exposures in our cities, the findings from Wright and colleagues highlight how important it is to understand disproportionate impacts on lifelong health outcomes from exposures even before the first breath. We need policies aimed at the most important exposures impacting lifelong health, including UFPs, and to promote transportation and environmental justice so that everyone has the same opportunity for a long and healthy life, regardless of where they are born. ■

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

Paloma I. Beamer, Ph.D.
Nathan Lothrop, Ph.D.
Asthma and Airway Disease Research Center and Mel and Enid Zuckerman College of Public Health
University of Arizona
Tucson, Arizona

References

1. Madaniyazi L, Xerxes S. Outdoor air pollution and the onset and exacerbation of asthma. *Chronic Dis Transl Med* 2021;7:100–106.
2. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: a systematic review. *Environ Res* 2017;159:519–530.
3. Lee A, Leon Hsu HH, Mathilda Chiu YH, Bose S, Rosa MJ, Kloog I, *et al.* Prenatal fine particulate exposure and early childhood asthma: effect of maternal stress and fetal sex. *J Allergy Clin Immunol* 2018;141:1880–1886.
4. Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. *Int J Public Health* 2019;64:547–559.
5. Bové H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, *et al.* Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun* 2019;10:3866.
6. Giechaskiel B, Lahde T, Suarez-Bertoa R, Clairotte M, Grigoratos T, Zardini A, *et al.* Particle number measurements in the European legislation and future JRC activities. *Combustion Engines* 2018;174:3–16.
7. Viitanen AK, Uuksulainen S, Koivisto AJ, Hämeri K, Kauppinen T. Workplace measurements of ultrafine particles: a literature review. *Ann Work Expo Health* 2017;61:749–758.
8. Rychlik KA, Secrest JR, Lau C, Pulczinski J, Zamora ML, Leal J, *et al. In utero* ultrafine particulate matter exposure causes offspring pulmonary immunosuppression. *Proc Natl Acad Sci USA* 2019;116: 3443–3448.
9. Wing SE, Larson TV, Hudda N, Boonyarattaphan S, Fruin S, Ritz B. Preterm birth among infants exposed to *in utero* ultrafine particles from aircraft emissions. *Environ Health Perspect* 2020;128:47002.
10. Wright RJ, Hsu H-HL, Chiu Y-HM, Coull BA, Simon MC, Hudda N, *et al.* Prenatal ambient ultrafine particle exposure and childhood asthma in the northeastern United States. *Am J Respir Crit Care Med* 2021; 204:788–796.
11. Lavigne E, Donelle J, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, *et al.* Spatiotemporal variations in ambient ultrafine particles and the incidence of childhood asthma. *Am J Respir Crit Care Med* 2019;199:1487–1495.
12. de Jesus AL, Rahman MM, Mazaheri M, Thompson H, Knibbs LD, Jeong C, *et al.* Ultrafine particles and $PM_{2.5}$ in the air of cities around the world: are they representative of each other? *Environ Int* 2019;129: 118–135.
13. Piock W, Hoffmann G, Berndorfer A, Salemi P, Fusshoeller B. Strategies towards meeting future particulate matter emission requirements in homogeneous gasoline direct injection engines. *SAE Int J Engines* 2011;4:1455–1468.
14. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ; The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.
15. Strickland MJ, Klein M, Flanders WD, Chang HH, Mulholland JA, Tolbert PE, *et al.* Modification of the effect of ambient air pollution on pediatric asthma emergency visits: susceptible subpopulations. *Epidemiology* 2014;25:843–850.
16. Mikheev VB, Brinkman MC, Granville CA, Gordon SM, Clark PI. Real-time measurement of electronic cigarette aerosol size distribution and metals content analysis. *Nicotine Tob Res* 2016; 18:1895–1902.

Shear Wave Elastography of the Diaphragm: Good Vibrations?

