benefits of this approach to mechanical ventilation extend beyond just those with acute lung injury (15). Lastly, elucidating the mechanisms of brain injury in survivors of cardiac arrest that can be modified by tidal volume (or other aspects of intensive care) may be a critical step in identifying the most effective approaches to improving cognitive outcomes after critical illness. A randomized trial of low tidal volume ventilation in cardiac-arrest survivors, for example, would ideally be designed with specific mechanisms of benefit in mind. Thus, prospective studies are now needed to examine potential mechanisms, including inflammation, changes in Pa_{CO_2}, and intrathoracic pressure shifts, before large, definitive trials are undertaken. Until such data are available, these important preliminary data suggest that low tidal volume ventilation should be considered whenever possible, including during the care of many patients recovering from cardiac arrest. ■

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

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References

1. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, *et al*. Part 8: Post-cardiac arrest care 2015: American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S465–S482.
2. Beitler JR, Ghafouri TB, Jinadasa SP, Mueller A, Hsu L, Anderson RJ, Joshua J, Tyagi S, Malhotra A, Sell RE, *et al*. Favorable neurocognitive outcome with low tidal volume ventilation after cardiac arrest. *Am J Respir Crit Care Med* 2017;195:1198–1206.
3. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, *et al*.; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
4. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, *et al*. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002;106:562–568.
5. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke* 2001;32:128–132.
6. Elmer J, Scutella M, Pullalarevu R, Wang B, Vaghasia N, Trzeciak S, Rosario-Rivera BL, Guyette FX, Rittenberger JC, Dezfulian C; Pittsburgh Post-Cardiac Arrest Service (PCAS). The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. *Intensive Care Med* 2015;41:49–57.
7. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, Shapiro NI, Trzeciak S; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. *Circulation* 2011;123:2717–2722.
8. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP; NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 2005;33:1–6, discussion 230–232.
9. González-López A, López-Alonso I, Aguirre A, Amado-Rodríguez L, Batalla-Solís E, Astudillo A, Tomás-Zapico C, Fueyo A, dos Santos CC, Talbot K, *et al*. Mechanical ventilation triggers hippocampal apoptosis by vagal and dopaminergic pathways. *Am J Respir Crit Care Med* 2013; 188:693–702.
10. Roberts BW, Karagiannis P, Coletta M, Kilgannon JH, Chansky ME, Trzeciak S. Effects of Pa_{CO_2} derangements on clinical outcomes after cerebral injury: a systematic review. *Resuscitation* 2015;91:32–41.
11. Schneider AG, Eastwood GM, Bellomo R, Bailey M, Lipcsey M, Pilcher D, Young P, Stow P, Santamaria J, Stachowski E, *et al*. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation* 2013;84:927–934.
12. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, Pettilä V, Varpula T, Skrifvars MB; FINNRESUSCI Study Group. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. *Crit Care Med* 2014;42:1463–1470.
13. Lee BK, Jeung KW, Lee HY, Lee SJ, Jung YH, Lee WK, Heo T, Min YI. Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. *Am J Emerg Med* 2014;32:55–60.
14. Eastwood GM, Schneider AG, Suzuki S, Peck L, Young H, Tanaka A, Mårtensson J, Warrillow S, McGuinness S, Parke R, *et al*. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016;104:83–90.
15. Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant J-Y, *et al*.; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428–437.

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Not Just Oxygen? Mechanisms of Benefit from High-Flow Nasal Cannula in Hypoxemic Respiratory Failure

Supplemental inhaled oxygen has been used as a therapeutic agent since the late eighteenth century and was used to treat acute hypoxemia as early as 1887 (1). In the modern era, it is administered to increase the alveolar partial pressure of oxygen (P_{O_2}) in the face of impaired matching of pulmonary ventilation and perfusion. In non-intubated patients with acute hypoxemic respiratory failure (AHRF), the effect of supplemental oxygen may be limited if the patient's inspiratory flow rate exceeds the flow of delivered oxygen, resulting in entrainment of ambient air.

