Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 78, NO. 10, 2021

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Beta-Blockers in the Critically Ill

Friend or Foe?*

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Beta-blockers are a commonly prescribed medication for patients with cardiovascular comorbidities, such as ischemia, heart failure, hypertension, and arrhythmias. Beta-blockers inhibit the sympathomimetic stimulation of β-1 adrenergic receptors primarily found on cardiomyocytes as well as the sinoatrial and atrioventricular nodes. This results in both a negative chronotropic and inotropic effect on the heart that leads to decreased blood pressure, heart rate, and myocardial work (1). Beta-blockers along with their beneficial cardiac profile also exhibit important metabolic and immunomodulatory effects (2,3) that are often overlooked.

Beta-blockers have become ubiquitous in the treatment of patients with heart failure and ischemic heart disease. The 2013 American College of Cardiology/American Heart Association Heart Failure guidelines recommend β-blockade in patients with a history of myocardial infarction or acute coronary syndrome and reduced ejection fraction to reduce mortality (4) and use of beta-blockers in all patients with reduced ejection fraction to prevent symptomatic heart failure and hospitalization.

During critical illness, the initial adrenergic stimulation may be beneficial; however, sympathetic overactivity, if persistent, may become deleterious, leading to further oxygen consumption, catabolism, hyperglycemia, hypercoagulability, cardiac dysfunction, modulation of systemic inflammatory cytokines, and ensuing multiorgan failure (2,5-7). There has been an ever-increasing interest in the role of beta-blockers in critically ill patients in blunting this adrenergic response (3). There is a growing body of literature regarding the role of beta-blockers in a wide variety of critically ill patients with sepsis and before major surgery, acute respiratory distress syndrome, and traumatic brain injury (8-13).

Several observational studies have shown a reduced mortality in patients in the intensive care unit who were on preadmission beta-blockers (14,15) and specifically those with acute respiratory failure (10). Furthermore, discontinuation of these drugs during their hospital stay was associated with higher mortality rates independent of the cause of respiratory failure.

The use of continuous infusion of esmolol, an intravenous short-acting beta-blocker, showed a decreased need for fluids and vasopressors as well as improved 28-day mortality in patients with sepsis (11). However, conflicting evidence exists in other critically ill populations (16), with individuals who received beta-blockers 30 days before elective cardiac surgery showing increased risk of death and stroke associated with an increased incidence of hypotension, bradycardia, and bleeding (17).

There remains a considerable gap in knowledge in the understanding of the complex balance between beneficial sympathetic stimulation and the multitude of derangements caused by persistent sympathetic overactivity in critically ill individuals. The use of beta-blockers has become ubiquitous in the treatment of patients with cardiac disease; however, there remains considerable variation on the optimal timing of the initiation, withholding, and restarting of beta-blocker therapy in critically ill patients.

The repurposing of medications to combat an ever-growing COVID-19 pandemic has reached fever pitch, with a variety of drug classes being used, with the vast majority showing unclear benefit. In this issue of the *Journal*, Clemente-Moragón et al (18) explore

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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Christie Ballantyne, MD, served as the Guest Editor for this paper.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.07.006

the use of intravenous metoprolol on alveolar inflammation and respiratory function in critically ill patients with COVID-19–related hypoxemic respiratory failure. Although the study has a small sample size, we commend the authors, who attempt to shed light on the important pathophysiologic underpinnings that help establish biological plausibility for this inexpensive, safe, and widely available medication.

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Host response to disease plays a central and pivotal role in critical illness and can lead to significant organ dysfunction and ensuing mortality. Different treatment modalities targeting this inflammatory response have been an intense area of research as well as a source of contention. The more important question is not its disease-specific effects on COVID-19 per se but, rather, its beneficial effects in critical illness in general due to sympathetic blunting and the subsequent immune-modulating effects of this drug class.

In this study, beta-blockers were instituted early in the disease course, which may play an important role in sympathetic blunting before the effects of the dysregulated inflammatory cascade that may lead to organ dysfunction. Patients in this study who received beta-blockers showed less lung inflammation, improved Pao_2:Fio_2 ratios and decreased ventilator days. However, there is clear selection bias because only those patients who are hemodynamically stable enough can receive beta-blockers. Several confounding factors include exposure to corticosteroids before randomization and analgesia/sedation practices that may blunt the inflammatory response.

An important consideration is that a large proportion of patients admitted to the intensive care unit have a high burden of cardiac disease. Cardioprotective medications have improved outcomes, but the management of these medications in critical illness remains unclear. There is clear evidence that beta-blocker exposure before and during ICU admission is protective, and abrupt withdrawal causes harm. One source of clinical variability that may lead to suboptimal treatment and poorer outcomes is the management of cardioprotective medications. Accordingly, there remains a considerable knowledge gap regarding the complex interplay between cardioprotective medications and critical illness, with no clear guidelines or consensus statements on the management of these medications.

Although a small-sized, single-center study amid a multitude of others exploring potential treatment modalities for COVID-19—this study uses a readily available, safe, and inexpensive medication; has a simple study design; and, most importantly, shows biological plausibility. Although observed in patients with COVID-19, this sets the groundwork for further research in the use of beta-blockade in the critically ill. Further studies are needed to elucidate and identify where along the inflammatory spectrum these critically ill patients lie, which patients would benefit from beta-blockers, and at what time point during their hospital stay.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute care, ARDS, COVID, metoprolol