



Opinion Paper

Hypertension and COVID-19: Potential use of beta-blockers and a call for randomized evidence

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ABSTRACT

Hypertension is one of the most common morbidities in COVID-19. Previous studies demonstrated that hypertension increases composite poor outcomes in patients with COVID-19. Beta-blockers is widely used as one of the most common antihypertensive agents. Beta-blockers may hold potential benefits in COVID-19 treatment, with current evidence of the potential mechanism of beta-blockers remains scarce. However, several mechanisms were suggested, including decreasing RAAS pathway activity and lowering the ACE2 levels, reducing cytokine storms, and may be beneficial in reducing mortality in ARDS related COVID-19. Further large-scale randomized clinical trials should be conducted before a definite recommendation can be drawn.

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COVID-19 currently causes not only health but also multisectoral problems worldwide. SARS-CoV-2 as the cause of COVID-19 is relatively identical to SARS-CoV and MERS-CoV in the way of receptor utilization in human infection. Angiotensin-converting enzyme-2 (ACE-2) receptor was used by SARS-CoV-2 for cell entry after ligation of spike protein in infecting host. This receptor is increased in patients with hypertension treated using renin-angiotensin inhibitors, which could promote virus entry.¹ Hence, hypertension may become one of the most common morbidities in COVID-19.² Previous meta-analysis also demonstrated that hypertension increases composite poor outcomes in patients with COVID-19.³

Five major antihypertensive agent classes were well established in the current guideline, including angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), diuretic, and beta-blocker.⁴ Beta-blockers, one of the most commonly used antihypertensive agents, are widely used particles that can antagonize beta-adrenergic receptors, thus reducing the adrenergic tone of the cardiac muscle and pacemaker cells.⁵

In the COVID-19, adrenergic system regulation of the renin-angiotensin-aldosterone system (RAAS) is crucial. Increased catecholamine levels will activate the adrenergic system leading to RAAS activation and an increase in ACE2, which promotes SARS-CoV-2 entry and results in COVID-19's complications. In response to the critically ill COVID-19, catecholamines will be increased, and this vicious cycle continues.⁶ Use of beta2-agonist nebulizer and norepinephrine in the setting of septic shock in COVID-19 may also contribute to increased catecholamines levels. The use of inhaled beta2-agonists should be avoided in the setting of ARDS, as mentioned before.⁷ Nebulizers of beta2-agonists may increase the expression of ACE2 in the alveolar epithelial cells, which may facilitate SARS-CoV-2 and worsen the condition.⁶

A retrospective multicenter cohort study by Chouchana et al⁸ evaluating effects of several antihypertensive agents on in-hospital mortality of COVID-19, with at least 30 days follow up, reported that risk of mortality was lower in CCB (aOR: 0.83, 95% CI: 0.70–0.99) and beta-blocker (aOR: 0.80 95% CI: 0.67–0.95). When restricting the analysis to monotherapeutic antihypertensive agents, the results of beta-blocker remain consistent (aOR: 0.67, 95% CI: 0.48–0.93). The authors hypothesize that beta-blocker effect may counteract deleterious sympathetic activation during the cytokine storm and severe disease.⁸ Another multicenter retrospective study by Yan et al⁹ in elderly COVID-19 patients, also showed beta-blocker use was associated with decreased mortality (aOR: 0.496, 95% CI: 0.268–0.919) and dyspnea (aOR: 0.792, 95% CI: 0.64–0.981). Multivariate analysis in a study by Pinto-Sietsma

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et al¹⁰ showed beta-blocker use was associated with a milder course after admission.

Current evidence of potential mechanism of beta-blockers in COVID-19 remains scarce. However, several mechanisms were suggested. First, beta-blockers can negatively block SARS-CoV-2 entry gate through regulation on the juxtaglomerular cells in kidneys, decreasing RAAS pathway activity and lowering the ACE2 levels.⁵ Beta-blockers reduce renin level by inhibiting the sympathetic system and decreasing angiotensin II, which has a detrimental effect on the cardiovascular system. Compared to ARB and ACEI, beta-blockers benefit by acting on upstream renin, decreasing the activity of both arms.⁶ Therefore, beta-blockers not only reduce the ACE2 receptors but also decrease angiotensin II levels. Similar to ACE2 receptor, cluster of differentiation 147 (CD147) was thought to facilitate SARS-CoV-2 entry.⁵ Previous study showed that propranolol triggers downregulation of CD147.¹¹ Hence, beta-blockers treatment will reduce SARS-CoV-2 entry by both ACE2 and CD147 down regulation.

