mechanisms of exacerbation nonresolution, then antibiotic resistant bacteria such as *Pseudomonas aeruginosa* or *Moraxella catarrhalis* should be prevalent. In fact, the recognition of *M. catarrhalis* as an important cause of COPD exacerbations came from several reports of patients failing treatment with a β-lactam antibiotic who were infected with a β-lactamase–producing strain of this pathogen (8). In this study, only 32% of patients could provide a sputum sample for bacteriology and only 15% of randomized patients had sputum that yielded a positive bacterial culture. This is not surprising given that most patients had very mild symptoms and did not display clinical characteristics suggesting they had a bacterial infection.

A final caveat to consider is the study power. The study was designed with a modest number of randomized patients and was only powered to detect a large (54%) prolongation in the time to next exacerbation in those treated with antibiotics. It is thus possible that the study findings are due to type II statistical error, whereby an important clinical effect goes undetected due to lack of power. Furthermore, this limitation in study power means that a subgroup analysis of patients with type 1 exacerbations would be too small to be reliable.

Despite these limitations, this important study informs our daily practice in managing exacerbations of COPD. It tells us that indiscriminate antibiotic retreatment in many patients with exacerbations of COPD is not of benefit, even if they have persistent symptoms (albeit mild) and/or an increased CRP. Such an approach will not reduce relapse rates or hasten the time to complete resolution. However, the study results do not inform us whether antibiotic treatment is useful when a patient experiences nonresolution with persistent or increased sputum purulence and/or a type 1 exacerbation. In fact, in clinical practice, these patients do not or should not be waiting 14 days for reassessment and additional management (9). A placebo-controlled trial in which only such patients are included in adequate numbers would be highly desirable to support or refute such a discriminate approach. In the meantime, we can reduce inappropriate antibiotic use and its undesirable consequences by stopping indiscriminate use. ■

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

Sanjay Sethi, M.D.
Jacobs School of Medicine
University of Buffalo
Buffalo, New York

Shawn D. Aaron, M.D.
The Ottawa Hospital Research Institute
University of Ottawa
Ottawa, Ontario, Canada

ORCID ID: 0000-0002-4762-3542 (S.D.A.).

References

1. Sethi S, Wrona C, Eschberger K, Lobbins P, Cai X, Murphy TF. Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;177: 491–497.
2. Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Müllerova H, Donaldson GC, *et al*. Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J* 2007;29:527–534.
3. Mallia P, Footitt J, Sotero R, Jepson A, Contoli M, Trujillo-Torralbo MB, *et al*. Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186: 1117–1124.
4. Ritchie AI, Brill SE, Vlies BH, Finney LJ, Allinson JP, Alves-Moreira L, *et al*. Targeted retreatment of incompletely recovered chronic obstructive pulmonary disease exacerbations with ciprofloxacin: a double-blind, randomized, placebo-controlled, multicenter, phase III clinical trial. *Am J Respir Crit Care Med* 2020;202:549–557.
5. Jacobs DM, Pandit U, Sethi S. Acute exacerbations in chronic obstructive pulmonary disease: should we use antibiotics and if so, which ones? *Curr Opin Infect Dis* 2019;32:143–151.
6. Leidy NK, Murray LT, Jones P, Sethi S. Performance of the EXAcerbations of chronic pulmonary disease tool patient-reported outcome measure in three clinical trials of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2014;11:316–325.
7. Sethi S, Anzueto A, Miravitlles M, Arvis P, Alder J, Haverstock D, *et al*. Determinants of bacteriological outcomes in exacerbations of chronic obstructive pulmonary disease. *Infection* 2016;44: 65–76.
8. Murphy TF, Parameswaran GI. Moraxella catarrhalis, a human respiratory tract pathogen. *Clin Infect Dis* 2009;49:124–131.
9. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008;359: 2355–2365.