Enter delivery of oxygen via a high-flow nasal cannula (HFNC). This newer mode of delivering supplemental oxygen at high flows (40–60 L/min) permits high $F_{I_{O_2}}$; the gas is heated and humidified

to avoid mucosal injury and patient discomfort, overcoming the key problems of past use of high flow rates. Since its recent entry into clinical practice, HFNC has proven remarkably successful. In a landmark trial of patients with AHRF, HFNC (compared with either standard oxygen therapy or noninvasive ventilation [NIV]) was associated with reduced mortality risk, higher ventilator-free days, and reduced risk of intubation in the subset of patients with moderate or severe hypoxemia (Pa_{O_2}:FI_{O_2} <200 mm Hg) (2). Subsequent large clinical trials have found that HFNC can prevent post-extubation respiratory failure (3) and may be superior to NIV in managing acute respiratory failure in immunocompromised patients (4). Because of its remarkable apparent clinical benefit, considerable attention has been devoted to understanding the mechanisms of action of HFNC.

There are a number of mechanisms by which HFNC could improve clinical outcomes (Figure 1): (*1*) washout of anatomic dead space and improved gas mixing in large airways (5); (*2*) heating and humidification of inhaled gas (6); (*3*) high nasal inspiratory flow; (*4*) generation of positive airway pressure (2–4 cm H_2O) that results in increased end-expiratory lung volume (7); and (*5*) increased alveolar P_{O_2} (as discussed previously). Consistent with these findings, HFNC improves oxygenation and reduces respiratory rate and inspiratory effort in patients with AHRF (2, 8, 9). Positive pressure may also reduce expiratory diaphragm loading (10), possibly preventing injurious eccentric diaphragm contractions (11). Based on these mechanisms, it is reasonable to hypothesize that HFNC improves patient outcomes by increasing oxygenation and acting on mechanisms believed to cause acute lung injury and/or diaphragm injury (Figure 1).

This hypothesis is supported by important new observations of the physiological effects of HFNC described by Mauri and colleagues (pp. 1207–1215) in this issue of the *Journal* (12). In a rigorously designed crossover trial comparing HFNC (40 L/min) to "standard" oxygen therapy (12 L/min) in patients with acute hypoxemia, they found that HFNC was associated with reduced inspiratory effort, lower respiratory rates and prolonged expiratory times, reduced minute ventilation with stable arterial Pa_{CO_2}, and improved oxygenation. They also reported that HFNC improved dynamic compliance, raised end-expiratory lung volume in both dependent and nondependent lung regions, and increased transpulmonary pressures while reducing transpulmonary driving pressure. These latter findings suggested that HFNC might reduce stress and strain within injured lungs.

This study did not precisely define how HFNC exerts these effects, and certain limitations to interpretation should be noted. As the authors pointed out, the reduction in respiratory rate and

