Glucocorticoids for ARDS: Just Do It!

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Glucocorticoids for ARDS

Just Do It!

ARDS places a significant burden on the healthcare system, with an estimated prevalence of 7% of ICU admissions and an unacceptable hospital mortality rate of 50%.[1] Pulmonary and systemic inflammation are the pathophysiologic hallmarks of this syndrome,[2] and activation of the glucocorticoid receptor in pulmonary and circulating cells is an essential step in restoring homeostasis.[3] While changing the ventilator settings to low tidal volume reduces systemic inflammation with a favorable impact on survival,[4] a concomitant antiinflammatory pharmacologic intervention should lead to a more rapid resolution of ARDS and earlier extubation. Among the antiinflammatory drugs, glucocorticoids have been the most investigated treatment in ARDS. Early trials[5–8] demonstrated that, when administered at high dose (*eg*, 30 mg/kg of body weight [2,100 mg for a patient weighing 70 kg] of methylprednisolone [or equivalent] per day for approximately 24 h) to cure or to prevent ARDS, glucocorticoids provided no survival benefit and even may have favored life-threatening superinfections. In the last 20 years, significant advances have been made in understanding the complex molecular mechanisms of action of glucocorticoids, while accumulated clinical data on low-dose, prolonged glucocorticoid treatment (methylprednisolone, 1 mg/kg/d [70 mg for a patient weighing 70 kg], or equivalent) in ARDS has shown significant improvement in inflammation and lung physiology with a favorable benefit/risk profile.[9–16] Glucocorticoids modulate almost all steps of the inflammatory process through genomic and nongenomic actions. In patients with ARDS, moderate doses of glucocorticoids were associated with a progressive increase in glucocorticoid receptor-mediated activities leading to significant reductions in nuclear factor-κB DNA binding and transcription of tumor necrosis factor and interleukin-1β.[10] Thereby, prolonged glucocorticoid treatment decreased both lung and circulating levels of various proinflammatory mediators at both early and late phases of the disease.[10–16] In animal models of acute lung injury, early administration of glucocorticoids showed protective effects on lung parenchyma with maintenance of tissue impedance and extracellular matrix.[15] In five randomized trials[11–14,16] of patients with acute lung injury or ARDS, prolonged treatment with glucocorticoids in moderate doses consistently improved gas exchange, lung injury score, and dramatically shortened duration of mechanical ventilation. Glucocorticoid treatment prevented the dissemination of inflammation to extrapulmonary organs and decreased the prevalence of cardiovascular dysfunction.[6–10,12] Needless to say, that for many physicians, a treatment that reduces pulmonary and systemic inflammation, improves lung mechanics and gas exchange, and prevents progression of multiple organ failure should become a standard of care for ARDS patients. The effect of prolonged glucocorticoid treatment on survival in ARDS remains controversial. In patients treated for persistent ARDS, *ie*, glucocorticoids were initiated after day 7 from the disease onset, one single-center randomized trial[11] showed dramatic increase in survival rate, whereas a recent multicenter trial[13] did not show any evidence for a survival benefit, and even suggested that when glucocorticoids are administered very late after 2 weeks of progression of the disease, they may cause harm. There are significant differences in between-studies design that may account for this discrepancy in results on survival. Among them, too short of a period allowed to wean glucocorticoids in the ARDSnet trial,[13] and concomitant use of a neuromuscular blocking agent were the most important. The current study by Meduri et al[14] in this issue of *CHEST* (see page 954) is the first multicenter randomized, placebo-controlled trial focusing on early and prolonged (2 weeks at full dose then tapered off $>$ 2 weeks) treatment with low- dose glucocorticoids (1 mg/kg per day [70 mg/d for a patient weighing 70 kg] of methylprednisolone). This study confirms the benefit from glucocorticoids on physiologic parameters and on ARDS complications, and suggested that this treatment improved short-term and long-term survival. The potential survival benefit was in keeping with a recently published *post hoc* analysis[12] of a randomized trial of low-dose glucocorticoids for

septic shock that included patients with ARDS and showed significant improvement in hospital and 1-year survival. Then, when data from these four randomized placebo-controlled trials on moderate dose of glucocorticoids for ARDS are pooled, accounting for 472 patients, the relative risk of short-term mortality was 0.81 (95% confidence interval, 0.66 to 0.99) in favor of treatment with glucocorticoids.[11–14] Glucocorticoids may induce serious adverse events; among them, GI bleeding, superinfection, blunted febrile response, hyperglycemia, and muscle weakness deserve specific attention to be prevented. These drug-related adverse events should not discourage physicians from treating ARDS patients with glucocorticoids, similar to our approach with prolonged methylprednisone treatment in patients admitted to the ICU with acute exacerbation of asthma or COPD.

