

## Crackles and Comets: Lung Ultrasound to Detect Pulmonary Congestion in Patients on Dialysis is Coming of Age

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The 2012 edition of *Harrison's Principles of Internal Medicine* states that "ultrasound imaging is not useful for the evaluation of the pulmonary parenchyma" (1). However, as these words were being written, evidence was accumulating that such imaging was indeed valuable in differentiating pulmonary congestion from chronic obstructive pulmonary disease in acutely dyspneic patients by the ability of ultrasound (US) to recognize extravascular lung water (2).

The US image of pulmonary congestion is quite dramatic and the result of an artifact from hyperechoic reverberations between the pleura and edematous pulmonary septa, giving the appearance of the exhaust of a rocket ship at liftoff. This characteristic finding is the equivalent of Kerley B lines seen on a routine chest x-ray. These images were initially termed lung rockets, then lung comets, and now, by an international panel of experts, simply B lines (3). The US study can be performed using a handheld device at the bedside. The finding of B lines is quite easy to recognize. Indeed, one investigator has suggested that, if the difficulty of interpreting these images was scaled on an elementary school to university level, B lines would be something taught to kindergarteners (4). An online search for images of US lung comets will offer many views of the finding.

Not long after the initial reports of this technique, it was applied to patients on dialysis (5). It quickly became apparent that moderate to severe lung congestion is present in most patients, usually asymptomatic, and more prevalent in patients with underlying cardiac disease (5–9). Ultrafiltration-induced volume removal during hemodialysis promptly reduces the severity of pulmonary congestion (*i.e.*, number of B lines) (10,11). However, a substantial minority of patients have persistent pulmonary congestion after the procedure (7,11).

The ease with which lung US is performed and the ongoing difficulty that nephrologists have in determining optimal targets for postdialysis weights have made inevitable a study such as the Lung Water Ultrasound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy (LUST) Trial. This is an ongoing, international, randomized trial with a target

enrollment of 500 patients on hemodialysis who have coronary artery disease in whom lung US is used to guide their ultrafiltration goals.

The underlying premise of the study is, of course, that pulmonary congestion is a proxy for a patient's volume status. Although this assumption is likely to be correct for most patients in the general population, its validity in patients on dialysis is far less certain. As long ago as 1966, cardiac catheterization studies showed that pulmonary edema may occur in patients on chronic dialysis with normal cardiac filling pressures (12). This was caused by an increased lung permeability, a finding that was documented in 1972 (13) and confirmed in subsequent studies; such a nonvolume-related increase in interstitial lung water is typically referred to as uremic lung (14,15). Its pathophysiologic basis is unclear but very likely caused by one or more of a variety of perturbations in patients on dialysis that may alter lung permeability, particularly uremic retention products and the consequences of chronic inflammation. The investigations that have been undertaken in this area have mainly been in the AKI setting. However, it is likely that many of the observations apply as well to ESRD. For example, IL-6, a central regulator of the inflammatory process, mediates increased lung permeability in a mouse model of AKI; IL-6 is commonly elevated in patients on dialysis (16–18).

The clinical data addressing the role of volume overload in US-documented pulmonary congestion in patients on dialysis are limited but indicate that volume status and the finding of US B lines are often discordant. In one report, patients identified as overhydrated by bioelectric impedance analysis did not differ in their lung comet score (B lines) from those with normal hydration status or those who were volume depleted by bioelectric impedance analysis; other reports concur (5,7,9). This discordance is at least in part explained by the high frequency of heart failure in patients on dialysis and its association with pulmonary congestion. Such congestion may occur in patients with heart failure who have little or no volume excess and thus, distort any underlying correlation of volume overload and the appearance of B lines (19). Cardiac ejection fraction was, in one study, the strongest independent predictor of lung water content (9).

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It seems likely that the extent of US-determined pulmonary congestion is a consequence of dual forces—hydrostatic pressure (volume overload, left heart failure) and increased lung permeability (uremia)—and that their relative importance varies among individual patients. The role of lung permeability raises another interesting consideration. If nonvolume-related pulmonary congestion can be diagnosed (perhaps by using lung US in conjunction with other means of volume assessment), then US B lines may prove to be a marker of uremia (inadequate solute removal by dialysis) and/or evidence of inflammatory injury, both with implications for diagnosis and therapy (20).

Large multicenter, randomized trials are often valuable not only for their primary objective but also, because of the many substudies that they generate. The report by the LUST Trial investigators published in this issue of the *Clinical Journal of the American Society of Nephrology* is one such study (21). It analyzes data on over 1000 lung US examinations along with standardized assessments for lung crackles and pedal edema in 79 patients in the study's active arm (*i.e.*, those in whom lung US was used to guide therapy). Overall, 65% of US examinations had evidence of pulmonary congestion, whereas lung crackles were heard in only 21% of the examinations; all patients, it should be recalled, had clinically evident coronary disease. Even with severe lung congestion by US, only 49% of patients had crackles on lung examination. Crackles were present in 5.4% of patients without US evidence of congestion. Thus, lung crackles are quite insensitive to the presence of interstitial lung edema but when present, clinically important. When lung congestion by crackles and US was graded by severity, the correlation of the two measures was quite poor (shared variance, 12%), making it hard to use crackles in any quantitative manner.

A secondary aim of the study was the correlation of pedal edema and US B lines. Edema was present before dialysis in only 10% of evaluations; it was absent in 80% of examinations with coexistent severe pulmonary congestion by US. This absence of edema, despite marked pulmonary congestion, has also been reported in a US study of patients on peritoneal dialysis (9).

Regardless of whether US B lines are good markers for volume status, they may be useful indicators of clinically important outcomes. In a cross-sectional study of 51 patients on peritoneal dialysis, US B lines were independent predictors of physical functioning (by the Kidney Disease Quality of Life Short Form), regardless of whether the pulmonary congestion was symptomatic (22). Another study prospectively observed 96 patients on hemodialysis and found that predialysis US B lines were a significant predictor of survival in contrast to body water (derived from multifrequency bioimpedance spectroscopy data), which was not (23). Its value as a predictor of cardiac events has also been documented (6).

It is hoped that the LUST Trial will shed light on whether reducing lung water in patients on hemodialysis with asymptomatic pulmonary congestion improves outcomes. Any such improvement using lung US-guided ultrafiltration may turn out to be caused by something more than simply improved volume management, because high levels of lung water may have adverse effects, even in patients who are not volume expanded. However, this correlation of lung water with outcomes should be viewed suspiciously

until further data are forthcoming given the association of increased lung water with impaired cardiac function. Inadequate statistical adjustment for heart disease could explain the association. Whether better dialysis (longer or more frequent) might improve nonvolume-related pulmonary congestion, reduce lung water, and eliminate B lines has yet to be explored or even considered.

I conclude that lung crackles in patients on dialysis are a useful finding but commonly absent, even in the presence of severely increased lung water as assessed by US. However, this increase in lung water is not necessarily caused by volume expansion and may, in part, reflect an underlying increase in lung permeability rather than simply being the consequence of altered hydrostatic forces.

I believe that lung US will prove to be of value in improving the care of patients on dialysis. From a practical standpoint, I hope that this technique can provide us with at least one simple benefit. How many times do we see patients on hemodialysis, perhaps a bit over their highest recent predialysis weight, appear in the emergency department on a Sunday night in pulmonary edema only for us to discover that ultrafiltration to a weight 2 or 3 kg below their putative target weight is just what is needed? If a routine lung US on the previous Friday before dialysis might make these events less likely, then sign me up!

#### Disclosures

None.

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