

## Epinephrine use in COVID-19: friend or foe?

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now overwhelming, spreading throughout the world, and has been declared a global pandemic by the WHO. So far, more than 4 million confirmed cases have been reported by WHO worldwide, including more than 290,000 deaths. And the treatment for the critically ill patients of COVID-19 remains a challenge.

The first report of pathological characteristics of the patient who died from severe infection with SARS-CoV-2 demonstrated an increased concentration of highly proinflammatory cytokines.<sup>1</sup> Actually, the cytokine storm mediated by overproduction of proinflammatory cytokines has been observed in a large population of critically ill patients with COVID-19.<sup>2</sup> Cytokine storms can result in cardiovascular collapse, multiple organ dysfunction, cardiac arrest, and death. Epinephrine, a vasoactive agent, has been routinely employed to the critical situation such as cardiac arrest. However, it remains uncertain whether epinephrine can also benefit the cardiac arrest following cytokine storms occurred in COVID-19 patients. This is a question that is easy overlooked but deserves deep consideration.

In a study published in *Nature*,<sup>3</sup> Staedtke *et al* used subcutaneously implanted osmotic pumps to continuously release epinephrine, norepinephrine or dopamine into mice treated with lipopolysaccharide (LPS). Mice with epinephrine, not norepinephrine or dopamine, showed an exacerbated disease course with higher levels of interleukin 6, tumour necrosis factor and chemoattractants compared with LPS-treated controls. This result revealed that epinephrine may fuel the cytokine storms. And the effect of epinephrine in initiating cytokine storms was further confirmed in a different model system of severe bacterial infection. Actually, it was known that immune cells such as macrophages activated by inflammatory stimuli induce catecholamines and respond to them in an autocrine manner, which amplifies the inflammatory response.<sup>4</sup> Even the idea that epinephrine acts to

promote cytokine storms seems to be counter-intuitive since the molecules of this class are used routinely to treat the low blood pressure associated with cytokine storms, these integrated evidences suggest that epinephrine can stimulate further cytokine and catecholamine release and this autocrine amplification cascade might worsen cytokine storms in those COVID-19 patients. Therefore, the clinic reassessment of the benefit of epinephrine for rescuing cardiac arrest caused by cytokine storms in those COVID-19 patients is urgently needed.

We retrospectively analysed 206 patients who diagnosed as COVID-19 and suffered a rescue treatment with epinephrine at Tongji Hospital in Wuhan, China from January 27 to March 1, 2020. It was noticed that only 4/206 (2%) of patients were survivors and discharged from hospital eventually. The severity of the disease may account mostly for the poor outcome. However, as expected from the established role of epinephrine in fueling the cytokine storms, the aggravated cytokine storms may have also played a role in the failure of the rescue.

Beyond rapid defibrillation and early initiation of cardiopulmonary resuscitation, there are few therapies that have been identified to improve survival for cardiac arrest patients reliably. The use of epinephrine during resuscitation is a mainstay of agent in cardiac arrest, however, the safety and effectiveness of this agent remains controversial.<sup>5,6</sup> Vasopressin has been proposed as an alternative to epinephrine in cardiac arrest, based on the finding that its levels were markedly higher in successfully resuscitated patients than in patients who died.<sup>7</sup> Compared with epinephrine, vasopressin has several advantages. First, it increases arterial peripheral resistance without resulting direct myocardial stimulation. Moreover, it is more resistant to acidosis and has a longer half-life. Most importantly, it does not fuel the cytokine storms. Although, for common cardiac arrest, compared with epinephrine, no advantage from the use of vasopressin has been identified in any of the outcomes from clinical studies, but for cardiac arrest in those COVID-19 patients, vasopressin still should be fully assessed considering the cytokine storms occurred in this special population which might limit the use of epinephrine.

Clinical decision making must balance the risks and benefits of treatment.

Therefore, it is time to reevaluate the effect of epinephrine use in COVID-19 patients with cytokine storms, and other agents such as vasopressin should be compared with epinephrine and fully assessed for their opportunities as an alternative strategy.

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