Moreover, in randomized controlled trials[11–14] on moderate-dose glucocorticoids, this treatment was not associated with increased risks of bleeding or superinfection. Infection surveillance, as shown in this study, is essential to identify infection in the presence of a blunted febrile response.[10] Tight glycemic control with insulin and avoidance of neuromuscular blocking agents are likely to minimize metabolic and neurologic complications. Short course with high-dose glucocorticoids (30 mg/kg [2,100 mg for a patient weighing 70 kg] of methylprenisolone for approximately 24 h) must not be administered to patients with ARDS. In contrast, it is this author's opinion that patients with ARDS, regardless of the stage of the disease (except for patients with ARDS persisting for >2 weeks), should be treated with prolonged, moderate-dose methylprednisolone as proposed by Meduri and colleagues.[11,14] Secondary measures implemented in this study to prevent complications associated with glucocorticoids are essential to achieve favorable results and should be an integral part of treatment.

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Atrial Septostomy

Why We Still Need It

Untreated idiopathic pulmonary arterial hypertension (PAH) is characterized by a progressive elevation of pulmonary artery pressure, followed by worsening right ventricular failure and ultimately death.[1] With the most aggressive medical approaches (continuous IV prostacyclin therapy), survival is only approximately 63% at 3 years.[2,3] Patients with idiopathic PAH and a patent foramen ovale (PFO) appear to live longer than those without a PFO.[4] Individuals with Eisenmenger syndrome (anatomic right-to-left shunt) have a better prognosis than those with PAH without a shunt, based on a slowly progressive increase in pressure and gradual evolution of right ventricular hypertrophy that enable the ventricle to cope with very high pressures.[5] Creation of an interatrial communication has been shown to preserve systemic output by decompressing the dysfunctional right ventricle, offering temporary clinical benefit to very ill patients with idiopathic PAH in whom therapy is failing.[6–9]

In this issue of *CHEST* (see page 977), Kurzyna and colleagues[10] from Warsaw, Poland present their experience with 14 balloon atrial septostomy (BAS) procedures in 11 patients, 9 of whom had idiopathic PAH. Based on the initial cardiac index (1.54 + 0.34 L/min m2), mixed venous O_2 saturation values, and pulmonary vascular resistance values, this was a cohort of patients with very advanced disease. The procedure led to significant improvement in immediate cardiac index (CI) [increase in CI in all but one patient], although other postprocedure hemodynamic parameters did not improve. Functional class improvement, albeit somewhat subjective, was encouraging, with five patients improving from New York Heart Association class III to II, and one patient improving from class IV to III. Considering the severity of disease, any benefit might be considered encouraging. As expected, the price to pay was compromised oxygenation. One critically ill patient died at day 24, and three others died during the 12-month follow-up; there were no procedure-related deaths. In this study, the baseline CI was lower than in several other previous series,[8,9] although there were fewer class IV patients than in the other studies. While overall survival did not differ from that predicted in historical control subjects, clearly, some patients benefited.

Over a decade ago, continuous IV epoprostenol became the first Federal Drug Administration-approved drug for PAH after demonstrating improved mortality in a prospective, randomized trial.[11] Four other drugs have since been approved, and lung transplantation has come to the clinical forefront. With these advances, why the interest in BAS? First, patients still worsen in spite of aggressive medical therapy[2,3]; and second, the story is a bit different many places outside of the United States. The authors have considerable experience with the management of PAH, but as in many countries have limited pharmacologic options. Their expertise with BAS has arisen from the need to provide therapy to very sick individuals. Most centers in the United States offer the procedure only rarely, and many experienced pulmonary hypertension clinicians have never performed one. While the drugs registered by the European Agency for the Evaluation of Medicinal Products (sildenafil, bosentan, and iloprost) are formally available in all European Union countries including Poland, availability does not equate with reimbursement by national health insurance, and cost is usually prohibitive. Certain drugs not registered in the European Union, such as treprostinil, can sometimes be applied for and obtained. Enrollment of patients in clinical trials in Poland enables a few patients to continue on drugs in the extension phase of the trial. Therapy for PAH is even less accessible in certain other Eastern European countries.

