also showed that lower arterial oxygen pressure (Pa_{O_2})/fraction of inspired oxygen (FI_{O_2}) ratio, higher CRP (C-reactive protein) concentrations, and lower platelet counts were independently associated with an increased risk of NIV failure.

However, we believe that using the Pa_{O_2}/FI_{O_2} ratio is a rather questionable means of predicting NIV failure. First, Pa_{O_2}/FI_{O_2} values are inherently inaccurate because the FI_{O_2} in a nonintubated patient is quite difficult to determine (2). And this is especially true in the context of non-ICU departments when using free-flow systems under the condition of a gas leak around the mask or helmet. Second, the Pa_{O_2}/FI_{O_2} threshold of 150 mm Hg is also rather controversial. In a study by Franco and colleagues (3), there were no differences in the 30-day mortality rate between patients with COVID-19 with baseline Pa_{O_2}/FI_{O_2} values of 101–150 mm Hg and patients with COVID-19 with baseline Pa_{O_2}/FI_{O_2} values of 151–200 mm Hg (24% and 26%, respectively). Third, in two other studies (4, 5) conducted outside the ICU, the mortality rates of patients with COVID-19 with even lower baseline Pa_{O_2}/FI_{O_2} values during NIV were better than that in the study by Bellani and colleagues: the rate was 17% in a study by Brusasco and colleagues (initial median Pa_{O_2}/FI_{O_2} of 119 mm Hg) (4), and the rate was 21% in a study by Nightingale and colleagues (initial median Pa_{O_2}/FI_{O_2} of 122 mm Hg) (5).

In our recent study, in patients with COVID-19 receiving NIV outside the ICU, the baseline Pa_{O_2}/FI_{O_2} index also did not differ between the success and failure groups, but we found that patients who experienced NIV failure had higher minute ventilation on the first day of NIV (due to a slightly higher tidal volume and a higher respiratory rate) (6), which, of course, may increase the risk of self-inflicted lung injury. These findings are in line with Bellani and colleagues' data, which also showed that the patients experiencing NIV failure had lower arterial carbon dioxide pressure levels. However, we must admit that today in non-ICU settings, it is rather difficult to identify robust markers of possible self-inflicted lung injury.

Bellani and colleagues also identified elevated levels of CRP as an independent predictor of NIV failure. Interestingly, in our study, an elevated D-dimer level was an indicator of the increased possibility of NIV failure (6). Both high CRP levels and high D-dimer levels are associated with the progression of COVID-19 and a higher mortality rate. So, progressive underlying processes in COVID-19 might need prolonged respiratory support and can be associated with NIV failure.

In conclusion, because the appropriate patient selection is the key to the successful application of NIV, further research is needed to identify reliable predictors of NIV failure in COVID-19–associated AHRF.

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

Sergey N. Avdeev, M.D.*
Andrey I. Yaroshetskiy, M.D.
Galia S. Nuralieva, M.D.
I.M. Sechenov First Moscow State Medical University (Sechenov University)
Moscow, Russia

ORCID IDs: 0000-0002-5999-2150 (S.N.A.); 0000-0002-1484-092X (A.I.Y.).

*Corresponding author (e-mail: serg_avdeev@list.ru)

References

1 Bellani G, Grasselli G, Cecconi M, Antolini L, Borelli M, De Giacomi F, *et al.*; COVID-19 Lombardy ICU Network. Noninvasive ventilatory support of patients with COVID-19 utside the intensive care units (WARd-COVID). *Ann Am Thorac Soc* 2021;18:1020–1026.
2 Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med* 2020;202:356–360.
3 Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, *et al.* Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020; 56:2002130.
4 Nightingale R, Nwosu N, Kutubudin F, Fletcher T, Lewis J, Frost F, *et al.* Is continuous positive airway pressure (CPAP) a new standard of care for type 1 respiratory failure in COVID-19 patients? A retrospective observational study of a dedicated COVID-19 CPAP service. *BMJ Open Respir Res* 2020;7:e000639.
5 Brusasco C, Corradi F, Di Domenico A, Raggi F, Timossi G, Santori G, *et al.*; Galliera CPAP-COVID-19 Study Group. Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. *Eur Respir J* 2021;57:2002524.
6 Avdeev SN, Yaroshetskiy AI, Tsareva NA, Merzhoeva ZM, Trushenko NV, Nekludova GV, *et al.* Noninvasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19. *Am J Emerg Med* 2021;39:154–157.
7 Bellani G, Grasselli G, Cecconi M, Antolini L, Borelli M, De Giacomi F, *et al.*; COVID-19 Lombardy ICU Network. Noninvasive ventilatory support of patients with COVID-19 utside the intensive care units (WARd-COVID). *Ann Am Thorac Soc* 2021;18:1020–1026.

Reply: Can We Reliably Predict the Failure of Noninvasive Ventilation in COVID-19–associated Acute Hypoxemic Respiratory Failure?

From the Authors:

We thank Dr. Avdeev and colleagues for their interest in our article (1) and for their comments, which allow us to clarify some points. Their main concern has to do with the prognostic value of the arterial oxygen tension (Pa_{O_2})/fraction of inspired oxygen (FI_{O_2}) ratio. First, we would like to emphasize the reliability of the FI_{O_2} even in noninvasive condition; despite the (most likely) presence of leaks, positive pressure will cause a unidirectional gas flow from the inner of the interface (face mask or helmet) toward the ambient pressure. Hence, there is no risk of room air contamination of the fresh gas flow mixture (2). This might not be the case in patients treated with high-flow nasal cannulas, who indeed may inhale room air (especially if breathing with an open mouth), but these patients were not included in our analysis.