Activation of beta-adrenergic receptors contributes to inflammatory cytokine secretion. Therefore, beta-blockers may be able to reduce cytokine storms in COVID-19. Beta-blockers have been shown to reduce a variety of pro-inflammatory cytokines, including IL-6, IL-1, IL-1 β , tumour necrosis factor- α (TNF α), T helper 17 (Th17), and interferon- γ (IFN γ).^{6,12} IL-6 also plays an essential role in the MUC5AC and MUC5B gene expression and increased mucus secretion, alleviated by beta-blockers.⁶ In addition, in the in vivo mouse model of NLRP3-associated peritonitis, carvedilol has been reported to inhibit NLRP3 inflammasome.¹³ Hence, inhibition of NLRP3 inflammasome decreases inflammation by reducing the NLRP3 downstream effectors IL-1 and IL-8.

Beta-blockers may be beneficial in reducing the mortality of ARDS in COVID-19. BASEL-II-ICU study by Noveanu et al¹⁴ reported that established beta-blocker therapy was associated with decreased mortality in patients with acute respiratory failure admitted to intensive care units. The observed effect might be explained by myocardial infarction protection and malignant ventricular arrhythmias prevention, which may lead to fatal pump failure.¹⁴ Vasanthakumar, in a hypothesis article, also suggests that Propranolol or Prazosin can be administered to decrease or prohibit pulmonary edema in COVID-19.⁶ A recent pilot trial by Clemente-Moragón et al (MADRID-COVID) demonstrated that intravenous administration of the metoprolol to critically ill COVID-19 patients with ARDS safely reduced lung inflammation associated with the disease. Compared with no treatment, metoprolol administration also resulted in better oxygenation and fewer days on invasive mechanical ventilation and intensive care unit. The authors suggest that metoprolol repurposing for ARDS treatment in COVID-19 patients is a safe and inexpensive strategy with the potential to improve outcomes.¹⁵

Furthermore, administration of norepinephrine in septic shock may further worsen COVID-19 condition due to increased catecholamine levels. Previous study showed that beta-blockers are safe and effective in sepsis or septic shock.¹⁶ Therefore, the use of beta-blockers or in combination with norepinephrine and COVID-19 related sepsis or septic shock may also hold promising outcomes.

Hypercoagulable state, a prevalent coagulation disorder in COVID-19, is known to be linked with adrenergic hyperactivation. Previous studies showed beta-blockers' role in reducing hypercoagulation parameters and preventing thrombosis complications in both animal and human models.^{17–19} Propranolol demonstrates decreased sustained elevated FVIII:C concentration in patients with venous thromboembolism.¹⁸

In COVID-19 patients on extracorporeal membrane oxygenation (ECMO), beta-blockers may improve the oxygenation level. A study by Bunge et al²⁰ reported use of beta-blockers, using primarily

metoprolol, in patients with hypoxemia on V-V ECMO was safe and associated with a moderate increase in SaO₂. In patients with hyperdynamic circulation, beta-blockers may reduce the amount of blood that the extracorporeal membrane would not oxygenate, reduce the intra-pulmonary shunt, and yield some myocardial protection.²⁰

Last but not least, cardio-selective beta-blockers are well-established agents in arrhythmia treatment and are a potential therapy in the management of QT prolongation due to COVID-19 therapies, which may include QT-prolonging drugs: azithromycin, chloroquine, and quinolone.⁵

In conclusion, beta-blockers may hold potential benefits in COVID-19 treatment, especially in hypertensive patients. Nonetheless, which specific beta-blocker agent works better in COVID-19 also needs to be defined. Furthermore, these beta-blockers' potentially essential therapeutic properties emphasize the need for expedited large-scale randomized clinical trials before a definite recommendation can be drawn.

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Authors' contributions

M.Y.A. and E.P.B.M conceived the idea, designed and drafted the work, revising critically for important intellectual content. All authors revised and approved the version to be published.

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Declaration of competing interest

The authors declare that they have no competing interests.