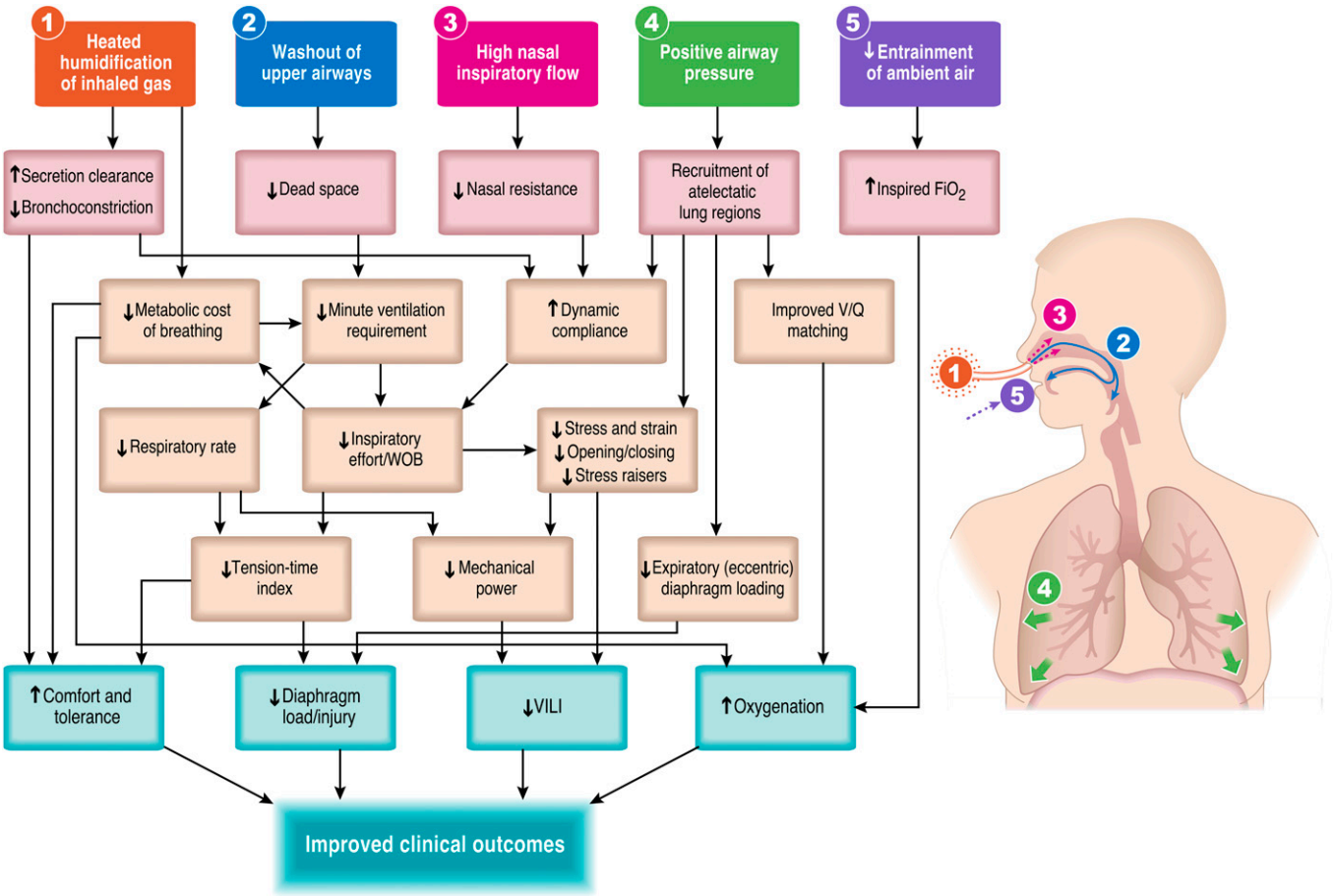

Figure 1. Mechanisms of action of high flow nasal cannula (HFNC) in acute hypoxemic respiratory failure. HFNC exerts a range of important and interdependent physiological effects on a variety of factors that may determine clinical outcomes for patients with acute respiratory failure. VILI = ventilator-induced lung injury; V/Q = ventilation/perfusion; WOB = work of breathing. Illustration by Jacqueline Schaffer.

minute ventilation might be attributable to more efficient CO_2 clearance or reduced respiratory muscle metabolism, or both. The improvement in dynamic compliance might arise from improved lung mechanics (possibly consequent to lung recruitment) or from the inspiratory pressure support derived from high inspiratory flow, or both. We cannot definitively conclude that the increased end-expiratory lung volume and higher transpulmonary pressures signified recruitment of collapsed alveolar units rather than mere inflation of previously open alveolar units.

The observed improvement in gas exchange was consistent with alveolar recruitment, but the higher Pa_{O_2} might have been due to less entrainment of room air. Because of the potential mechanistic importance of alveolar recruitment in AHRF, it would have been helpful to work out how much the increased $F_{I_{O_2}}$ contributed to improved oxygenation. For example, this might have been accomplished by titrating the $F_{I_{O_2}}$ to ensure that pharyngeal P_{O_2} was similar in both groups before measuring Pa_{O_2}. These limitations do not detract from the significance of the findings. It is possible that all of the mechanisms listed in Figure 1 are important to varying degrees among patients.

Are the physiological effects of HFNC documented by Mauri and colleagues responsible for its putative impact on clinical outcomes? It is impossible to know for sure; mechanistic studies, however beautifully conducted, generally delineate the mechanisms that the investigator sets out to study, not the whole range of potential mechanisms of benefit. Nevertheless, these findings are in accord with the growing appreciation for the importance of ventilation-induced lung injury and load-induced diaphragm injury in spontaneously breathing patients with AHRF. The stress and strain applied to the lung by the strenuous exertions of the respiratory muscles—recently delineated as patient self-inflicted lung injury (13)—and the potentially injurious respiratory load applied to the fragile septic diaphragm (14, 15) may result in injury to the patient before intubation. A number of physiological effects of HFNC would intervene on both of these mechanisms to prevent injury and accelerate recovery (Figure 1).