Unfortunately, BAS is contraindicated in those patients who are in the most dire need of intervention; those with markedly elevated pulmonary vascular resistance, arterial oxygen saturations $< 80\%$ at rest, and severe right-heart failure (low CI and high right atrial pressure) appear more likely to worsen or die after BAS.[6–9,12] Massive right-to-left shunting may result in inadequate pulmonary blood flow and severe hypoxemia. Thus, there appears to be a window of opportunity for this procedure, and the authors of this study from Warsaw caution that the preferred approach for BAS is elective rather than "rescue," although this distinction may sometimes be blurred in clinical practice. While this investigation is small and uncontrolled, it reminds us that despite advances in the approach to treating PAH, septostomy is alive and relied on. While the study design is not ideal, it is the best that can be done; we will likely never see a prospective, randomized trial, and the procedure will remain best performed in the hands of a small number of experienced clinicians. At present, it is indicated for advanced New York Heart Association class III and class IV patients with recurrent syncope and/or right-heart failure despite all available medical treatments, unless the disease is simply too advanced.[7,12] It is used either as a palliative bridge to lung transplantation or as the sole treatment modality when other options are not available.

Medical therapy for PAH continues to evolve. In addition to the currently Food and Drug Adminis-

tration-approved drugs (epoprostenol, treprostinil, iloprost, bosentan, and sildenafil), other related and unrelated drugs are being explored. Completely new directions include the use of imatinib, a drug that selectively suppresses the tyrosine kinase pathway conveying potent antiproliferative effects. This drug has proven effective in case reports of very ill PAH patients in whom aggressive therapy fails.[13] Therapy for PAH is expensive, ranging from $10,000 to $35,000/yr for single-agent oral therapy, to well over $100,000/yr for parenteral therapy. Both cost and availability limit therapeutic options, particularly outside of the United States. Thus, BAS maintains a place in the therapeutic armamentarium for PAH; and in certain countries, it may be of critical importance, whether as a bridge to possible additional therapy, or the potential opportunity for a few more months of life. Still, we need better treatment and better access to it, particularly in patients with very advanced PAH. This disease is a worldwide problem, without worldwide access to therapy.

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The Staging System for Non-small Cell Lung Cancer

Time for an Overhaul?

The current staging system for non-small cell lung cancer (NSCLC) has served us well for a number of years.[1] It has helped us in the evidence-based planning of treatment, the discussion of prognosis with our patients, and also the conduct and interpretation of clinical trials. The advent of positron emission tomography (PET) scanning has clearly improved the accuracy of this staging, with the outcome being both the upstaging and downstaging of our patients. It will be interesting to see whether upstaging via PET scanning (with subsequent exclusion of some patients from futile surgery) will result in better 5-year survival rates for patients undergoing surgery.

Perhaps the most complex and unsatisfactory aspect of our TNM staging system is in the assessment of nodal (N) disease. *Clinical staging* of N disease can involve the use of a number of investigation modalities including CT scan, PET scan, mediastinoscopy, and, more recently, endobronchial ultrasound with transbronchial needle aspiration. *Pathologic staging* of N disease, on the other hand, includes intraoperative lymph node sampling and formal node clearance. At present, mediastinal node (N2) disease is lumped together in stage IIIA. However there is a huge variation in

the extent of N2 disease, ranging from incidental nodal metastases found in the final pathology of surgical specimens (but not clinically evident) right through to bulky multistation, unresectable lymphadenopathy. Clearly, these variations in stage IIIA (N2) disease have far-reaching implications with respect to both therapy and prognosis. Lumping all stage IIIA (N2) disease into one stage is clearly inappropriate, and we need formal recognition of a subclassification of stage IIIA (N2) disease that takes into account these variations. There have been previous calls for such a change in the classification of N2 disease.[2]

So, in this setting of complex N disease assessment, along comes this elegant study by Lee and colleagues[3] published in the current issue of *CHEST* (see page 993). These authors have prospectively analyzed both the risk factors for extranodal extension in NSCLC patients and its adverse impact on prognosis. The presence of extranodal extension (*ie*, the presence of cancer cells beyond the capsule of the involved nodes) is associated with female gender, adenocarcinoma, advanced disease stage, vascular invasion, and the overexpression of p53. To me, there are three main implications of this study with respect to the importance of extranodal extension, as follows:

1. The presence of extranodal extension has an adverse impact on prognosis. In particular, those patients with stage IIIA disease but no extranodal extension did better than patients with stage II disease with extranodal extension. This finding not only emphasizes the prognostic importance of extranodal extension but also highlights one of the deficiencies of our current staging system. Clearly, any staging system should accurately reflect prognosis, and if it does not, then changes need to be made to that system.
2. The presence of extranodal extension may have an impact on the indications for, and benefits of, adjuvant chemotherapy. A recent analysis of the adjuvant chemotherapy trials[4] has confirmed the benefits of this therapy; however, these benefits are largely stage-specific, with the greatest benefits shown in patients with stage II and III disease. The presence of extranodal extension may represent a further subgroup of patients in whom adjuvant chemotherapy is even more appropriate and beneficial. Further trials are required to address this issue.
3. The presence of extranodal extension may have an impact on the indications for, and benefits of postoperative radiotherapy (PORT). The widely discussed and controversial meta-analysis of PORT[5] concluded that PORT had an adverse impact on survival for patients with all stages of disease apart from stage IIIA (N2). These results have been criticized on the basis of the inclusion of studies involving outdated radiotherapy and treatment-planning methods; however, despite these potential limitations, it is fair to say that the role of PORT remains unclear, and when we request PORT we do so with some trepidation. Again, this subgroup of patients with extranodal extension may represent a subgroup in which PORT may turn out to be both appropriate and beneficial.

So, where to now? In my view, this study by Lee and colleagues[3] further emphasizes the need for the clarification of N disease in our NSCLC staging system. This system needs to take into account both the vagaries of N2 disease and the presence or absence of extranodal extension. While we do not want to unnecessarily overcomplicate matters too much, we do need a staging system that more accurately reflects the modern-life complexities in lung cancer management. Lee and colleagues[3] are to be applauded for further muddying the waters (!) of nodal disease assessment.

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Clarion Call for Trials Assessing "Cardiopulmonary" Agents To Reduce Morbidity and Mortality in Inflammatory Lung Diseases

Investigators[1] from the University of New Mexico provide in this issue of *CHEST* (see page 1006) a provocative analysis suggesting novel, lifesaving therapy for patients with COPD and influenza/pneumonia. This work focuses on the potential use of statins in these syndromes, and the conclusions are based on a matched cohort study and two separate case-control studies.

The broadest, mechanistic rationale for this study derives from the fact that the pathogenesis of both diseases involves activation of inflammatory and immune processes that cause progressive lung tissue damage and account for morbidity and mortality. Indeed, diverse forms of pulmonary inflammation lead to systemic inflammatory activation with consequences that are much more widespread than merely in the lungs. For example, animal models of lung inflammation show augmentation of the rate of atherosclerosis accumulation in the coronary vessels and aorta.[2] Such observations help to explain the association between pulmonary inflammation and cardiac morbidity and mortality. Thus, medications currently associated with cardiovascular risk reduction might have a substantial impact on the clinical outcome of patients suffering from pulmonary inflammation by at least reducing the cardiovascular component of adverse morbidity and mortality. But in addition, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, through pleiotropic mechanisms, can directly mitigate lung inflammation and injury, thereby making these agents dual cardiopulmonary protectants.[3–7] These agents present extremely attractive opportunities to simultaneously improve both lung disease and cardiovascular comorbities.

In spite of feverish work, the feared, imminent influenza pandemic may well occur when antiviral agents and vaccines are unavailable in a timely fashion.[8] In addition, there is a real need to identify new therapeutic strategies in COPD because, aside from cessation of cigarette smoking, and use of oxygen therapy in patients with very severe COPD, most therapeutic interventions are of a symptomatic nature, with little or contradictory evidence as to whether outcome or disease progression are affected positively.[9]

Statins possess pleiotropic effects that can modulate immune and inflammatory responses quite dramatically and which are not due to lipid-lowering properties.[6,7] Frost et al[1] sought evidence indicating that such effects might be of clinical benefit in these special patient populations. They provide a compelling analysis with multiple strengths, including the large size of the cohort, the requirement for at least a 90-day follow-up in all strata of the analysis, demonstration of mortality benefits through both a matched cohort approach and a case-control approach, and demonstration of a potential dose-response effect that has not been previously shown. The results add substantially to this emerging area of investigation and confirm prior work in the COPD population[10] and in the arena of community-acquired pneumonia.[11]