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References

- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8, e21. [https://doi.org/10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8).
- Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA - J Am Med Assoc*. 2020;323:1574–1581. <https://doi.org/10.1001/jama.2020.5394>.
- Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *JRAAS - J Renin-Angiotensin Aldosterone Syst*. 2020;21. <https://doi.org/10.1177/1470320320926899>.
- Williams B, Mancia G, Spiering W, et al. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. <https://doi.org/10.1093/eurheartj/ehy339>, 2018.
- Heriansyah T, Nur Chomsky I, Febrianda L, Farahiya Hadi T, Andri Wihastuti T. The potential benefit of beta-blockers for the management of COVID-19

- protocol therapy-induced QT prolongation: a literature review. *Sci Pharm*. 2020;88:55. <https://doi.org/10.3390/scipharm88040055>.
6. Vasanthakumar N. Beta-adrenergic blockers as a potential treatment for COVID-19 patients. *Bioessays*. 2020;42, 2000094. <https://doi.org/10.1002/bies.202000094>.
 7. Sweeney R Mac, McAuley DF. Acute respiratory distress syndrome. *Lancet*. 2016;388:2416–2430. [https://doi.org/10.1016/S0140-6736\(16\)00578-X](https://doi.org/10.1016/S0140-6736(16)00578-X).
 8. Chouchana L, Beeker N, Garcelon N, et al. Association of antihypertensive agents with the risk of in-hospital death in patients with Covid-19. *Cardiovasc Drugs Ther*. 2021;1–6. <https://doi.org/10.1007/s10557-021-07155-5>.
 9. Yan F, Huang F, Xu J, et al. Antihypertensive drugs are associated with reduced fatal outcomes and improved clinical characteristics in elderly COVID-19 patients. *Cell Discov*. 2020;6:77. <https://doi.org/10.1038/s41421-020-00221-6>.
 10. Pinto-Sietsma SJ, Flossdorf M, Buchholz VR, et al. Antihypertensive drugs in COVID-19 infection. *Eur Hear J - Cardiovasc Pharmacother*. 2020;6:415–416. <https://doi.org/10.1093/ehjcvp/pvaa058>.
 11. Xie W, Xie H, Liu F, et al. Propranolol induces apoptosis of human umbilical vein endothelial cells through downregulation of CD147. *Br J Dermatol*. 2013;168:739–748. <https://doi.org/10.1111/bjd.12193>.
 12. Barbieri A, Robinson N, Palma G, Maurea N, Desiderio V, Botti G. Can beta-2-adrenergic pathway Be a new target to combat SARS-CoV-2 Hyper-inflammatory Syndrome?—lessons learned from cancer. *Front Immunol*. 2020;11:1. <https://doi.org/10.3389/fimmu.2020.588724>.
 13. Wong WT, Li LH, Rao YK, et al. Repositioning of the β -blocker carvedilol as a novel autophagy inducer that inhibits the NLRP3 inflammasome. *Front Immunol*. 2018;9. <https://doi.org/10.3389/fimmu.2018.01920>.
 14. Noveanu M, Breidhardt T, Reichlin T, et al. Effect of oral beta-blocker on short and long-term mortality in patients with acute respiratory failure: results from the BASEL-II-ICU study. *Crit Care*. 2010;14, R198. <https://doi.org/10.1186/cc9317>.
 15. Clemente-Moragón A, Martínez-Milla J, Oliver E, et al. Metoprolol in critically ill patients with COVID-19. *J Am Coll Cardiol*. 2021;78:1001–1011. <https://doi.org/10.1016/j.jacc.2021.07.003>.
 16. Li J, Sun W, Guo Y, Ren Y, Li Y, Yang Z. Prognosis of β -adrenergic blockade therapy on septic shock and sepsis: a systematic review and meta-analysis of randomized controlled studies. *Cytokine*. 2020;126. <https://doi.org/10.1016/j.cyto.2019.154916>.
 17. Gruszecki M, Rólkowski R, Pawlak R, Buczek W. Propranolol prevents the development of venous thrombosis in rats by a platelet-dependent mechanism. *Pol J Pharmacol*. 2001;53:5–10.
 18. Hoppener MR, Kraaijenhagen RA, Hutten BA, Büller HR, Peters RJG, Levi M. Beta-receptor blockade decreases elevated plasma levels of factor VIII: C in patients with deep vein thrombosis. *J Thromb Haemostasis*. 2004;2:1316–1320. <https://doi.org/10.1111/j.1538-7836.2004.00851.x>.
 19. Känel R Von, Kudielka BM, Helfricht S, et al. The effects of aspirin and nonselective beta blockade on the acute prothrombotic response to psychosocial stress in apparently healthy subjects. *J Cardiovasc Pharmacol*. 2008;51: 231–238. <https://doi.org/10.1097/FJC.0b013e318161ea63>.
 20. Bunge JJH, Diaby S, Valle AL, et al. Safety and efficacy of beta-blockers to improve oxygenation in patients on veno-venous ECMO. *J Crit Care*. 2019;53: 248–252. <https://doi.org/10.1016/j.jcrc.2019.06.024>.