CRITICAL CARE

COMMENTARY

# Beta 2 antagonism in acute respiratory failure

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**Abstract**

*Post hoc* analyses from the B-type natriuretic peptide for Acute Shortness of Breath Evaluation (BASEL)-II-ICU study suggest an association between beta-blocker usage at admission and improved mortality in patients treated in the intensive care unit for acute respiratory failure. Although this evidence is encouraging, there is a need for a phase 2 proof-of-concept randomized controlled trial of beta-blocker therapy in patients admitted with acute respiratory failure.

In this issue of *Critical Care*, Noveanu and colleagues [1] present intriguing observational data from the B-type natriuretic peptide for Acute Shortness of Breath Evaluation (BASEL)-II-ICU study evaluating the association between beta-blocker therapy and mortality in 314 patients. Current dogma suggests a role for beta 2 agonism in the management of respiratory disease, most notably in asthma and chronic obstructive pulmonary disease (COPD). Beta 2 agonism was also recently investigated in the intensive care unit (ICU) for acute respiratory distress syndrome (ARDS) [2]. In addition to bronchodilatation and improvements in ventilatory mechanics, purported beneficial effects include improved endothelial function, cytoprotection, an anti-inflammatory effect, increased surfactant production, and increased alveolar fluid clearance [3]. However, despite these potential beneficial effects, a large randomized controlled trial (RCT) of nebulized salbutamol in ARDS, which has been published only in abstract form, was stopped early for futility. In addition, there is ongoing controversy over the safety of long-acting beta 2 agonists in the management of asthma, and data suggest that beta 2 agonism may increase cardiovascular morbidity in those with risk factors for cardiovascular disease [4].

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The BASEL-II-ICU study was a prospective randomized trial evaluating the effect of BNP-guided therapy versus standard care in ICU patients with acute respiratory failure [1]. Beta-blocker therapy instituted before or after ICU care was associated with improved mortality both in-hospital and at 1 year in multivariable analyses. This association was demonstrated in stratified analyses for both cardiac and non-cardiac causes of acute respiratory failure. Among the factors limiting the generalizability of the data were the strict exclusion criteria, and many conditions commonly seen in the ICU, including sepsis, shock, renal failure, trauma, and prior cardiopulmonary resuscitation, were excluded. Furthermore, only 13% of the cohort with acute respiratory failure received invasive mechanical ventilation, although 50% did receive non-invasive mechanical ventilation. It would also be useful to know what causes of death were modified by beta 2 antagonism in acute respiratory failure. Another limitation of this observational data is that the models are at substantial risk of over-fitting given that the authors evaluated 40 variables despite having only 51 in-hospital deaths [5].

Why might beta 2 agonism be ineffective and antagonism be beneficial in acute respiratory failure? First, many patients admitted with acute respiratory failure will suffer cardiac ischemia, a condition that potentially can be prevented with a beta-blocker [6]. Beta-receptors form an integral component of the sympathetic nervous system. The three beta-receptor subtypes help coordinate neural, circulatory, gastrointestinal, digestive, urinary, hematological, metabolic, and immune function during the 'fight-or-flight response' induced by periods of stress. Initially, beta agonism diverts energy to vital organs and upregulates homeostatic mechanisms such as platelet activation and coagulation; however, prolonged beta adrenergic activation may prove detrimental. Data from RCTs have shown a beneficial effect of beta-blocker therapy in the treatment of chronic heart failure [7]. Observational data suggest a possible beneficial role for beta antagonism in trauma [8], including traumatic brain injury [9], and sepsis [10]. Two other studies have highlighted the benefits and risks of beta-blockers. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), an RCT of 45,852 acute myocardial

infarction patients randomly assigned to a beta-blocker or placebo, surprised many clinicians when it demonstrated no impact on 30-day mortality [11]. This trial demonstrated less re-infarction and ventricular fibrillation with beta-blocker therapy, but these beneficial effects were counterbalanced by an excess of death due to shock with beta-blocker therapy. Similarly, the Perioperative Ischemic Evaluation Study (POISE-1), an RCT of 8,351 non-cardiac surgery patients randomly assigned to a beta-blocker or placebo, demonstrated that a perioperative beta-blocker prevented perioperative myocardial infarction but increased the risk of death or stroke [12]. In POISE-1, the negative consequences of beta-blockade appeared to have occurred through an excess of clinically important hypotension. This excess is similar to the excess of cardiogenic shock witnessed with beta-blockade in COMMIT. These data highlight the potential benefits of a beta-blocker but also the need to exclude patients in shock or at high risk of shock and to intensely monitor and manage hemodynamic instability. Reassuringly, current data suggest that cardio-selective beta-blockers do not induce respiratory physiological impairment. In particular, beta-blockers are associated with improved outcomes in patients with COPD [13], a group theoretically at high risk from bronchospasm with beta antagonism.

