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Trimetazidine and COVID-19-induced acute cardiac injury: a missed key

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To the editor,

In the beginning, the famous saying of Imam Ali said, "Two are insatiable: a seeker of knowledge and a seeker of money." That is why we started writing this letter, because we are seekers of knowledge.

It has been shown that 20% of COVID-19 patients had signs of acute cardiac injury (ACI) as measured by high-sensitive troponin [1]. Even after controlling for confounding factors, COVID-19-induced ACI is associated with a fourfold increase in mortality [1].The underlying mechanism for ACI in COVID-19 is related to a higher expression of angiotensin converting enzyme 2 (ACE2) in cardiomyocytes than other tissues, which is exploited by SARS-CoV-2 for entry into the host cells [2]. SARS-CoV-2 spike protein binds to ACE2 causing down-regulation of this receptor [2]. ACE2 has a protective effect on cardiomyocytes by reducing angiotensin II (AngII)-induced cardiac fibrosis, hypertrophy, and diastolic dysfunction [11]. Recombinant ACE2 reduces AngII and pressure overload-induced myocardial remodeling [11]. Therefore, ACE2 is regarded as a crucial negative regulator of AngII-induced cardiac disease and complications.

Therefore, the direct cytopathic effect of SARS-CoV-2 may lead to direct ACI in COVID-19 [2]. However, hyperinflammation, exaggerated immune response, and the development of cytokine storm could be the possible pathway for indirect ACI in COVID-19 [2].

Pharmacological therapy of ACI in COVID-19 is essential to prevent heart failure and cardiac fibrosis. In general, cardiac ischemia, heart failure, thrombotic disorders, and other cardiovascular complications in COVID-19 are treated with standard treatment approaches [3]. Colchicine, renin inhibitors, aldosterone receptor antagonists, and the neprilisin inhibitor sacubitrile have been shown to be effective in the treatment of ACI in COVID-19 [3].

Trimetazidine (TMZ), an anti-anginal agent, inhibits β-oxidation of fatty acids by blocking long-chain Acetoacetyl-CoA thiolase (thiolase II), leading to enhancement of glucose oxidation by cardiomyocytes [4]. Through energy preservation, TMZ improves cellular homeostasis and prevents intracellular reduction of adenosine triphosphate (ATP) [4]. Also, TMZ is effective against cardiac fibrosis and ischemic-reperfusion injury through modulation of cardiac fibroblast activity and the Akt/caspase-3 signaling pathway, respectively [4]. Therefore, TMZ might be

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effective in the management of acute coronary syndrome and other ischemic events in COVID-19 [5]. Additionally, inhibitors of fatty acid oxidation impair SARS-CoV-2 entry and replication [6]. Thus, TMZ through inhibition of the β-oxidation of fatty acids may attenuate the pathogenesis of SARS-CoV-2 infection.

Remarkably, TMZ has anti-inflammatory and antioxidant effects by inhibiting activation of nuclear factor kappa B (NF-κB) and production of reactive oxygen species (ROS) [7]. Therefore, TMZ exerts a cardio-protective effect through attenuation of mitochondrial dysfunction, inflammation, oxidative stress, and apoptosis [7]. As well, nuclear factor erythroid related factor 2 (Nrf2) which is the main transcription factor of the antioxidant mechanism, is stimulated by TMZ [7]. Indeed, induction of oxidative stress and activation of NF-κB signaling pathway are linked with ACI in COVID-19 [8]. Thus, TMZ could be effective against ACI in COVID-19 through activation of Nrf2 and suppression of NF-κB signaling pathway.

Recently, Wu et al. found that TMZ is effective against viral myocarditis because of its anti-inflammatory and immunomodulatory effects [9]. TMZ reduces cardiac inflammation in heart failure by inhibiting release of pro-inflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) [10].

Taken together, in virtue of its anti-inflammatory and antioxidant effects, TMZ might be a proposed drug for the management of ACI in COVID-19. In this regard, experimental, preclinical, and clinical studies are warranted.

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Conflict of interest The authors have no conflicts of interest to declare.

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