Regarding the threshold value of the Pa_{O_2}/FI_{O_2} ratio, we agree that this is somewhat arbitrary and that the chance of noninvasive ventilation (NIV) failure increases continuously with decreasing $Pa_{O_2}/$

FI_{O_2}. At the same time, the 150-mm Hg threshold is gaining increasing value in the literature in both invasively (3) and noninvasively ventilated patients (4, 5) and could provide a pragmatic guideline, particularly useful in these pandemic times. Irrespective of any *a priori* hypothesis, our data showed a robust association with outcome. Regarding the paper by Franco and colleagues (6), Avdeev only focuses on the patients with a Pa_{O_2}/FI_{O_2} ratio in the 100–200-mm Hg interval, but if one considers the entire population, mortality was 30% versus 21% under or above the 150-mm Hg threshold. Regarding the lower mortality observed in the nice study by Nightingale and colleagues (7), this was recorded in a much younger population than ours (52 vs. 68 years old), whereas the study from Brusasco and colleagues (8) did not include patients not eligible for resuscitation (as opposed to our study, in which 28% of patients had a do-not-intubate decision). Moreover, the baseline Pa_{O_2}/FI_{O_2} reported in both articles was collected before continuous positive airway pressure (CPAP) initiation; because CPAP rapidly and significantly improves Pa_{O_2}/FI_{O_2} (9), as also shown in Table 1 by Avdeev and coworkers, the severity of the populations is not comparable with ours.

Very interestingly, the article by Avdeev and coworkers shows a difference (albeit statistically nonsignificant) between success and failure in the values of Pa_{O_2}/FI_{O_2} only if these were measured during NIV as opposed to during standard oxygen. This is totally in line with a recent finding by Coppadoro and colleagues (9) and emphasizes that Pa_{O_2}/FI_{O_2} has a prognostic value for NIV failure only if measured during NIV. At the same time, we fully agree with Avdeev, Yaroshetskiy, and Nuralieva (10) that the risk of patient self-inflicted lung injury is of paramount importance during NIV, and their finding on the role of minute ventilation is extremely relevant. This, unfortunately, was not measured in our study because of the predominant use of helmets, which do not allow this measurement. Moreover, when our study was designed (mid-March 2020), the evidence on the crucial role of coagulopathy in coronavirus disease (COVID-19) was still emerging, and, unfortunately, we did not collect D-dimers. It would have been an extremely interesting finding.

In summary, we believe that Pa_{O_2}/FI_{O_2}, if measured during NIV, remains a key element to predict NIV failure or success, but it must be combined with indexes of patient self-inflicted lung injury and inflammatory and coagulation markers. ■

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

Giacomo Bellani, M.D., Ph.D.
University of Milano-Bicocca
Milan, Italy
and
San Gerardo Hospital
Monza, Italy

Maurizio Cecconi, M.D.*
Humanitas Clinical and Research Center
Milan, Italy
and
Humanitas University
Milan, Italy

Giacomo Grasselli, M.D.
Foundation Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy
and
University of Milan
Milan, Italy

ORCID IDs: 0000-0002-3089-205X (G.B.); 0000-0002-1735-1400 (G.G.).

*Corresponding author (e-mail: maurizio.cecconi@hunimed.eu).

References

1 Bellani G, Grasselli G, Cecconi M, Antolini L, Borelli M, De Giacomi F, *et al.*; COVID-19 Lombardy ICU Network. Noninvasive Ventilatory Support of COVID-19 Patients Outside the Intensive Care Units (WARd-COVID). *Ann Am Thorac Soc* 2021;18:1020–1026.
2 Bellani G, Patroniti N, Greco M, Foti G, Pesenti A. The use of helmets to deliver non-invasive continuous positive airway pressure in hypoxemic acute respiratory failure. *Minerva Anestesiol* 2008;74: 651–656.
3 Maiolo G, Collino F, Vasques F, Rapetti F, Tonetti T, Romitti F, *et al.* Reclassifying Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2018;197:1586–1595.
4 Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, *et al.*; LUNG SAFE Investigators; ESICM Trials Group. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med* 2017;195:67–77.
5 Thille AW, Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care* 2013;17: R269.
6 Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, *et al.* Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020;56:2002130.
7 Nightingale R, Nwosu N, Kutubudin F, Fletcher T, Lewis J, Frost F, *et al.* Is continuous positive airway pressure (CPAP) a new standard of care for type 1 respiratory failure in COVID-19 patients? A retrospective observational study of a dedicated COVID-19 CPAP service. *BMJ Open Respir Res* 2020;7:e000639.
8 Brusasco C, Corradi F, Di Domenico A, Raggi F, Timossi G, Santori G, *et al.*, Galliera CPAP-Covid-19 study group. Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. *Eur Respir J* 2021;57:2002524.
9 Coppadoro A, Benini A, Fruscio R, Verga L, Mazzola P, Bellelli G, *et al.* Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. *Crit Care* 2021; 25:80.
10 Avdeev SN, Yaroshetskiy AI, Nuralieva GS. Can We Reliably Predict the Failure of Non-invasive Ventilation in COVID-19-associated Acute Hypoxemic Respiratory Failure? *Ann Am Thorac Soc* 2021;18: 1594–1595.