The data emerging from beta adrenergic modulation in respiratory failure mirror those of statins. Statins were initially designed as cholesterol-lowering agents to reduce cardiovascular risk, and their pleiotropic effects were soon realized and matched by observational data showing associations between statin use and improved outcomes in cohorts with pneumonia and lung injury. Because a small prospective phase 2 RCT suggested potential benefit [14], statins are being investigated as a therapy for ARDS in at least two large RCTs in Europe and the US. Now, an appropriate phase 2 proof-of-concept RCT investigating beta 2 antagonism in acute respiratory failure with strict eligibility criteria would be an appropriate approach to define the role of beta-blockers in acute respiratory failure.

**Abbreviations**

ARDS, acute respiratory distress syndrome; BASEL, B-type natriuretic peptide for Acute Shortness of Breath Evaluation; BNP, B-type natriuretic peptide; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; POISE-1, Perioperative Ischemic Evaluation Study; RCT, randomized controlled trial.

**Competing interests**

AstraZeneca (London, UK) funded the drugs for the POISE-1 trial, for which PJD was the principal investigator. AstraZeneca manufactures metoprolol CR and beta-blockers. RMS and DFM declare that they have no competing interests.

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**References**

1. Noveanu M, Breidthardt T, Reichlin T, Gayat E, Potocki M, Pargger H, Heise A, Meissner J, Twerenbold R, Muravitskaya N, Mebazaa A, Mueller C: **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.
2. Perkins GD, McAuley DF, Thickett DR, Gao F: **The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial.** *Am J Respir Crit Care Med* 2006, **173:**281-287.
3. Perkins G, McAuley D, Richter A, Thickett D, Gao F: **Bench-to-bedside review: beta2-Agonists and the acute respiratory distress syndrome.** *Crit Care* 2004, **8:**25-32.
4. Au DH, Curtis JR, Every NR, McDonell MB, Fihn SD: **Association between inhaled β-agonists and the risk of unstable angina and myocardial infarction.** *Chest* 2002, **121:**846-851.
5. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR: **A simulation study of the number of events per variable in logistic regression analysis.** *J Clin Epidemiol* 1996, **49:**1373-1379.
6. Lim W, Qushmaq I, Devereaux PJ, Heels-Ansdell D, Lauzier F, Ismaila AS, Crowther MA, Cook DJ: **Elevated cardiac troponin measurements in critically ill patients.** *Arch Intern Med* 2006, **166:**2446-2454.
7. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH: **The effect of carvedilol on morbidity and mortality in patients with chronic heart failure.** *N Engl J Med* 1996, **334:**1349-1355.
8. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, Niederbichler AD, Ipaktchi K, Wahl WL: **Beta-blocker use is associated with improved outcomes in adult trauma patients.** *J Trauma* 2007, **62:**56-62.
9. Cotton BA, Snodgrass KB, Fleming SB, Carpenter RO, Kemp CD, Arbogast PG, Morris JAJ: **Beta-blocker exposure is associated with improved survival after severe traumatic brain injury.** *J Trauma* 2007, **62:**26-35.
10. de Montmollin E, Aboab J, Mansart A, Annane D: **Bench-to-bedside review: beta-adrenergic modulation in sepsis.** *Crit Care* 2009, **13:**230.
11. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group: **Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial.** *Lancet* 2005, **366:**1622-1632.
12. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: **Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial.** *Lancet* 2008, **371:**1839-1847.
13. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB: **Use of β blockers and the risk of death in hospitalised patients with acute exacerbations of COPD.** *Thorax* 2008, **63:**301-305.
14. Craig TR, Duffy MJ, Shyamsundar M, McDowell C, O'Kane C, Elborn JS, McAuley DF: **A randomized clinical trial of hydroxymethylglutaryl-CoA reductase inhibition for acute lung injury (The HARP study).** *Am J Respir Crit Care Med* 2010 Sep 24. [Epub ahead of print].

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