Ventilator Circuit Trash May Be a Research Treasure

Acute respiratory distress syndrome (ARDS) is estimated to underlie 10% of ICU admissions worldwide and continues to kill between 35% and 46% of those it afflicts despite fundamental improvements in critical care medicine during the last 50 years (1, 2). With the exception of low tidal volume ventilation in the management of ARDS (3), no therapy has reproducibly been shown to specifically treat ARDS, in part because of the heterogeneity of the disorder and limited understanding of its pathogenesis. A major barrier in the field is the lack of a research tool that enables noninvasive collection of distal airspace samples to help better characterize ARDS.

In this issue of the *Journal*, McNeil and colleagues (pp. 1027–1035) present a simple method for noninvasive sampling of the distal airspace of mechanically ventilated patients by analyzing proteins captured in ventilator circuit heat moisture exchange (HME) filters, which are routinely discarded as trash in critical care units (4). Extending on promising earlier studies describing the utility of extracting bacterial DNA from ventilator filters for microbiological studies (5, 6), McNeil and colleagues demonstrate the feasibility of protein collection from ventilator circuit filters and describe close correlation with simultaneously collected distal airspace fluid (4). To validate their methodology, the authors first demonstrate that the protein composition of fluid centrifuged from HME filters closely matches paired samples of edema fluid (i.e., fluid collected by suctioning the distal airspace without lavage) (7) by high-resolution mass spectrometry. Using this unbiased approach, there was strong correlation of protein spectral intensities for matched HME filter and edema fluid samples from mechanically ventilated patients with ARDS, hydrostatic, or mixed pulmonary edema. In contrast, comparing protein spectral intensities between patients revealed decreased correlation, which suggests that paired HME fluid and edema fluid samples from the same patient are more alike than samples from different patients. The authors further validate their methodology by demonstrating similar total protein levels and individual protein concentrations (by ELISA or electrochemiluminescence assay) of common lung injury biomarkers using paired HME filter and edema fluid samples from a panel of six mechanically ventilated patients, four of whom were included in the aforementioned mass spectrometry analysis. Taken together, these findings suggest that the noninvasive collection of distal airspace proteins with relatively high fidelity is possible simply by diverting a ventilator circuit filter from the rubbish bin to the laboratory bench.

There are many exciting potential research applications of the HME filter approach. The noninvasive airspace sampling enables serial collection with no additional risk to patients, and theoretically expands the feasibility of biomarker and discovery analysis to a larger pool of subjects who can and are willing to participate. At this time, the most abundant patient specimens available for ARDS research are peripheral blood samples, whereas alveolar samples may be absent or only available from a single time point because of the risks inherent in performing bronchoscopy in critically ill patients with severe hypoxemic respiratory failure (8). Although important work has been done by many using plasma biomarkers (9), the ability to directly sample the airspace perhaps as frequently as every 12 hours through HME filter collection may yield novel insights into the natural history of ARDS progression versus resolution, as well as endotypes that may guide investigation into targeted therapies (10). Furthermore, clinical research recruitment can be limited by the reluctance of family members and other decision makers to consent to diagnostic procedures undertaken in pursuit of research; however, collecting would-be trash as a research tool would appear to pose an even lower risk than peripheral blood sampling, yet may provide a more accurate representation of airspace biology (11).

