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REPLY: Biological Plausibility Behind the Benefits of Intravenous Metoprolol in Severe COVID-19

We appreciate the constructive comments from 3 groups about our recently published MADRID-COVID pilot trial (1).

In their letter, Prof Chen and colleagues point out the relevance of mechanical ventilation (MV) settings when evaluating acute respiratory distress syndrome (ARDS) treatment. In our study, MV was set according to physicians' criteria following practice guidelines (2). All patients were managed with volume-controlled ventilation and changed to pressure-support mode on weaning. The latter had already occurred by day 4 of the study in 3 of 12 metoprolol-treated patients in and in 0 control subjects. There were no differences in tidal volume applied at baseline (5.8 mL/kg [IQR: 5.5-6.1 mL/kg] in the control group vs 6.1 mL/kg [IQR: 5.5-6.4 mL/kg] in the metoprolol group; $P = 0.487$) or at day 4 (5.7 mL/kg [IQR: 5.4-5.8 mL/kg] vs 6.3 mL/kg [IQR: 5.6-7.8 mL/kg]; $P = 0.105$). Similarly, driving pressure was not different between groups at baseline (11 mm Hg [IQR: 8-12.5 mm Hg] vs 10.5 mm Hg [IQR: 8.5-15 mm Hg]; $P = 0.907$). Prof Chen and colleagues comment on the appropriate statistical tests considering repeated echocardiographic measurements. Their claim is correct, especially to rule out the possibility that any difference is the result of incorrect analyses. However, we want to highlight the very small (and not significant) differences in the echocardiographic variables across time between groups. Regarding the use of corticoids, we already described this in the first paragraph of the Results section of the paper. In summary, there were no differences between groups.

Dr Roquetaillade and colleagues highlight the well-described effect of cardiac output (CO) on intrapulmonary shunt. This effect has been demonstrated in physiological studies in animal and clinical settings under controlled conditions. However, the magnitude of the effect of interventions that potentially modify both lung physiology and CO is difficult to calculate. Given our study design and purpose, some precautions should be taken when evaluating the relationship between these 2 variables. First, neither shunt fraction nor CO was directly calculated. Second, because velocity time integral was similar before and after metoprolol administration, assumptions about potential changes in CO are derived from heart rate. The effect of a transitory reduction in heart rate on intrapulmonary shunt is unknown. Beyond an effect on the ratio of Pao_2 to the fraction of inspired oxygen, we observed a strong trend toward a reduction in days on MV and of intensive care unit admission. The latter observation supports the suggestion that metoprolol administration was not associated with any deleterious effect on oxygen delivery.

Dr Wang and colleagues have concerns about the use of other drugs. Janus kinase inhibitors were not used. Tocilizumab was used before intensive care unit admission in 2 and 5 patients in the control and metoprolol groups, respectively. Tocilizumab has been associated with a reduction in the rate of progression to MV (3), and thus we can assume that it was not effective in the recruited population because all patients were intubated despite treatment with this agent. It is also important to remark that at baseline (ie, after intubation and after tocilizumab treatment), lung function and inflammation were similar in both groups. Dr Wang and colleagues also mention the importance of bacterial coinfection as a confounder. In our study, only 1 patient in each group had a bacterial coinfection. The low incidence of bacterial coinfection probably reflects that patients were enrolled in the trial early after being admitted to the intensive care unit. However, we would like to point out that given the association between neutrophil extracellular traps and bacterial infections, as well as their possible relevance in ARDS pathophysiology (4), we already started to evaluate the effect of metoprolol in ARDS of different origins (not just COVID-19) in a larger study (MAIDEN [Metoprolol in Acute respIratory DistrEss syNdrome] randomized clinical trial). Finally, we already highlighted that the open label design of our study is a limitation. Nevertheless, given the clear effect of metoprolol on heart rate, blinding is a difficult task even if placebo is used as comparator. In any case, as we already highlighted, our results set the basis of future larger studies testing the benefits of metoprolol in patients with ARDS.

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

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