The Dark Side of Spontaneous Breathing during Noninvasive Ventilation
From Hypothesis to Theory

Breathing by our own respiratory muscles is physiologically natural. The diaphragmatic contraction with spontaneous breathing (vs. muscle paralysis) tends to distribute ventilation into dorsal, well-perfused lung regions, the benefit of which was first observed in healthy subjects or anesthetized patients (1). Subsequent to these classical studies, the role of spontaneous breathing in critically ill patients has been vigorously examined (2); now it is well known that spontaneous breathing during mechanical ventilation brings various benefits to ICU patients (e.g., better gas exchange, maintenance of peripheral muscles, and diaphragm function) (2, 3). Of course, because liberation from the ventilator has been a

Originally Published in Press as DOI: 10.1164/rccm.202005-1612ED on May 20, 2020

major goal among ICU patients, all patients with this goal will need to transition to spontaneous breathing effort. Therefore, facilitation of spontaneous breathing during mechanical ventilation has a central place in the ICU.

In the 1980s, however, there were some studies (i.e., case reports and animal studies) alerting physicians to the risk of spontaneous breathing in acute respiratory failure (4, 5), concluding that "a trial of paralysis should be considered in patients with Adult Respiratory Distress Syndrome who exhibit vigorous activity of the respiratory muscles when maintenance of arterial oxygenation is a life-threatening problem" (4). About two decades later, a randomized clinical trial regarding muscle paralysis was performed and it was found that early muscle paralysis improved 90-day mortality in severe acute respiratory distress syndrome (ARDS) (6). This clinical trial indirectly supports the risk of spontaneous effort in severe ARDS. Since then, the risk of spontaneous effort and its potential mechanisms have been extensively discussed (7, 8). So far, accumulating evidence indicates that spontaneous effort during mechanical ventilation may worsen lung injury, especially when spontaneous effort is vigorous and lung injury is severe (7, 8). In 2017, this concept of effort-dependent lung injury was applied to *nonintubated* patients with high respiratory drive in acute hypoxemic respiratory failure, with the assumption that a process similar to effort-dependent lung injury might be involved, and the term "patient self-inflicted lung injury" (P-SILI) was coined (9). Thus, P-SILI is a new hypothesis without enough direct evidence; most of the evidence has been extrapolated from clinical and experimental data derived from mechanically ventilated subjects with spontaneous-effort (i.e., effort-dependent) lung injury (9).

In this issue of the *Journal*, the elegant clinical study by Tonelli and coworkers (pp. 558–567) may evolve the concept of P-SILI from a hypothesis to a theory substantiated by clinical evidence (10). Tonelli and coworkers (10) carefully estimated the intensity of spontaneous breathing effort in 30 patients with acute hypoxic *de novo* respiratory failure ($Pa_{O_2}/FI_{O_2} \approx 125$ mm Hg) by using esophageal balloon manometry during the first 24 hours of noninvasive mechanical ventilation (NIV) and tested the hypothesis that vigorous spontaneous effort may worsen lung injury (estimated by chest X-ray), resulting in NIV failure in severe acute respiratory failure. Several intriguing findings were revealed by Tonelli and coworkers (10).

First, Tonelli and coworkers (10) found that vigorous spontaneous effort (i.e., a negative swing in esophageal pressure [ΔPes] ≈ -34 cm H_2O) was present in patients with severe acute respiratory failure before starting NIV and that reduced lung volume seems to proportionally increase the strength of spontaneous effort because the negative correlation between the intensity of spontaneous effort (estimated by ΔPes) and lung compliance (estimated by dividing V_T by the change in transpulmonary pressure) was clearly observed (*see* Figure E4 of Reference 10). Of note, reduced lung volume has important effects on the force–length relationship and curvature of the diaphragm (11). Thus, the lower the lung volume is, the more force the diaphragm can generate (10, 12). This finding revealed by Tonelli and coworkers (10) may highlight the importance of an adequate amount of positive end-expiratory pressure (PEEP) to restore lung volume and thus decrease spontaneous effort in severe acute respiratory failure. In a randomized clinical study comparing the delivery of NIV with a helmet and the delivery of NIV with a face mask in patients with ARDS, NIV with a helmet could deliver higher PEEP, resulting in less spontaneous effort (suggested by a lower respiratory rate), a lower intubation rate, and better survival (13). Importantly, less spontaneous effort was observed in the helmet group (vs. the face-mask group) despite less pressure support (13).

