EDITORIALS

Restoring Airway Surface Liquid in Cystic Fibrosis

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The current pathophysiological model of cystic fibrosis lung disease assumes that defective expression, trafficking, or function of the cystic fibrosis transmembrane regulator (CFTR) protein leads to impaired epithelial chloride secretion and sodium hyperabsorption. This process, in turn, results in the depletion of airway surface liquid and abnormal mucociliary transport. Retention of mucus is thought to favor bacterial overgrowth, which then triggers a cycle of repeated or chronic infections associated with intense neutrophilic airway inflammation.

Defective mucociliary transport itself can cause airway inflammation, as has been shown in mice that have an overexpression of the beta subunit of the epithelial sodium channel, which causes depletion of airway surface liquid and neutrophilic airway inflammation in the absence of infection.[1] Current treatment approaches aim to improve airway clearance, eradicate or suppress the growth of bacterial pathogens, and attenuate airway inflammation. Although these treatment strategies have improved the survival of patients with cystic fibrosis, they fail to target the underlying defect by restoring airway surface liquid.

Previous studies in a small number of patients with cystic fibrosis showed that inhalation of hypertonic saline increased mucociliary transport.[2] Even though hypertonic saline could potentially increase the amount of airway surface liquid, it was thought that this effect should be rather short-lived, since sodium applied to the epithelial surface would rapidly be taken up through active transport mechanisms. In this issue of the *Journal*, Donaldson et al.[3] demonstrate that this assumption is probably incorrect, since the administration of hypertonic saline not only had a prolonged effect on the amount of airway surface liquid in epithelial cells from patients with cystic fibrosis in vitro but also resulted in a sustained improvement of mucociliary transport. Although the exact mechanism of the prolonged action remains to be elucidated, these observations suggest that inhaled hypertonic saline may indeed be a therapeutic option for increasing the volume of airway surface liquid in patients with cystic fibrosis (Fig. 1).

Will this change in mucociliary transport translate into long-term benefits for patients? Elkins et al.[4] demonstrate in this issue of the *Journal* that twice-daily inhalation of a hypertonic saline solution over 48 weeks has positive effects on two important aspects of cystic fibrosis lung disease. In a multicenter study, they found a moderate improvement in lung function among treated patients, as compared with the control group that inhaled normal saline. More important, patients receiving hypertonic saline showed a marked reduction in the frequency of pulmonary exacerbations. Although previous studies have demonstrated the short-term benefits of hypertonic saline with respect to pulmonary function, this study offers the first evidence of its long-term efficacy in patients with cystic fibrosis.

What are the implications of these two studies in regard to treatment? Although the study by Elkins et al. was well designed, it has some limitations. The improvement in lung function was rather small, and the confidence intervals of the two groups overlapped at all time points during the study. No decline in pulmonary function was observed in the control group during the study period, which raises the question of whether the combination of normal saline with bronchodilators had a beneficial effect on lung function. The decrease in the number of pulmonary exacerba-

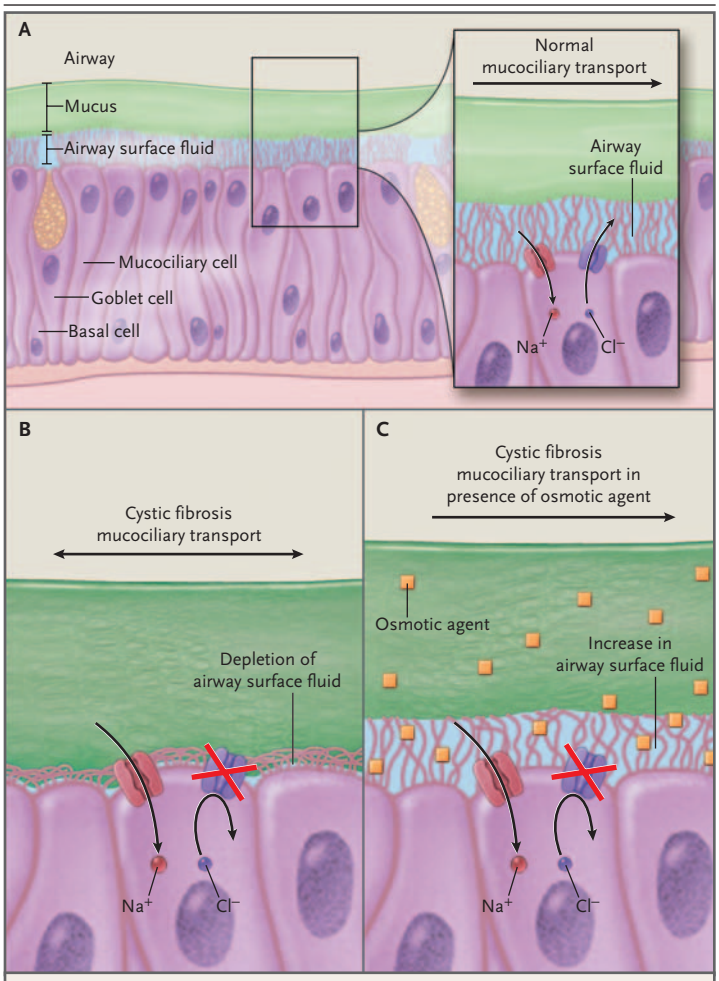

Figure 1. Mucociliary Transport in the Healthy Lung and in Cystic Fibrosis.
A fluid layer that is maintained through a balance of chloride secretion and sodium absorption covers the surface of airway epithelial cells. The airway surface fluid supports a thin mucus layer produced by mucosal secretory glands. The mucus layer is transported by respiratory cilia from the lower airways to the airway opening (Panel A). In cystic fibrosis, defective chloride secretion and sodium hyperabsorption lead to the depletion of the layer of airway surface fluid, with consecutive breakdown of mucociliary transport (Panel B). Osmotic agents increase the volume of airway surface fluid through an increase in water influx, thereby restoring mucociliary function (Panel C). For simplicity, inflammatory cells are not shown.

tions in patients treated with hypertonic saline was more impressive but largely confined to the first three months of treatment and was paralleled by a decrease in compliance among patients over time.