Why are studies that examine physiological mechanisms underlying treatment effects important? First, by advancing our understanding of how a treatment works, they help us better understand the disease process itself. If HFNC improves outcomes, then at least one of the mechanisms affected by HFNC has an important impact on outcome (possibly all). Second, mechanistic studies may suggest approaches to improve the therapy. For example, if decreased entrainment of room air is the key mechanism, then other approaches, such as helmet NIV or other innovative methods, may prove useful. Third, as described by Mauri and colleagues, the effect of HFNC varies considerably among patients. A better understanding of the underlying mechanisms may help identify patient subgroups most likely to benefit from HFNC. In these patients, HFNC should perhaps be initiated early in the clinical course. Similarly, such insights may help identify patients most likely not to respond to HFNC. This is important because outcomes in patients in whom HFNC fails are poor (possibly due to delayed intubation) (16). Perhaps the monitoring tools used by Mauri and colleagues (esophageal pressure, electrical impedance tomography) may prove useful to help with such clinical decisions.

The authors of this study have shown how much may be learned from the careful, rigorous application of physiological tools at the bedside. In this age of molecular medicine, big data, and genomics, there is still a major role for physiology in the care of our most critically ill patients. ■

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

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References

1. Heffner JE. The story of oxygen. *Respir Care* 2013;58:18–31.
2. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, *et al*.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372: 2185–2196.
3. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuena R, Fernández R. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA* 2016;315:1354–1361.
4. Frat J-P, Ragot S, Girault C, Perbet S, Prat G, Boulain T, Demoule A, Ricard J-D, Coudroy R, Robert R, *et al*.; REVA Network. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Respir Med* 2016;4:646–652.
5. Möller W, Feng S, Domanski U, Franke K-J, Celik G, Bartenstein P, Becker S, Meyer G, Schmid O, Eickelberg O, *et al*. Nasal high flow reduces dead space. *J Appl Physiol (1985)* 2017;122: 191–197.
6. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015;148:253–261.
7. Parke RL, Bloch A, McGuinness SP. Effect of very-high-flow nasal therapy on airway pressure and end-expiratory lung impedance in healthy volunteers. *Respir Care* 2015;60:1397–1403.
8. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. *Respir Care* 2015;60:1369–1376.
9. Rubin S, Ghuman A, Deakers T, Khemani R, Ross P, Newth CJ. Effort of breathing in children receiving high-flow nasal cannula. *Pediatr Crit Care Med* 2014;15:1–6.
10. Pellegrini M, Hedenstierna G, Roneus A, Segelsjö M, Larsson A, Perchiazzi G. The diaphragm acts as a brake during expiration to prevent lung collapse. *Am J Respir Crit Care Med* [online ahead of print]. 6 Dec 2016; DOI: 10.1164/rccm.201605-0992OC.
11. Gea J, Zhu E, Gáldiz JB, Comtois N, Salazkin I, Fiz JA, Grassino A. Functional consequences of eccentric contractions of the diaphragm [in Spanish]. *Arch Bronconeumol* 2009;45:68–74.

12. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, Pesenti A. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017;195:1207–1215.
13. 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.
14. Ebihara S, Hussain SNA, Danialou G, Cho W-K, Gottfried SB, Petrof BJ. Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. *Am J Respir Crit Care Med* 2002;165:221–228.
15. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, Rittayamai N, Lanys A, Tomlinson G, Singh JM, *et al*. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. *Am J Respir Crit Care Med* 2015;192:1080–1088.
16. Kang BJ, Koh Y, Lim C-M, Huh JW, Baek S, Han M, Seo H-S, Suh HJ, Seo GJ, Kim EY, *et al*. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med* 2015;41: 623–632.

