$$\Delta MOX_{2h} = ([Sp_{O_2,6h} / (Fi_{O_2,6h} \times MV_{6h})] - [Sp_{O_2,0h} / (Fi_{O_2,0h} \times MV_{0h})]) \times MV_{0h}.$$

ΔMOX, which reflects the change of respiratory drive after HFNC, was able to distinguish HFNC failure only at 6 hours but not at 2 hours after HFNC. The AUROC was 0.59 at 2 hours and 0.79 at 6 hours. The sensitivity and specificity were 58.6% and 93.9% at 6 hours after HFNC, respectively. However, the AUROC of VOX index, which reflects the absolute increase of respiratory drive, was much higher (0.93) at 6 hours after HFNC.

On the other hand, more severe patients enrolled in our study, compared with the study by Li and colleagues (3), might be the main reason for the poor predictive value of ΔMOX after a short time of HFNC (2 h). Compared with the report by Li and colleagues, a higher acute physiologic assessment and chronic health evaluation II score (21 vs. 18) and a higher intubation rate (46.7% vs. 22.9%) were observed in patients in our study.

Therefore, as the use of a change of MV does not provide any additional benefit in terms of prediction of HFNC failure, the use of the normal VOX index may be recommended. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Effect of COVID-19 in Pulmonary Hypertension

To the Editor:

Montani and colleagues should be commended for their excellent effort in comprehensively analyzing the effect of coronavirus disease (COVID-19) in patients with pulmonary hypertension (PH) (1). However, I noticed a few issues related to the interpretation of the findings of this study. First of all, the hemodynamic and phenotypic characterization of PH is unclear. The authors stressed that all patients had precapillary PH without providing data related to pulmonary arterial wedge pressure (PAWP). In this study, all patients were older (>60 yr of age) and had one or multiple risk factors for coronary artery disease and heart failure. The risk factors for systolic and diastolic left ventricular dysfunction included systemic hypertension, obesity, diabetes, chronic renal failure, immunosuppression and other cardiac diseases (2). Patients exposed to these risk factors are likely to develop heart failure with preserved or reduced ejection fraction. The cardiac index data (median, 2.8 L/m/m^2; range, 2.2–3.5 L/m/m^2) in the survivor and nonsurvivor groups indicated a heterogeneous population of patients composed of groups with heart failure with preserved and reduced ejection fraction. In this scenario, hemodynamic characterization on the basis of PAWP becomes necessary to exclude isolated postcapillary PH (IpcPH) and combined post- and precapillary PH (CpcPH). Heart failure with preserved or reduced ejection fraction nearly always leads to CpcPH or IpcPH (3). In this heterogeneous population, the primary pathologies must have originated in the left ventricle in most patients, and PH seemed a secondary manifestation of heart failure. A normal right atrial pressure (6–9 mm Hg) in the presence of high brain natriuretic peptide or N-terminal pro–brain natriuretic peptide in nearly 50% of patients also indicated left ventricular failure with normal right ventricular function.

It is indeed surprising that all these diverse etiologies manifest only in precapillary PH. Unarguably, mortality due to COVID-19 in this population cannot be attributed entirely to precapillary PH. Nevertheless, a few risk factors (smoking, chronic respiratory disease) could have manifested entirely in precapillary PH. Therefore, readers would be curious to know the hemodynamic characterization of PH on the basis of PAWP and stratification of clinical outcomes after COVID-19. Furthermore, a comparison of clinical outcomes in isolated precapillary PH, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction would have been meaningful. The authors may conclude that patients with heart failure or precapillary hypertension who contracted COVID-19 had high rates of hospitalization and in-hospital mortality.

The considerably lower values of D_{LCO} in the nonsurvivors are noteworthy. Lung parenchymal lesions appeared more extensive in nonsurvivors, and the severity of precapillary PH grades cannot

Originally Published in Press as DOI: 10.1164/rccm.202209-1790LE on October 17, 2022

entirely explain lower D_{LCO}. Therefore, it is conceivable to conclude that structural lung lesions, not precapillary PH, contributed to mortality.