Although the article[1] demonstrates a dose-dependent gradient in response, the precise dose dependency of effect for any particular outcome or any particular pleiotropic mechanism cannot be fully ascertained from this study. If such therapy was to be implemented, it is unclear how to determine a protective dose in the setting of an influenza pandemic or for more general use in COPD patients. The results suggest, however, that titration to maximally tolerated doses might be a reasonable, initial approach pending further studies, especially randomized trials. The diversity of the databases mandated a focus on in-hospital deaths only. While this pragmatic approach yields a clear-cut and compelling end point, particularly with respect to acute influenza-related deaths that are often in the hospital, the analysis does not provide an assessment of the potential, overall impact of statin therapy in COPD that has a more protracted course, characterized by a high degree of both outpatient and inpatient morbidity and mortality. It is not clear whether this limitation of the study might have resulted in an overestimation or underestimation of putative effects of stains in COPD. Indeed, the beneficial effects on mortality must be viewed as speculative due to inevitably imperfect elimination of all variables that might potentially confound the final results and the potential for ascertainment and treatment biases. Thus, in spite of the novel and interesting results, the evidence provided by this sort of retrospective analysis is valuable mainly for providing a compelling rationale for executing randomized clinical trials that will more clearly define the magnitude of effect and the characteristics of patients that will benefit the most. Even so, the current article is extremely valuable because it suggests that statin therapy may well be efficacious in real-world application to COPD patients and possibly for acute influenza. Moreover, if randomized clinical trials confirm a level of efficacy similar to what was noted in this trial

(risk reductions in the 40 to 80% range), then such therapy may also be extremely efficient or cost-effective.

The threat of an influenza pandemic continues to loom, and COPD is increasing in prevalence. While afflicted patients need symptomatic therapy, adjunctive approaches may bear more fruit with respect to improvement of long-term prognosis. In the sphere of COPD, there has been a long-standing recognition of the benefit of β-blockers for improving long-term outcome in COPD patients, although in practice this benefit is always weighed against an exaggerated perception of risk of deterioration of lung function. This often leads to underutilization of this class of drug in COPD.[12] In contrast, drugs such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have potentially beneficial effects directly on lung inflammation while having been proven in both coronary patients and, with respect to the angiotensin drugs, in patients with congestive heart failure, which is commonly associated with COPD.[13] It stands to reason that these drugs may lead to very important advances in the therapy of patients with lung disease. The investigators at the University of New Mexico are to be congratulated for adding more evidence supporting execution of randomized clinical trials using these agents that stand an excellent chance of improving the natural history of extremely large populations with diverse forms of inflammatory lung disease, in particular COPD.

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Comet Tails in High-Altitude Pulmonary Edema

Diagnostic Portent or Streak in the Sky?

High-altitude pulmonary edema (HAPE) is a form of noncardiogenic pulmonary edema, which affects between 0.2% and 15% of people who ascend to altitudes between 2,500 and 5,000 m,[1,2] and which may be fatal if not recognized and treated promptly. Given the increasing number of people traveling to alpine regions for work or pleasure, improving our ability to prevent, diagnose, and manage HAPE would be of great benefit, as would an increased understanding of its pathophysiology. With regard to new prophylactic drugs, Maggiorini et al[3] recently demonstrated a benefit for the phosphodiesterase inhibitor tadalafil and the corticosteroid dexamethasone in preventing HAPE in known susceptible individuals. On the diagnostic front, Fagen-

holz and colleagues[4] in this issue of *CHEST* (see page 1013) describe a relatively simple diagnostic technique that has the potential to enhance our understanding of the time course of the disease and to facilitate research on other important questions related to its development.

Prior work in patients with pulmonary edema at sea level has demonstrated that chest ultrasonography can be used to detect the presence of extravascular lung water by identifying "comet-tail" artifacts created by microreflections of the ultrasound beam within interlobular septa thickened by the presence of increased lymphatic fluid consistent with interstitial and/or alveolar edema.[5–7] Fagenholz et al[4] brought this technique to Pheriche, Nepal (elevation, 4,240 m), performing studies on 11 consecutive patients with clinically diagnosed HAPE (*ie*, without using chest radiographs) as well as 7 control patients with no evidence of altitude illness or respiratory compromise. Using a blinded assessment of the ultrasonographic data, they demonstrated that the patients with HAPE had statistically significantly higher comet tail scores and lower oxygen saturations than the control patients, and demonstrated a fall in comet tail scores with the resolution of HAPE symptoms. Using regression analysis, they also showed an inverse relationship between comet tail scores and oxygen saturation whereby the oxygen saturation decreased by 0.67% for each 1-point increase in the comet tail score. A further interesting result was the finding that comet tail scores were higher in the right lung, an observation that fits with previously described HAPE patterns in which the edema tends to begin in the right middle lobe.