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Elementary, My Dear Watson! The Accumulating Evidence for the Lung Clearance Index in Monitoring Early Cystic Fibrosis Lung Disease

With the advent of universal newborn screening for cystic fibrosis (CF) and the development of CF transmembrane conductance regulator (CFTR) modulator therapies, the focus of disease management in young children with CF has turned toward primary prevention—arresting disease before significant symptoms or deterioration have occurred (1). With this shift has arisen a need for more sensitive and feasible measures of pulmonary function in the infant and preschool age group. Interest in the lung clearance index (LCI), measured by multiple-breath washout (MBW) testing, has surged in recent years. LCI is more sensitive than FEV_1 in identifying children with CF, better correlates with bronchiectasis on chest computed tomography scan and inflammation on bronchoalveolar lavage (2, 3), and preschool LCI correlates with both LCI and FEV_1 at school age (4, 5). The majority of studies performed using LCI to date have been in older children and involved cross-sectional measures. In this issue of the *Journal*, Stanojevic and colleagues (pp. 1216–1225) have taken a simple, elegant approach to investigating the utility of LCI as a longitudinal measure of disease progression in preschool children (6). Their results strongly support the use of LCI as a clinical trial endpoint in preschool children with CF and further the case for its use in clinical care as well.

Stanojevic and colleagues enrolled 78 preschool children with CF and, critically, 72 healthy control subjects in a multicenter study, performing MBW and spirometry at enrollment and 1, 3, 6, 9, and 12 months, to mimic both common time points in clinical research and routine visit schedules in CF clinical practice (6). Confirming prior cross-sectional studies, both LCI and FEV_1 were significantly different in children with CF compared with healthy control subjects at enrollment, though LCI was far more likely to be in the abnormal range. The critical new finding from this longitudinal study was that LCI significantly worsened over time in the CF group but did not change in the healthy control subjects, whereas FEV_1 did not decline significantly in either group. These results indicate that LCI can track disease progression in young patients with mild disease, and FEV_1 cannot. The slope of LCI with age remained significant even when measures in the CF group were restricted to those children asymptomatic at the time of testing. Furthermore, older age at enrollment, history of growth of *Staphylococcus aureus*, chronic use of inhaled antibiotics (a proxy for infection with *Pseudomonas aeruginosa*), and history of multiple hospitalizations for pulmonary exacerbation were associated with elevated (worse) LCI at enrollment. LCI and FEV_1 z score were weakly correlated at each study visit, although FEV_1 z score remained within normal limits for the majority of children with CF throughout the study.

The second major finding from the study was that LCI was elevated in patients who were experiencing a pulmonary exacerbation, reflecting acute worsening of lung disease. Among patients with CF but not healthy control subjects, both cough and pulmonary exacerbations (defined as cough plus treatment with oral antibiotics) were associated with a worse LCI; nasal symptoms alone were not. In contrast, both upper and lower airway symptoms were associated with a lower FEV_1 in both patients with CF and healthy control subjects, suggesting that FEV_1 is less discriminatory than LCI in detecting acute worsening in lung disease. Further study is needed to investigate the role LCI might play in the management of respiratory infections in preschool children with CF, particularly in determining need for antibiotics for pulmonary exacerbation. Interestingly, among children with CF, occurrence of pulmonary exacerbation and higher baseline LCI were significant predictors of an elevated LCI, but an elevated LCI did not predict future pulmonary exacerbations.

This study adds to the growing body of literature supporting the use of LCI as an outcome measure in research studies, particularly in young children and those with mild disease. As CFTR modulators begin to be studied in preschool children, such outcome measures are of paramount importance. This study provides an estimate of the slope of LCI over time, its between- and within-subject variability, and the effect of pulmonary exacerbations on the measure, providing invaluable data for the planning of future clinical trials. Feasibility of both MBW and spirometry was high and improved with subsequent testing visits; this measure can be considered in studies of children as young as 2.5 years of age.

Although this study continues to advance the cause for adoption of MBW in CF, issues still remain, particularly regarding use of MBW testing in clinical care. Perhaps the most important limitation to the widespread adoption of MBW testing is the lack of normative data for LCI, particularly in the pediatric population and with nitrogen washout. Reference data must be gas- and device-specific, if not institution-specific, as the impact of dead space (and how to account for this in calculations of LCI and FRC) and syncing of flow and gas signals have yet to be fully answered (7–11). The authors of this study modified commercially available supplies to minimize dead space, limiting generalizability. The Exhalyzer D