hemodynamic effects of diffuse pulmonary microthrombi in some patients with COVID-19 respiratory failure. Pulmonary microthrombi and associated chemokine-mediated vasoconstriction increase PVR, whereas pulmonary vasodilation decreases PVR; when both processes occur simultaneously, each can "cancel out" the hemodynamic effect of the other. The coexistence of both obliterative and vasodilatory processes in the pulmonary vasculature is reminiscent of what can occur in chronic liver disease, specifically portopulmonary hypertension (obliterative) and HPS (vasodilatory) (11). At the end-stage of COVID-19 respiratory failure, the balance between vasodilatory and obliterative processes may tip heavily toward obliterative, ultimately leading to severe RV failure and cardiogenic shock (12).

Although vasodilatory and obliterative processes may mutually offset each other hemodynamically, their coexistence may synergistically amplify the gas exchange abnormalities that occur in COVID-19 respiratory failure. Vasodilated regions experience increased blood flow, creating low ventilation–perfusion ratios. Microthrombi and vasoconstriction in other areas of the lung reroute additional blood flow to the vasodilated regions and further drive down the ventilation–perfusion ratio, culminating in significant hypoxemia. The simultaneous presence of both vasodilatory and obliterative processes creates the ultimate in ventilation–perfusion mismatch and may explain the marked disconnect between gas exchange and compliance noted in COVID-19 respiratory failure (13). ■

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References

1. Reynolds AS, Lee AG, Renz J, DeSantis K, Liang J, Powell CA, *et al*. Pulmonary vascular dilatation detected by automated transcranial Doppler in COVID-19 pneumonia [letter]. *Am J Respir Crit Care Med* [online ahead of print] 6 Aug 2020; DOI: 10.1164/rccm.202006-2219LE.
2. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome: a liver-induced lung vascular disorder. *N Engl J Med* 2008;358:2378–2387.
3. Zhang XJ, Katsuta Y, Akimoto T, Ohsuga M, Aramaki T, Takano T. Intrapulmonary vascular dilatation and nitric oxide in hypoxemic rats with chronic bile duct ligation. *J Hepatol* 2003;39:724–730.
4. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–128.
5. Boissier F, Razazi K, Thille AW, Roche-Campo F, Leon R, Vivier E, *et al*. Echocardiographic detection of transpulmonary bubble transit during acute respiratory distress syndrome. *Ann Intensive Care* 2015;5:5.
6. Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G, Zeidman A, *et al*. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *Clin Transl Med* 2020;10:e44.
7. Pagnesi M, Baldetti L, Beneduce A, Calvo F, Gramegna M, Pazzanese V, *et al*. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart* 2020;106:1324–1331.
8. Kelly G, Alexander P, Clifford M. Pediatrica Intensiva Podcast, 2.2 The Frontlines of COIVD19: Italian intensivists Gio Colombo & Lorenzo Grazioli 2 weeks into their enormous epidemic. [updated 2020 Mar 21]. Available from: http://pedsintensiva.libsyn.com/22-the-frontlines-of-covid19.
9. Bull TM, Clark B, McFann K, Moss M; National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med* 2010;182:1123–1128.
10. Beiderlinden M, Kuehl H, Boes T, Peters J. Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography. *Intensive Care Med* 2006;32:852–857.
11. Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension: the pulmonary vascular enigmas of liver disease. *Clin Liver Dis (Hoboken)* 2020;15:S13–S24.
12. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute cor pulmonale in critically ill patients with covid-19. *N Engl J Med* 2020;382:e70.
13. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1299–1300.

Opioids for Dyspnea in Chronic Obstructive Pulmonary Disease: Short on the Details

To the Editor:

In a recently published guideline on pharmacologic management of chronic obstructive pulmonary disease (COPD), Nici and colleagues (1) make a "conditional recommendation" for using opioids among individuals experiencing refractory dyspnea. The recommendation rests on a meta-analysis conducted by the authors that demonstrated that in "patients with advanced refractory dyspnea, there was a statistically and clinically meaningful improvement in dyspnea with opioid treatment" (standardized mean difference [SMD] in dyspnea scores for opioids vs. placebo = −0.60; 95% confidence interval [CI],

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−1.08 to −0.13) (1). The authors do not outline the results of their pooled analysis in detail (such as with a Forrest plot) and explain that such detail will be independently published later.

