

Timing of Tocilizumab Use and COVID-19

Dear Editor,

We would like to share ideas on “Impact of Timing of Tocilizumab Use in Hospitalized Patients With SARS-CoV-2 Infection.”¹ Singh et al concluded that early use of anti-interleukin 6 therapy may be associated with improved hospital mortality and reduction in progression to more severe COVID-19. Tocilizumab is a possible useful drug for management of COVID-19. Since this was a retrospective study, it is difficult to control for confounding factors. Matching for groups might be useful. However, some parameters might also be confounded. For example, in some areas of the world, ferritin levels might be confounded by thalassemia or parasitic infestation.²⁻³ Nevertheless, those 2 disorders are not common in areas such as New York City. In the United States, metabolic syndrome might be a more important source of confusion with ferritin levels.⁴

Also, various alternative therapies given to patients might affect outcome in the present study. Combining tocilizumab with systemic steroid therapy may produce more favorable outcomes. Different types of respiratory support also affect these rates.⁵ Different respiratory support also affects outcome of therapy.⁶ Moreover, in the present report, Singh et al¹ mentioned only that there was no improvement in clinical outcome if the drug was given at the time the subject required respiratory support. According to a recent report, reductions in mortality risk vary depending on the level of support at tocilizumab start, including stratifications for conventional oxygen therapy, noninvasive ventilation, invasive ventilation, and no support.⁶ In a recent report, it was found that the maximal dose limit was sufficient in the management of obese subjects.⁷ Finally, the present report cannot reflect actual time that the drug was given. The illness period of subject, including prehospitalization, might be variable and it cannot decide whether drug was given early or not.

Rujittika Mungmunpantipantip
Viroj Wiwanitkit
Bangkok, Thailand

The authors have disclosed no conflicts of interest.

DOI: 10.4187/respcare.09678

REFERENCES

1. Singh AK, Oks M, Husk G, Dechario SP, Mina B, Singh K, et al. Impact of timing of tocilizumab use in hospitalized patients with SARS-CoV-2 infection. *Respir Care* 2021;66(12):1805-1814.
2. Adil A, Sobani ZA, Jabbar A, Adil SN, Awan S. Endocrine complications in patients of beta thalassemia major in a tertiary care hospital in Pakistan. *J Pak Med Assoc* 2012;62(3):307-310.
3. Miller JL. Iron deficiency anemia: a common and curable disease. *Cold Spring Harb Perspect Med* 2013;3(7):a011866-a011866.
4. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in US adults. *Diabetes Care* 2004;27(10):2422-2428.
5. Brosnahan SB, Chen XJC, Chung J, Altshuler D, Islam S, Thomas SV, et al. Low-dose tocilizumab with high-dose corticosteroids in patients hospitalized for COVID-19 hypoxic respiratory failure improves mortality without increased infection risk. *Ann Pharmacother* 2021:1060028021102888. 10600280211028882.
6. Milic J, Banchelli F, Meschiari M, Franceschini E, Ciusa G, Gozzi L, et al. The impact of tocilizumab on respiratory support states transition and clinical outcomes in COVID-19 patients. A Markov model multi-state study. *PLoS One* 2021;16(8):e0251378.
7. Raja K, Daniel N, Morrison S, Patel R, Gerges J, Nadeem K, et al. Impact of tocilizumab on clinical outcomes in COVID-19-associated cytokine release syndrome: a single-center Experience. *J Pharm Pract* 2021;8971900211028208.

Peak Expiratory Flow During MI-E: ETT vs Face Mask. Which Is the Optimal PEF Cutoff to Choose?

To the Editor:

We read with great interest the manuscript by Hyun SE et al¹ who compared the effect of mechanical insufflation-exsufflation (MI-E) on peak expiratory flows (PEF), through endotracheal tube (ETT) or facial mask, and assessed expiratory flows during different pressure levels set on the device. The authors found a significant decrease in PEF when MI-E was applied through the ETT (with inner diameter ranging from 6.5 mm–8 mm) and that expiratory flows were significantly influenced by MI-E pressure setting, achieving the highest PEFs when +50/–50 cm H₂O of insufflation-exsufflation pressure was applied (177.4 L/min [165.9–188.8]).

These interesting results are in line with most previous laboratory studies²⁻⁴; nevertheless, we would like to comment on a few critical aspects of this work.

