early prediction (within 1 h) of HFNC failure (4). As inspired by the work (1), we combined ROX and VOX indices and retrospectively analyzed the data from the previous study (4) using EIT-based VT and RR (EIT-based min volume [MV]) at 1 hour after HFNC. This parameter ΔEMOX was calculated as follows:

$$\Delta\text{EMOX} = [\text{SpO}_{2,1h}/(\text{FiO}_{2,1h} \times \text{MV}_{\text{EIT},1h}) - \text{SpO}_{2,0h}/(\text{FiO}_{2,0h} \times \text{MV}_{\text{EIT},0h})] \times \text{MV}_{\text{EIT},0h}.$$

ΔEMOX at 1 hour after HFNC was able to distinguish HFNC failure ($P < 0.05$). The area under the receiver operating characteristic curve was 0.72 (same as ROX_{1h}). The sensitivity and specificity were 51.4 and 100, respectively, versus 77.1 and 63.6 for ROX_{1h}.

The VT calculation in the study (1) averaged the volume within 1 minute during stable NIV, whereas MV combines both VT and respiratory rate that reflects the respiratory drive within 1 minute. Given that respiratory efforts during spontaneous breathing could be assessed by EIT (5) and EIT data might be connected to the centralized ICU system, the combination of ROX and VOX with EIT-based MV might be more practical in clinical routine, that requires further validation. ■

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Reply to Li *et al.*

From the Authors:

We read with great interest the letter by Li and colleagues and thank them for their interest in our work (1).

We fully agree that tidal volume (VT) that occurred during high-flow nasal cannula (HFNC) may not be the same as the VT measured with noninvasive ventilation (NIV) used at low degrees of support. However, this does not affect VT measured with NIV response to an early increase in respiratory drive in each patient. Although the accuracy of VT remains controversial, it should be pointed out that our study is merely a proof of concept to demonstrate that an index incorporating VT performs better than an index relying on respiratory rate.

To the best of our knowledge, there does exist only a few monitoring techniques that enable VT measurement under HFNC, such as a time-of-flight camera (2). However, it has not been widely used at the bedside. Tidal impedance change measured by electrical impedance tomography (EIT) correlates well with VT in individuals. However, such a correlation is not constant among patients. A universal cutoff value reflecting respiratory drive cannot be derived from EIT data alone. Although this method is not perfect, monitoring VT with low support level NIV in patients with HFNC is thus far a clinically acceptable and simple method. If well prepared, switching HFNC to NIV takes only a few seconds and may not result in derecruitment of the alveoli. Nevertheless, alternative ways to evaluate VT in patients under HFNC should be explored.

The second point raised by Li and colleagues is that for the calculation of Volume-OXygenation (VOX), the absolute VT might not be necessary. It is our opinion that the absolute value of VT is essential to estimate the absolute value of an early increase in the respiratory drive during HFNC. The parameter ΔEMOX proposed by Li and colleagues, that uses EIT-based VT and respiratory rate (EIT-based min volume [MV]) at 1 hour after HFNC, only reflects the change in respiratory drive before and 1 hour after HFNC but not the absolute increase in respiratory drive in each patient. Therefore, it is not surprising that ΔEMOX has only a moderate value in predicting HFNC failure (area under the receiver operating characteristic curve [AUROC], 0.72).

To verify that absolute elevation of VT rather than changes in VT after HFNC is a better predictor of HFNC failure, we retrospectively analyzed the data from our previous study, mimicking Dr. Li and colleagues' ΔEMOX formula. The parameter ΔMOX (MV-OXygenation) at 2 hours and 6 hours after HFNC was calculated as follows (Sp_{O_2} = oxygen saturation as measured by pulse oximetry):

$$\Delta\text{MOX}_{2h} = ([\text{Sp}_{\text{O}_2,2h} / (\text{Fi}_{\text{O}_2,2h} \times \text{MV}_{2h})] - [\text{Sp}_{\text{O}_2,0h} / (\text{Fi}_{\text{O}_2,0h} \times \text{MV}_{0h})]) \times \text{MV}_{0h}$$

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

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. ■

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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

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