Diaphragm ultrasound is rapidly gaining popularity in the ICU, as it allows a bedside, safe, repeatable, and noninvasive assessment of respiratory muscle function. Current main applications include the measurement of thickness and inspiratory thickening fraction (TFdi) (1). Both decreases and increases in diaphragm thickness were reported early in the course of mechanical ventilation, which seemed modulated by contractile activity (i.e., TFdi) (2) and with atrophy strongly associated with prolonged ventilation and ICU duration (3); however, how such findings relate to functional alterations in the muscle are yet uncertain. The application of shear wave elastography is an emerging novel technique to provide biomechanical information of large tissue structures by quantifying the shear wave speed and converting that to the Shear Modulus (SM). Briefly, this technique relies on the creation of a vibration source by the acoustic radiation force from a focused ultrasound beam, resulting in the generation of a shear wave. Tracking the propagating shear waves orthogonal to this ultrasound beam allows for the quantification of shear wave speed (v) and the directly related SM (i.e., $SM = \rho \times v^2$, with ρ the density of the tissue). SM reflects elastic tissue properties, and a higher diaphragmatic SM indicates a stiffer muscle. In the context of other ultrasound applications or indices, such as strain imaging, TFdi, and tissue Doppler imaging, shear wave elastography might be the most promising modality for qualitative assessment of diaphragm muscle properties. The assessment of changes in SM during the breathing cycle may reflect diaphragm contractile activity

Originally Published in Press as DOI: 10.1164/rccm.202107-1605ED on August 9, 2021

in healthy volunteers (4, 5); however, only moderate associations were recently found in a small subgroup of spontaneously breathing mechanically ventilated patients (6). In contrast, changes in end-expiratory SM throughout the course of ICU stay may provide important insights into the development of detrimental alterations in muscle quality during mechanical ventilation and critical illness (i.e., development of fibrosis or injury), allowing for a better understanding of the diaphragm myotrauma concept.

In this issue of the *Journal*, Aarab and colleagues (pp. 797–806) presented in a large cohort of ICU patients ($n = 102$) a heterogeneous pattern of changes in end-expiratory diaphragm SM during the first week of ICU stay: SM did not change in 8%, increased in 51%, and decreased in 41% of patients (7). Their coprimary aim was to relate this SM evolution to changes in diaphragm thickness. Increases in diaphragm thickness in one-third of the patients were associated with a decrease in diaphragmatic SM, which may imply the development of diaphragm injury. Next, they performed an elegant experimental study in piglets that were under controlled ventilation for 3 days. SM changes between Days 0 and 3 were assessed and evaluated in relation to diaphragm thickness, force production, and histology. Although diaphragm thickness did not change during this 3-day study period, a decrease in SM was associated with a loss in diaphragm force production, fiber atrophy, and a higher lipid accumulation in the muscle (7).

These data have important implications, as the authors make a strong case for the presence of structural changes in the diaphragm tissue of ICU patients that can be assessed noninvasively. At the same time, the results suggest that these changes are very heterogeneous among patients and yet complex to interpret from a pathophysiological and mechanistical perspective. What does an SM value mean with respect to overall diaphragm tissue quality? And which change in SM will translate in a clinically relevant muscle impairment? Although a 10% cutoff for SM changes to categorize patients was based on the reliability of the findings of their previous work (8), a change larger than this threshold does not directly imply functional alterations. Furthermore, for thin structures like the diaphragm, shear wave speed is not only dependent on the mechanical properties but also highly correlated with thickness. Consequently, measured SM values will increase when diaphragm thickness increases even if the mechanical properties remain unchanged. The presented results in critically ill patients and piglets may sound discrepant at first: a decreased SM was associated with increases in diaphragm thickness in ICU patients, whereas decreases in SM were related to atrophy in pigs without changes in thickness (7). However, both findings indicate that the tissue becomes softer, irrespective of a thickness change. Interpretation of SM findings is further challenged by the various associations between changes in diaphragm thickness and SM that were reported (Figure E7 of Reference 7), and potential (patho)physiological mechanisms are presented to guide the reader through these results (Table E9 of Reference 7). We should, however, realize that thickness and SM are two distinct measures: SM is related to both thickness and the mechanical properties, and, therefore, it should not be the aim to use changes in thickness for prediction of SM.