Hyun SE et al¹ concluded that insufflation-exsufflation pressures of at least +50/–50 cm H₂O should be necessary to achieve an efficient PEF, previously defined as ≥ 160 L/min. Indeed, this cutoff has been the standard since 1996 when Bach JR et al⁵ proposed it as criteria to extubate and decannulate patients with ventilatory failure although, importantly, PEF measurement was performed after removal of the artificial airway. More recently, Jiang J et al⁶ reviewed values from 9 studies that assessed PEF cutoffs during weaning to predict successful extubation. Most of the studies used PEF cutoffs < 160 L/min, ranging from 35 L/min in mixed ICU subjects⁷ to 113.7 L/min in medical ICU subjects,⁸ with significant prediction of extubation success. Similarly, we recently evaluated PEF during MI-E set at +40/–40 cm H₂O with mid-inspiratory flow in intubated and sedated critically ill patients and found that PEFs of 96.9 ± 20.6 L/min⁹ were sufficient to improve sputum clearance. We agree with Hyun SE¹ that, in critically ill patients on invasive mechanical ventilation, higher MI-E pressures may be necessary to reach efficient PEFs; however, considering the aforementioned discrepancies in PEF cutoffs, it would be inadequate to conclude that MI-E set at insufflation-exsufflation pressures < +50/–50 cm H₂O are unable to produce an efficient PEF.

Sputum clearance is improved when flow bias, which results from the difference between PEF and peak inspiratory flow (PIF), favors expiratory flows.^{10,11} Thus, inspiratory flow should also be considered as a determinant factor when assessing the most effective setting during MI-E. For instance, Volpe M et al¹⁰ compared a standard MI-E maneuver with equal insufflation-exsufflation pressure and high inspiratory flow against an optimized maneuver, including higher exsufflation pressure than insufflation pressure and low inspiratory flow. Interestingly, the standard maneuver generated a higher PEF; but flow bias and, consequently, cephalad sputum displacement were better during the optimized setting. Unfortunately, in the present study there is a lack of information regarding the set inspiratory flow, PIF, and the resulting flow bias, which limits the

interpretation of the results and the impact of the purposed setting.

To date, scientific evidence on the efficacy and safety of MI-E during invasive mechanical ventilation is scant. Nevertheless, the study by Hyun SE et al¹ as well as previous studies demonstrates that critical factors such as the studied population, inspiratory-expiratory pressure and flow settings, or PEF cutoff should be considered when MI-E is implemented. Additional clinical studies are needed to elucidate the role of MI-E and setting adequacy in intubated and critically ill patients in ICU.

Roberto Martínez Alejos
Montpellier University
School of Physiotherapy
Montpellier, France

Joan Daniel Martí Romeu
Antoni Torres
Hospital Clínic de Barcelona
Pneumology
Barcelona, Spain

The authors have declared no conflicts of interest.

DOI: 10.4187/respcare.09671

REFERENCES

- Hyun SE, Lee SM, Shin HI. Peak expiratory flow during mechanical insufflation-exsufflation: endotracheal tube versus facemask. *Respir Care* 2021;66(12):1815-1823.
- Guérin C, Bourdin G, Leray V, Delannoy B, Bayle F, Germain M, Richard JC. Performance of the cough-assist insufflation-exsufflation device in the presence of an endotracheal tube or tracheostomy tube: a bench study. *Respir Care* 2011;56(8):1108-1114.
- Sánchez-García M, del Pino-Ramírez Á, Núñez-Reiz A, Busto-González B, Romero-Romero F, Martínez-Sagasti F, et al. Preliminary experience on the safety and tolerability of mechanical “insufflation-exsufflation” in subjects with artificial airway. *Intensive Care Med Exp* 2018;6(1):8.
- Nunes LDC, Rizzetti DA, Neves D, Vieira FN, Kutchak FM, Wiggers GA, Peçanha FM. Mechanical insufflation/exsufflation improves respiratory mechanics in critical care: randomized crossover trial. *Respir Physiol Neurobiol* 2019;266:115-120.
- Bach JR, Saporito L. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. *Chest* 1996;110(6):1566-1571.
- Jiang C, Esquinas A, Mina B. Evaluation of cough peak expiratory flow as a predictor of successful mechanical ventilation discontinuation: a narrative review of the literature. *J Intensive Care* 2017;5:33-31-5.
- euret P, Roux C, Auclair A, Nourdine K, Kaaki M, Carton M-J. Interest of an objective evaluation of cough during weaning from mechanical ventilation. *Intensive Care Med* 2009;35(6):1090-1093.
- Duan J, Zhou L, Xiao M, Llu J, Yang X. Semiquantitative cough strength score for predicting reintubation after planned extubation. *Am J Crit Care* 2015;24(6):e86-90.
- Martínez-Alejos R, Martí JD, Li Bassi G, Gonzalez-Anton D, Pilar-Diaz X, Reginault T, et al. Effects of mechanical insufflation-exsufflation on sputum volume in mechanically ventilated critically ill subjects. *Respir Care* 2021;66(9):1371-1379.
- Volpe MS, Naves JM, Ribeiro GG, Ruas G, Amato MBP. Airway clearance with an optimized mechanical insufflation-exsufflation maneuver. *Respir Care* 2018;63(10):1214-1222.
- Volpe MS, Amato MBP. Is it time to monitor flow bias during mechanical ventilation? *Respir Care* 2011;56(12):1970-1971.