Hypoxia in acute cardiac injury of coronavirus disease 2019: lesson learned from pathological studies

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Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has infected 972,303 people and caused 50,322 deaths all over the world according to the latest WHO report.[1] As a highly contagious disease, COVID-19 has killed more people than severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) combined, despite an relatively low case-fatality rate.[2,3] Although it mainly attacks respiratory system, other systems including cardiovascular system are also influenced by COVID-19. Acute cardiac injury (ACI) is also one of the noteworthy issues which researchers have noticed in several studies.[4–7]

According to the study by Chen, et al.[8], ACI was among the most common critical complications during exacerbation of COVID-19. In the newly published article, researchers found that ACI was not only a common condition among hospitalized patients with COVID-19, but also was associated with high risk of in-hospital mortality.[9] Another cohort study also showed that ACI was associated with fatal outcome of patients with COVID-19, especially in patients with underlying cardiovascular diseases (CVD).[10]

The underlying mechanism of ACI in COVID-19 patients is still under debate. Some different theories maybe try to explain this phenomenon.

Angiotensin-converting enzyme 2 (ACE2) plays an important role in both the normal heart function and the development of hypertension.[11,12] SARS-CoV-2 causes COVID-19 by binding of the spike protein to ACE2, which further causes the disturbance of renin-angiotensin system (RAS) and causes ACI in COVID-19.[13]

Acute myocarditis is also believed to be responsible for ACI in COVID-19. Alhoghani, et al.[14] reported a case with significant cardiac involvement infected by middle east respiratory syndrome coronavirus (MeRS-CoV). The laboratory test was negative for viruses known to cause myocarditis and cardiovascular magnetic resonance revealed evidence of acute myocarditis. Similarly, Inciardi, et al.[15] reported a healthy 53-year-old patient developed acute myocarditis with systolic dysfunction, which confirmed on cardiac magnetic resonance imaging, and diagnosis of COVID-19 was confirmed one week later. However, there is no pathological evidence for this theory.

Overexuberant inflammatory response is believed to be another possible mechanism for ACI. Wan, et al.[16] observed that the level of interleukin-6 (IL-6) in severe COVID-19 patients is significantly higher than mild patients.

Hypoxia is another extremely important mechanism of ACI in COVID-19 patients. Wan, et al.[16] reported that 31.2% of COVID-19 patients had dyspnea and the proportion of patients who complained dyspnea is 63.9% in intensive care unit patients. According to the retrospective studies we mentioned above, the patients with ACI have higher respiratory rate and invasive mechanical ventilation rate, this means that patients with ACI were manifested higher risk of hypoxia.[4–6] According to the two cohort studies by Chen, et al.[8] and Shi, et al.[9], patients with ACI were more likely to accompanied with acute respiratory distress syndrome (ARDS) compared with patients without ACI.

However, what is the main mechanism of ACI in COVID-19 patient is still unclear.

Xu, et al.[17] reported the first pathological result of COVID-19 patient, which showed little inflammatory infiltrates and no signs of substantial damage in the heart tissue.
Interestingly, the first two COVID-19 cases of autopsy in China also revealed no abnormal findings in heart tissue.[18] Another report regarding to three cases of minimally invasive autopsies showed the lungs from COVID-19 patients manifest significant pathological lesions, including the alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation and hyaline membrane formation, still, there was no evidence of direct damage to the heart.[19]

All of the pathological studies showed no sign of direct damage to the heart. So, we believe that hypoxia is the main mechanism of ACI in COVID-19 patients. As a matter of fact, all of the studies we mentioned above demonstrated that patients with ACI were more likely to undergo invasive mechanical ventilation and more severe condition in hypoxia.

It is important to illustrate the main mechanism of ACI in these patients, because the mortality of COVID-19 is high in severe and critical patients.[4-7] As we mentioned above, patients with ACI were more likely to be severe and critical cases. For patient with ACI, more aggressive airway management procedures and supportive measurement, such as invasive mechanical ventilation or even extracorporeal membrane oxygenation (ECMO), should be considered in these patients.[20]

In conclusion, the underlying mechanism of ACI in COVID-19 is complicated (Figure 1). But according to the pathological findings, the main mechanism of ACI in COVID-19 could be hypoxia. However, our hypothesis is only based on limited number of pathological cases and autopsy cases, more evidence is still needed in future studies with pathological results.

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Figure 1. The potential mechanism of acute cardiac injury in COVID-19. COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; MODS: multiple organ dysfunction syndrome; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RAS: renin-angiotensin system; UCG: ultrasound cardiogram.
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