The heterogeneity in associations between thickness changes and SM is also not surprising from a clinical perspective. Indeed, patients can have important diaphragm dysfunction without reduced diaphragm thickness (2), indicating that other factors are at play. The concept of diaphragm fiber atrophy characterized by decreased fiber cross-sectional area is well evidenced (9–11) and was again confirmed by Aarab and colleagues (7). Decreased fiber cross-sectional area with diaphragm inactivity is a physiological response, but whether muscle disuse also results in injury and changes in SM is yet uncertain. Aarab and colleagues (7) provide new insights to this: the decreased SM found in some piglets despite no change in muscle thickness suggests that injury may be present with diaphragm inactivity; however, we should yet be very careful translating these findings to the ICU patient. Notably, recent pilot data demonstrated the presence of fibrosis in the diaphragm of deceased critically ill patients with coronavirus disease (COVID-19) (12). How this relates to other pathological changes on histology and whether fibrosis also develops during non–COVID-19 critical illness should be further studied. In this light, the application of shear wave elastography might be a novel future technique to identify the development of fibrosis noninvasively.

Are we now ready to implement diaphragm shear wave elastography in clinical practice? Probably, but its complexity should not be underestimated, mostly because it is challenging to measure shear wave speed reliably in a thin muscle such as the diaphragm, but also because factors such as probe location, lung volume, timing of SM measurements within the breathing cycle (sample rate is only 2 Hz), and the presence of the tendinous layer within the diaphragm could affect the obtained results. This may (partly) explain the large variability in SM sometimes observed in patients (Figure E3 of Reference 7).

In conclusion, Aarab and colleagues (7) present important and novel translational work on the noninvasive assessment of diaphragm muscle quality using shear wave elastography. Still, much needs to be unraveled on a clinical and preclinical level to understand SM values in the context of deteriorating diaphragm muscle function, and optimal image protocols need to be studied. Their work has again stressed that (assessing) the impact of mechanical ventilation and critical illness on the diaphragm is highly complex. The authors have identified several tantalizing avenues for further investigation that may lead to a better understanding of alterations in diaphragm ultrastructure in the critically ill. Ultimately, this could help identify clinical approaches for diaphragm-protective mechanical ventilation. ■

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

Annemijn H. Jonkman, M.Sc.
Department of Intensive Care Medicine
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Chris L. de Korte, Ph.D.
Department of Radiology and Nuclear Medicine
Radboud University Medical Center
Nijmegen, the Netherlands

References

1. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, *et al.* Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients: a narrative review. *Intensive Care Med* 2020;46:594–605.

2. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, *et al.* Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. *Am J Respir Crit Care Med* 2015;192: 1080–1088.
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. Bachasson D, Dres M, Niérat M-C, Gennisson JL, Hogrel JY, Doorduin J, *et al.* Diaphragm shear modulus reflects transdiaphragmatic pressure during isovolumetric inspiratory efforts and ventilation against inspiratory loading. *J Appl Physiol (1985)* 2019;126:699–707.
5. Chino K, Ohya T, Katayama K, Suzuki Y. Diaphragmatic shear modulus at various submaximal inspiratory mouth pressure levels. *Respir Physiol Neurobiol* 2018;252-253:52–57.
6. Fossé Q, Poulard T, Niérat M-C, Virolle S, Morawiec E, Hogrel JY, *et al.* Ultrasound shear wave elastography for assessing diaphragm function in mechanically ventilated patients: a breath-by-breath analysis. *Crit Care* 2020;24:669.
7. Aarab Y, Flatres A, Garnier F, Capdevila M, Raynaud F, Lacampagne A, *et al.* Shear wave elastography, a new tool for diaphragmatic qualitative assessment: a translational study. *Am J Respir Crit Care Med* 2021; 204:797–806.
8. Flatres A, Aarab Y, Nougaret S, Garnier F, Larcher R, Amalric M, *et al.* Real-time shear wave ultrasound elastography: a new tool for the evaluation of diaphragm and limb muscle stiffness in critically ill patients. *Crit Care* 2020;24:34.
9. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, *et al.* Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327–1335.
10. van den Berg M, Hooijman PE, Beishuizen A, de Waard MC, Paul MA, Hartemink KJ, *et al.* Diaphragm atrophy and weakness in the absence of mitochondrial dysfunction in the critically ill. *Am J Respir Crit Care Med* 2017;196:1544–1558.
11. Hooijman PE, Beishuizen A, Witt CC, de Waard MC, Girbes AR, Spoelstra-de Man AM, *et al.* Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. *Am J Respir Crit Care Med* 2015;191:1126–1138.
12. Shi Z, de Vries HJ, Vlaar APJ, van der Hoeven J, Boon RA, Heunks LMA, *et al.*; Dutch COVID-19 Diaphragm Investigators. Diaphragm pathology in critically ill patients with COVID-19 and postmortem findings from 3 medical centers. *JAMA Intern Med* 2021;181: 122–124.