It should also be noted that the maintenance antibiotic therapy for the study population differed from that used in many cystic fibrosis centers. Although approximately 80 percent of patients in both groups were infected by *Pseudomonas aeruginosa*, less than 15 percent of the population received inhaled tobramycin. This protocol differs considerably from current practice in the United States, where the majority of patients infected by *P. aeruginosa* receive inhaled tobramycin as part of their routine care. Since inhaled tobramycin has been shown to have a positive effect on both lung function and pulmonary exacerbations,[5] the effect of hypertonic saline may be less pronounced when used in other patient populations.

These studies do not determine whether the improvement in mucociliary transport arises from an increase in the volume of airway surface liquid, from an increase in airway clearance through the induction of cough, or from a combination of the two processes. The only other medication with proven efficacy in improving airway clearance in patients with cystic fibrosis is recombinant human DNase (rhDNase).[6] A previous crossover trial showed that hypertonic saline was inferior to rhDNase, but that study focused on pulmonary function and, in contrast to that by Elkins et al., did not assess pulmonary exacerbations as an outcome measure.[7] It is notable that the beneficial effects seen in the study by Elkins et al. were independent of concurrent use of rhDNase, so it is unlikely that hypertonic saline will replace rhDNase treatment in patients with cystic fibrosis. Rather, hypertonic saline may become an option for adjuvant therapy.

Although a benefit has been shown, will patients accept this new therapy? Hypertonic saline has an unpleasant taste and induces coughing; these features may limit its acceptance and hence its efficacy as a long-term therapy. In addition, the proposed protocol of hypertonic saline inhalation involves two inhalations of 4 ml, which would add at least 30 minutes of time to the patient's already burdensome daily treatment schedule. Fortunately, faster and more effective inhalation devices are in development and may make add-on therapy by inhalation more acceptable to the patient. In addition, another osmotic agent, mannitol, which can be administered as a dry powder by metered-dose inhaler, is being evaluated. If mannitol is shown to be effective, it may offer a less time-consuming alternative to hypertonic saline in the future.

What are some of the open questions related to restoring the volume of airway surface liquid by inhalation of osmotic active agents? In a way similar to the action of other medications ad-

ministered by inhalation, deposition will preferentially occur in areas not obstructed by plugs of mucus. The most affected areas may therefore not benefit from this treatment approach. The verification of this hypothesis would support the early use of such drugs in cystic fibrosis before mucus can accumulate extensively in the lung. Moreover, hypertonic droplets undergo hygroscopic growth in a water-vapor–saturated environment such as the respiratory tract — a factor that will increase the size of the particles during inhalation and favor a more central deposition.[8] This finding makes it less likely that an adequate amount of the substance will enter the smaller airways, the area where cystic fibrosis lung disease is thought to originate. In addition, the small airways have an overall surface area that far exceeds the surface area of the central airways. It is not clear what quantity of an osmotic active agent is needed for the complete restoration of airway surface liquid in the small airways of patients with cystic fibrosis. Unless nebulizers could specifically target this area of the bronchial tree, the feasibility of this approach may potentially be limited by the amount of fluid that can safely be delivered through the larger airways. Therefore, pharmacologic intervention with a direct effect on chloride secretion, on sodium hyperabsorption, or both may ultimately be more effective in restoring the volume of airway surface liquid. In the meantime, hypertonic saline offers a new treatment strategy for patients and brings us closer to targeting the underlying abnormality, rather than the consequences of defective mucociliary clearance.

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Reducing the Risk of Gynecologic Cancer in the Lynch Syndrome

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The first description of a kindred with hereditary nonpolyposis colorectal cancer (HNPCC) in 1925 was based on the family history of a woman who later died from endometrial cancer. On the basis of a detailed interview by Michigan pathologist Aldred Scott Warthin with this woman (his seamstress) and with other members of "Family G," Warthin described a large kindred with hereditary colorectal and endometrial cancers.[1] Sixty-eight years later, Henry Lynch broadened the spectrum of hereditary cancers in the HNPCC syndrome to include ovarian cancer, transitional-cell cancer of the renal pelvis, and less often, stomach, small-intestine, pancreatic, and other types of cancer.[2,3]

In this issue of the *Journal*, Schmeler and colleagues[4] report the results of a retrospective study examining the occurrence of endometrial and ovarian cancer in women with the Lynch syndrome and documented germ-line mutations in the mismatch-repair genes *MSH2*, *MLH1*, and *MSH6* who had undergone prophylactic hysterectomy alone or with bilateral salpingo-oophorectomy, as compared with controls who did not have prophylactic surgery. No endometrial cancers occurred in the 61 women who underwent hysterectomy, whereas endometrial cancers occurred in 69 women of 210 who did not undergo hysterectomy. Similarly, no ovarian or peritoneal cancers were diagnosed in the 47 women who underwent bi-