The majority of patients in this study received pulmonary vasodilator therapy. Considering the patient population in this study, many patients could have PH due to left heart disease (4). The authors refuted this hypothesis and contended that pulmonary arterial hypertension (PAH)–specific medications may not be protective during COVID-19. Pulmonary vasodilator therapy has not been shown to improve outcomes in PH due to left heart disease. Therefore, it may not be logical to refute the hypothesis, as the beneficial effects of PAH-specific medications could have been counteracted by possible harmful effects in PH due to left heart disease. Moreover, the nonsurvivors had poor D_{LCO}, and patients with poor D_{LCO} have a different kind of vasculopathy and are less responsive to PAH therapy (5). Furthermore, the investigators should have also aimed to provide echocardiographic data and medications used to treat comorbidities.

In conclusion, symptomatology and cardiac catheterization data of PH and heart failure are often indistinguishable in older populations with multiple comorbidities. Isolated precapillary PH should be clearly differentiated from IpcPH and CpcPH, as PAH-directed therapy may not be appropriate for all three phenotypes of PH. The impact of PAH-directed therapy in a mixed population of individuals with PH and COVID-19 may not be assessed distinctly. ■

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Reply to Jha

From the Authors:

We thank the author for their interest in our recent article on the French prospective cohort of coronavirus disease (COVID-19) in patients with pulmonary hypertension (PH) (1). First of all, the author wondered if all patients in our study truly had precapillary PH. As stated in the methods, all patients' data were extracted from the French registry, which includes well-phenotyped patients with PH, all having undergone complete hemodynamic evaluation, and has led to many publications in recent decades (2, 3). All patients included in this analysis had precapillary PH at the time of diagnosis, in accordance with the current definition during the inclusion period (i.e., a mean pulmonary arterial pressure of ⩽25 mm Hg, a normal pulmonary arterial wedge pressure [PAWP] of ⩽15 mm Hg, and pulmonary vascular resistance of >3 Woods units) (4). According to international definitions, this excluded the presence of PH due to left heart diseases (group 2 PH) as the main cause of PH in this population. The most recent right heart catheterization data for these patients yielded a median PAWP of 10 (interquartile range, 7–13) mm Hg. At the last hemodynamic evaluation before COVID-19, a small subgroup of 14 patients (6.6% of the overall 213 patients) had combined pre- and postcapillary PH with PAWP >15 mm Hg, which is in accordance with the age and comorbidities reported in this population as well as the possibility of ventricular interdependence. The etiologies of PH among these patients were PH associated with chronic respiratory diseases ($n = 6$), idiopathic pulmonary arterial hypertension (PAH) ($n = 4$), anorexigen-associated PAH ($n = 2$), and chronic thromboembolic PH ($n = 2$). We disagree with the assumption that the high prevalence of comorbidities is, on its own, indicative of postcapillary PH and also wish to correct the author's statement that all patients were >60 years of age, as the interquartile ranges for age in the groups presented in our Table 1 include patients in their 40s and 50s. Recent national registries highlight frequent pulmonary and cardiovascular comorbidities in patients with PAH (3, 5, 6). In the French PH Registry, systemic hypertension, obesity, diabetes, coronary heart disease, and atrial fibrillation were recorded in 50%, 32%, 25%, 14%, and 11%, respectively, in a large population ($n = 1{,}611$) of subjects with idiopathic, heritable and anorexigen-associated PAH (3). The prevalence of comorbidities was broadly similar in the present study, especially if we put in perspective that our cohort included patients with groups 3 and 4 PH, classically associated with older age and more frequent comorbidities. Indeed, the assumption that normal right atrial pressure in the presence of high brain natriuretic peptide or N-terminal pro–brain natriuretic peptide indicates left ventricular failure with normal right ventricular function has no meaning in a population with precapillary PH

Originally Published in Press as DOI: 10.1164/rccm.202210-1889LE on October 17, 2022