Lung Fissural Integrity: It's Written in the Genes

The field of interventional pulmonology is currently a-buzz with innovations in endobronchial procedures that challenge the traditional place of surgery in managing severe emphysema with hyperinflation. Leading one of the charges in this field is the practice of deploying endobronchial valves (EBV), which, backed now by close to 20 years of research, compares favorably with standard medical care in improving lung function and exercise capacity (1–3), quality of life (4), and survival (5) in selected cohorts.

The criteria for EBV deployment have been derived from the National Emphysema Treatment Trial of lung volume reduction surgery (6): inclusion and exclusion criteria were governed by extent and regional distributions of emphysema, but distinctions between heterogeneous versus homogeneous or upper versus lower zone disease are not now considered barriers to such treatment (7, 8). Indeed, both the Food and Drug Administration in the United States and the National Institute for Health and Care Excellence in the United Kingdom have approved EBV therapy in eligible patients. However, there is an important caveat in patient selection, namely, the "leaky fissure"; an intact barrier between "treated" and "untreated" lobes, preventing exchange of gases, is a mandatory predictor of success (9). Accordingly, a key feature of assessment prior to EBV treatment is determining fissural integrity on high-resolution computed tomography (HRCT), a surrogate for absent interlobar collateral ventilation.

Fissural integrity varies between lobes, and the minor fissure is the most frequently incomplete: the average completeness of the two major fissures is an estimated 82%, whereas the minor fissure averages 62% (10). Visual inspection of fissural integrity lacks precision and is increasingly being supplanted by automated methods (11). A fissural integrity "score" >95% is generally regarded the threshold for achieving at least 350 ml target lobe volume reduction, with completeness <80% usually warranting referral for alternative procedures including lung volume reduction surgery or investigational treatments such as vapor or coils (12). Those with intermediate scores (i.e., 80–95% complete) generally undergo a Chartis test of collateral ventilation in which the diffusion of gases into a target lobe, with its airway occluded, is detected (12). The consequences, for example, for participants in two randomized controlled trials of EBV treatment were exclusions on account of collateral ventilation of 16.5% (1) and 9.2% (2). There is no mainstream remedy at present.

Differences in fissural integrity have been appreciated since 1947 (13), and a number of cadaveric studies in diverse populations, despite the potential confounding effects of methodological heterogeneity, have suggested a possible link to ethnicity (14). However, the determinants and natural course of fissural integrity are unclear. For example, it is presently unknown whether fissural completeness decreases as emphysema severity increases. The study by van der Molen and colleagues (pp. 807–816) in this issue of the *Journal* is a welcome contribution to the field (15). The authors collected data of just under 10,000 participants from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study (16); the study population comprised African American and non-Hispanic White individuals aged 45–80 years at enrollment, with

Originally Published in Press as DOI: 10.1164/rccm.202106-1526ED on August 5, 2021