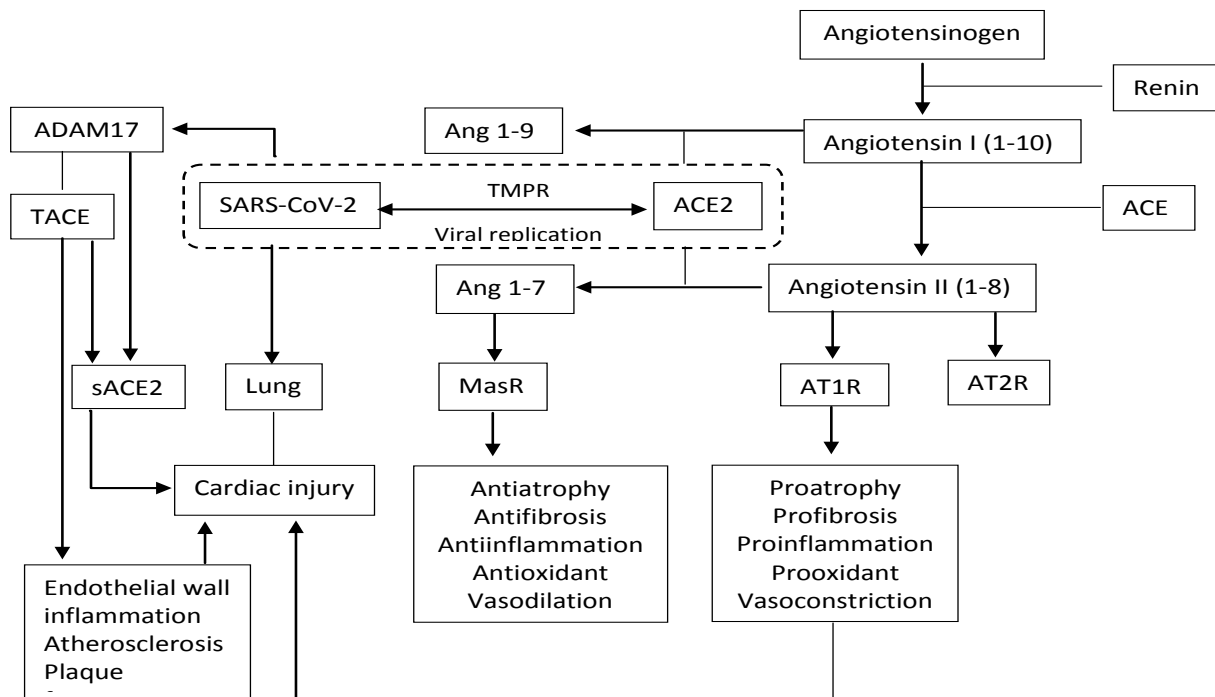


FIGURE 1. Pathomechanism of COVID-19, ACE2 and cardiac injury. ACE: Angiotensin Converting Enzyme; ACE2: Angiotensin Converting Enzyme 2; ADAM: A Disintegrin and Metalloprotease-17; Ang 1-7: Angiotensin 1-7; Ang 1-9: Angiotensin 1-9; AT1R: Angiotensin II type 1 Receptor; AT2R: Angiotensin II type 2 Receptor; MasR: Mas Receptor; SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus 2; sACE2: soluble Angiotensin Converting Emzyme 2; TACE: Tumor necrosis factor Alpha Converting Enzyme; TMPRSS2: Transmembrane protein serine 2.

It has been proposed that treatment of hypertension with renin-angiotensin system (RAS) inhibitors may influence SARS-CoV-2 binding to ACE2, promoting the progress of COVID-19.<sup>24</sup> RAS inhibitors cause a compensatory increase in tissue levels of ACE2<sup>25</sup> and may be detrimental in patients exposed to SARS-CoV-2.<sup>26</sup> There is no clear evidence and association that using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) lead to up-regulation and circulating levels of ACE2 in human tissues.<sup>27</sup> Because of that reasons, no clinical evidence to support the effects of RAS inhibitors in COVID-19 patients and also guidelines from major cardiovascular societies stated that patients on ACEI or ARB should not stop their medications.<sup>27,28</sup>

## CONCLUSION

SARS-CoV-2 is thought to infect host cells through ACE2 to cause COVID-19, while also causing cardiac injury, although the specific mechanisms are uncertain. In this era of pandemic, a cardiologist should know the cardiac implication of COVID-19 and the use of ACEI and ARB in COVID-19 patients.

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