Simple in its design, the study provides relatively clear evidence of the utility of chest ultrasonography in detecting and following the course of pulmonary edema formation at high altitude. While the authors deserve credit for conducting this study in a remote environment with very limited clinical resources, it should be noted that the study is not without limitations. For example, although a blinded observer assessed the ultrasonography data, the person performing the ultrasound was not blinded as to the clinical status of the patient. Given that obtaining good ultrasound images is highly operator-dependent, the lack of adequate blinding is not an insignificant concern. In addition, although cardiogenic causes of pulmonary edema are unlikely in the clinical setting in which the authors were working, they did not take any steps to rule out a cardiogenic source of the comet tails by, for example, assessing left ventricular function or pulmonary capillary wedge pressure. Finally, as the authors note, this study represents the first use of this technique in the evaluation of HAPE, and, as such, the results have yet to be validated in further studies. Although worthy of consideration, none of these issues appear to seriously undermine the results of the article.

The question that logically follows from this intriguing study will be the ultimate utility of this technique in the assessment of pulmonary symptoms at high altitude. Interestingly, although this was a clinical study of patients with a high probability of known HAPE, we would argue that the utility of this technique in the diagnosis and management of patients with HAPE is likely to be limited for several reasons; HAPE will remain a disease that is diagnosed and managed largely on clinical grounds. First, although, as the authors argue, the portable ultrasound machine is cheaper than a radiography system, it is still an expensive machine that is unlikely to be available on a regular basis at remote sites where HAPE might develop. Even if the device and trained operators were available in remote locations, it is not clear that its use would change clinical decision making or management, as no data exist to demonstrate whether the technique has increased diagnostic accuracy when compared to clinical impression alone and/or conventional radiography when available in resort areas. Along similar lines, if the oxygen saturation improves as the comet tail score falls, one could simply follow the oxygen saturation as a measure of clinical improvement rather than rely on the more complicated ultrasonography technique. Further work will need to be done to determine whether the observed changes in comet tail scores are specific for pulmonary edema or if other acute and chronic lung processes with septal thickening or multifocal infiltrates such as pneumonia might cause a similar appearance. Last, will it be possible to distinguish cardiac edema from noncardiac edema, the prognoses and treatment of which may differ?

Although the clinical utility of the technique might be limited, it holds great promise as a research tool for studying various aspects of HAPE. One area, in particular, in which the technique could be of great use is in resolving the question of subclinical edema at high altitude. While multiple studies have documented an incidence of overt HAPE between 0.2% and 15%, a 2002 study by Cremona et al[8] suggested that, based on evidence of increased lung closing volumes at high altitude, up to 75% of climbers without overt HAPE at 4,559 m may actually have "subclinical" pulmonary edema. This was a surprising result, which has yet to be validated in subsequent studies. One of the reasons it has been difficult to establish whether subclinical edema occurs to this extent pertains to the difficulties in developing accurate measures of its existence. The "gold standard" for detecting extravascular lung water would be quantitative Hounsfield unit measurements of lung density and the presence of ground-glass opacification on chest CT scans. Because this technique is not available in remote locations and because conven-

tional radiographs are insensitive for detecting early edema, other techniques such as electrical impedance tomography[9] and lung closing volumes[8] have been employed with only mixed results. Chest ultrasonography, if validated by CT imaging, may provide a reliable, easy alternative to these often complicated methods for detecting the presence of subclinical edema and may allow better assessment of the true incidence of this phenomenon. Additional avenues of investigation in which this technique might be useful would include following both HAPE-susceptible and non-HAPE-susceptible individuals as they ascend to high altitude, and comparing the rate of comet tail formation in these groups or determining whether there is a correlation between comet tail score and the rise in pulmonary artery pressures (measured by echocardiography) that is the pathophysiologic hallmark of HAPE.[10–12]

The work of Fagenholz et al suggests that answering these and other questions about edema formation at high altitude might be easier than reliance on the previously noted techniques. It is perhaps fitting that their demonstration of the utility of this relatively simple alternative was based on a study conducted in the Khumbu Valley of Nepal, a land where "simple" is the order of the day and the complexities of life rarely intervene in people's daily affairs.

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