Nici and colleagues (1) neglect to specify for the reader that out of the 12 trials included in their meta-analysis on opioids for dyspnea in COPD, only 3 reported statistically significant positive results for opioids over placebo, and the remaining 9 were negative. Furthermore, one of the three positive trials involved individuals with COPD, not secondary to tobacco smoke exposure but instead secondary to mustard gas (2); thus, this study is associated with bias. Along with the overall pooled estimate, it would have been helpful for Nici and colleagues (1) to concurrently present such important details, to provide readers with a more comprehensive and balanced view of their meta-analysis. When considering the results of a meta-analysis, it is instructive to know if a positive signal is being driven by a majority of studies included, versus a small number, and if the latter case, whether such studies might be associated with bias.

The authors also overlook acknowledging two other recently published meta-analyses on the topic of opioids for dyspnea in COPD (3, 4), using nearly the same evidence base yet reporting strikingly different findings. Considering 10 out of 12 trials that Nici and colleagues (1) did, Ekström and colleagues (3) in 2015 reported a markedly lower SMD in dyspnea scores for opioids over placebo (−0.35; 95% CI, −0.53 to −0.17). Subsequently, in 2016, a meta-analysis was published by Barnes and colleagues (4), and when considering studies involving only individuals with COPD, this group reported an SMD in dyspnea scores similar to that of Ekström and colleagues (5), but not statistically significant (SMD −0.49 [95% CI, −1.08 to 0.10] for trials where dyspnea scores were compared with baseline, and SMD −0.21 [95% CI, −0.45 to 0.04] for trials where dyspnea scores were compared with the pretreatment period). The SMD estimates from the aforementioned two meta-analyses show, at best, a small improvement in dyspnea intensity with opioids and fall below the threshold that Nici and colleagues (1) set as clinically meaningful (SMD >0.50). It is challenging to reconcile the SMD estimate of Nici and colleagues (1) with that of Ekström and colleagues (3) and Barnes and colleagues (4), without more details being provided by the former authors.

Finally, Nici and colleagues' (1) literature search terminated in July 2019. However, since then, two more randomized controlled trials have been published that evaluated opioids for dyspnea in advanced COPD (5, 6). Both trials reported negative results, and the study by Currow and colleagues (5) is the largest and, arguably, best-quality trial on the topic conducted to date. Therefore, Nici and colleagues' (1) recommendation regarding opioids for dyspnea in COPD does not incorporate the most up-to-date, best-quality evidence on the topic.

On such an important and controversial topic as using opioids to treat refractory dyspnea in COPD, in a guideline document, it behooves Nici and colleagues (1) to provide readers much more detail about their meta-analysis, including what, why, and how data got pooled. ■

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References

1. Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, *et al*. Pharmacologic management of chronic obstructive pulmonary disease: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e56–e69.
2. Shohrati M, Ghanei M, Harandi AA, Foroghi S, Harandi AA. Effect of nebulized morphine on dyspnea of mustard gas-exposed patients: a double-blind randomized clinical trial study. *Pulm Med* 2012;2012:610921.
3. Ekström M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease: a systematic review. *Ann Am Thorac Soc* 2015; 12:1079–1092.
4. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016;3: CD011008.
5. Currow D, Louw S, McCloud P, Fazekas B, Plummer J, McDonald CF, *et al*.; Australian National Palliative Care Clinical Studies Collaborative (PaCCSC). Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. *Thorax* 2020;75:50–56.
6. Ferreira DH, Louw S, McCloud P, Fazekas B, McDonald CF, Agar MR, *et al*.; Australian National Palliative Care Clinical Studies Collaborative (PaCCSC). Controlled-release oxycodone vs. placebo in the treatment of chronic breathlessness-a multisite randomized placebo controlled trial. *J Pain Symptom Manage* 2020;59:581–589.

Reply to Vozoris

From the Authors:

We appreciate the opportunity to clarify Dr. Vozoris's questions concerning the American Thoracic Society (ATS) clinical practice guideline (CPG) on the pharmacological treatment of chronic obstructive pulmonary disease (COPD) (1). Dr. Vozoris's questions relate to the specific clinical question addressed in the ATS guideline concerning the use of opioids for COPD. Dr. Vozoris specifically highlights concerns related to the lack of specific details of the meta-analysis used to assess the benefits and risks of the impact of opioids on dyspnea.

Although there was not enough space in the ATS CPG to detail every systematic review relevant to the clinical questions addressed, we acknowledge that there have been previous systematic reviews and meta-analyses on opioids. Our meta-analysis differed from the meta-analysis by Eckström and colleagues and by Barnes and colleagues in that our search resulted in one additional study not included in the

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