Second, Tonelli and coworkers (10) found that persistent vigorous spontaneous effort after the induction of NIV was associated with worsening lung injury (estimated by chest X-ray in Figure E6 of Reference 10) and was the earliest and most accurate parameter to predict NIV failure (Figures 4 and E1A of Reference 10; Table 3 of Reference 10). To estimate how much spontaneous effort was involved to distend the lung, they further investigated the ratio of the ΔPes to the change in transpulmonary pressure during NIV (Figure E1C of Reference 10). Interestingly, Tonelli and coworkers (10) found that a higher proportion of spontaneous effort in comparison with total lung-distending pressure caused a higher incidence of NIV failure, despite the similar total lung-distending pressure. These are the most striking clinical data to support P-SILI in severe acute respiratory failure. Under the same amount of total lung-distending pressure, whether generated by their own spontaneous breathing (i.e., active condition) or by mechanical ventilation (i.e., passive condition), lung injury should theoretically be the same (14), but the authors claimed this was not true. As the authors described, vigorous spontaneous effort can cause additional lung damage by local overdistension in dorsal lung regions associated with pendelluft and increased lung perfusion (8, 15).

We cannot say that the clinical study by Tonelli and coworkers (10) provides enough scientific evidence to confirm the concept of P-SILI, as this was still a physiological, exploratory study with 30 patients. However, Tonelli and coworkers' (10) observations are very important and clinically relevant. These new clinical data will reassure us about our current clinical practice of avoiding excessive spontaneous effort and delayed intubation during NIV in acute respiratory failure. While waiting for a large, appropriately designed clinical trial, we should carefully monitor spontaneous activity (e.g., physical examination, airway occlusion pressure, and ΔPes) in patients with acute respiratory failure under NIV. If vigorous spontaneous effort is persistent after the induction of NIV, such effort should probably be manipulated by treatment of acidosis, careful use of sedation and analgesia, adjusting the amount of PEEP, or early intubation. ■

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

Takeshi Yoshida, M.D., Ph.D.
Department of Anesthesiology and Intensive Care Medicine
Osaka University Graduate School of Medicine
Suita, Japan

References

1. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology* 1974;41:242–255.
2. Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, Von Spiegel T, *et al*. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001;164:43–49.
3. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, *et al*. Mechanical ventilation-induced diaphragm atrophy strongly

impacts clinical outcomes. *Am J Respir Crit Care Med* 2018;197: 204–213.
4. Coggeshall JW, Marini JJ, Newman JH. Improved oxygenation after muscle relaxation in adult respiratory distress syndrome. *Arch Intern Med* 1985;145:1718–1720.
5. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Med* 1988;15:8–14.
6. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, *et al*.; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–1116.
7. Güldner A, Pelosi P, Gama de Abreu M. Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome. *Curr Opin Crit Care* 2014;20:69–76.
8. Yoshida T, Fujino Y, Amato MB, Kavanagh BP. Fifty years of research in ARDS: spontaneous breathing during mechanical ventilation. Risks, mechanisms, and management. *Am J Respir Crit Care Med* 2017;195: 985–992.
9. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017;195:438–442.
10. Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, *et al*. Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in *de novo* respiratory failure: a pilot study. *Am J Respir Crit Care Med* 2020; 202:558–567.
11. Pengelly LD, Alderson AM, Milic-Emili J. Mechanics of the diaphragm. *J Appl Physiol* 1971;30:797–805.
12. Laghi F, Harrison MJ, Tobin MJ. Comparison of magnetic and electrical phrenic nerve stimulation in assessment of diaphragmatic contractility. *J Appl Physiol (1985)* 1996;80:1731–1742.
13. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2016;315: 2435–2441.
14. Engelberts D, Malhotra A, Butler JP, Topulos GP, Loring SH, Kavanagh BP. Relative effects of negative versus positive pressure ventilation depend on applied conditions. *Intensive Care Med* 2012; 38:879–885.
15. Kallet RH, Alonso JA, Luce JM, Matthay MA. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. *Chest* 1999; 116:1826–1832.