Although the authors present a novel and clever approach to sampling the distal airspaces, its readiness for immediate and broad adoption remains unclear. First and foremost, a limited number of patients with paired analysis of both edema fluid and HME filter fluid are presented: four by proteomic analysis (Figures 2 and 3 from Reference 4) and six by direct protein measurement (Figures 4 and 5 from Reference 4). The authors attribute this small number to limiting patient selection to those in whom they were able to obtain edema fluid. They reported a preference to use undiluted airspace fluid and therefore avoided bronchoalveolar lavage. However, restricting patient selection to those in whom edema fluid can be obtained may limit generalizability of their findings because only a subset of patients with ARDS have frank edema fluid, and the authors note that edema fluid is more readily obtained early in a patient's ventilator course (7, 12). Furthermore, reliance on collecting frank edema fluid appears to have enriched the tested cohort for patients with a hydrostatic mechanism of pulmonary edema: four of the six patients with paired samples were assessed to have either a mixed or hydrostatic etiology of their edema. Future studies that enable comparison of HME fluid to lavage samples may increase confidence that the methodology is more broadly applicable across the heterogenous clinical landscape of ARDS research. In addition, limited data are provided to determine how filter dwell time and/or endogenous proteases potentially affect detection and measurement of protein concentrations. Finally, it remains unproven whether other molecules such as RNA, lipids, and so on can be reliably and accurately collected from ventilator circuit filters but may be promising avenues for future research.

Despite potential limitations, a major strength of the study is that ARDS and hydrostatic HME fluid showed distinct proteomic profiles by liquid chromatography-tandem mass spectrometry, with ARDS samples notable for increased protease/antiprotease and inflammatory markers. Moreover, the authors present compelling findings using HME filters in a larger cohort of 34 patients that are consistent with an expected ARDS protein phenotype; for example, increased total protein and matrix metalloproteinase 9 levels compared with hydrostatic controls. The ability to use HME filters for eliciting clinical phenotypes in ARDS research will require further validation, but it nevertheless raises exciting possibilities and addresses a major barrier in the field. Going forward, future studies should build on the framework described by McNeil and colleagues in a larger number of patients, across multiple centers,

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and with the use of lavage fluid to determine whether ventilator trash may truly be a research "treasure." ■

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DELPHIning Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is a fibroinflammatory interstitial lung disease (ILD) that develops when a susceptible individual inhales aerosolized (typically) organic antigens to which they have been repeatedly exposed and become sensitized. The immunological mechanisms involved in HP—those that are activated after antigen exposure and those that orchestrate disease development—are complex and not fully understood (1). Clinically, HP often breeds challenges and frustration for healthcare providers: patients with HP can present in nearly as many ways as there are causes, and perhaps more than for any other pulmonary condition, diagnosing HP with confidence requires diagnosticians to put down their stethoscopes and don their detective hats. Unfortunately, in all too many cases, when chest imaging and pathological specimens scream HP, for us sleuths, an even remotely plausible offending antigen can remain stubbornly elusive (2).

Although I always ask, I have yet to find a potato riddler, paprika slicer, pituitary snuff taker, or maple bark splitter among my patients with HP. But we all occasionally get lucky, as I did when I recently found a patient with textbook HP who owned three parrots—one . . . in a cage . . . in her bedroom . . . hanging directly over her bed! And another patient whose rural home had no bathroom, only a homemade outdoor latrine (which was really just an outhouse, except that instead of going into a hole underneath the latrine, waste was collected on a large metal sheet). Every week, my patient dried the collected waste in the sun and then spread it over his large garden!

HP is typically regarded as having three forms (acute, subacute, and chronic), which do not necessarily occur sequentially within a given patient (e.g., patients with chronic HP [cHP] may never have had acute or subacute HP). In addition, there is extensive overlap among their clinical phenotypes, particularly the subacute and chronic forms. Although it is not always the case, diagnosing the acute (and often the subacute) form can be straightforward: episodic symptoms, temporally related to an identified exposure, point directly to the diagnosis and the offending antigen. Confidently diagnosing cHP is typically far more challenging. Symptoms develop insidiously and may progress linearly rather than episodically, thus blurring the line between any putative exposure and clinically apparent disease. In cHP, high-resolution computed tomography (HRCT) scans show evidence of fibrosis but may not reveal distinctive features (e.g., extensive, upper-lobe, centrilobular ground glass nodules), thus injecting additional diagnostic uncertainty and forcing clinicians to more seriously consider other pulmonary conditions (commonly, idiopathic pulmonary fibrosis).

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