Insights into Critical Care and Post-ICU Opiate Administration

Opiate prescriptions skyrocketed over the last three decades and were followed by overdoses and deaths, which exceeded the mortality rate of motor vehicle accidents in the United States (1). In this context, Wunsch and colleagues in this issue of the *Journal* (pp. 568–575) examined whether adult ICU patients, whose ICU opiate prescriptions are estimated at 80%, continue receiving opiates after hospital discharge (2). The databases supporting their analysis describe a population in Ontario, Canada. This province accounts for 44% of Canadian opiate consumption in a country that ranks second worldwide in narcotic *per capita* prescription rates. In Ontario, 25% of opiate prescriptions fuel illicit use (3).

The investigators identified opiate prescriptions between 2013 and 2015 at 7 days, and 1 year after hospital discharge in opiate-naive adult ICU survivors who had been invasively mechanically ventilated and matched non-ICU patients. Prior substance use disorders and/or mental illnesses were identified through diagnostic codes. Logistical regression and odds ratio analyses also incorporated comorbidity, demographics, and receipt of at least one benzodiazepine prescription in the year preceding ICU admission.

Opioids were prescribed to 20% of ICU survivors at 7 days and to 2.4% of survivors 1 year after hospital discharge more often in surgical patients than medical patients (33% vs. 7.6% at 7 d and 4.1% vs. 1.6% at 1 yr). Interestingly, 21 patients received methadone or buprenorphine in the year after ICU admission. ICU survivors' opioid prescriptions rates were lower at 7 days (20% vs. 34%) and slightly higher at 1 year (2.6%) than those of non-ICU patients (1.5%).

The authors conclude an "analgesia-first" approach to ICU sedation does not result in high rates of subsequent long-term opioid use. Their findings echo preliminary results from a U.S. medical unit reporting 7% ICU survivors with opiate prescriptions at hospital discharge (4) and contrast with ICU survivors with traumatic brain injuries, in whom opiate prescriptions were 41% at 1 month and 21% at 12 months after ICU (5).

Thus, prescribing opiates to most ICU patients does not seem to lead to a high likelihood of long-term use. Beyond this, three aspects of the opiate administration described in the critically ill patients in this study warrant reflection.

The authors recognize the limitation of not having pain measurements, opioid doses, or the ability to determine opiate administration appropriateness during ICU care and hospitalization in these 25,085 opiate-naive ICU survivors, focusing instead on the postdischarge period. An analgesia-first approach in the ICU infers the documentation of pain and its resolution. In British Columbia, most ICUs enter pain, as well as sedation and delirium assessment data, into the British Columbia Patient Safety and Quality Council's critical care database (3). Such "granular" pain assessments, if compared with ICU opiate administration, may better identify not only appropriate opiate use but also drivers for subsequent long-term opiate exposure.

Effective pain management is a major preoccupation for ICU patients and their families (6). Recognizing pain, differentiating it from other symptoms, and administering effective analgesia remain significant challenges in critically ill patients (6). Pain assessments and opiate prescribing vary enormously and are greatly influenced by belief, bias, staffing ratios, and local culture (7). ICU physicians perform pain assessments in under 40%

Originally Published in Press as DOI: 10.1164/rccm.202005-1815ED on May 28, 2020