resistance training, it does show that quadriceps resistance training during a severe exacerbation of COPD can (*1*) prevent discharge of patients with muscle function worse than that which they had at admission, and (*2*) assist such patients in maintaining function during and possibly after the exacerbation phase. Also, even though only the quadriceps muscles were targeted for training, one can speculate that similar training for different muscles would yield comparable results.

This interesting study may have practical consequences for the hospital management of acute COPD exacerbation, beyond usual medical therapy. First, it restores the importance of a nonpharmacological therapy at the earliest onset of disability. Second, it emphasizes the role of physical therapy in the acute hospital setting. However, a study of the same protocol in a more severely ill population (e.g., in patients suffering from respiratory insufficiency, who are more likely to be hospitalized) should be performed to confirm both the feasibility and the effectiveness of this training strategy.

It would have been interesting if the authors had explored recovery of daily activities, which is a direct consequence of better muscle function. Indeed, a rehabilitation course including limb training may positively influence this outcome in severely ill patients (14, 15). Future research in patients with COPD exacerbations should highlight this point, thus conveying an even more powerful message to practitioners.

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Bronchiectasis

A Continuum of Ion Transport Dysfunction or Multiple Hits?

Bronchiectasis, a syndrome characterized by chronic cough with purulent sputum and bronchial dilation involving more than one lobe on computed tomography scans, remains in many cases a pathophysiological dilemma. Bronchiectasis is often considered to result from a failure of lung defense that leads to chronic airway infection, airway wall damage, and airway ectasia. In this issue of the *Journal* (pp. 1078–1084), Bienvenu and colleagues investigate the pathogenesis of bronchiectasis in a large cohort of subjects in whom known causes of bronchiectasis were thought to have been excluded (1).

In their study, Bienvenu and colleagues focus on the potential role of abnormal airway ion transport, as indexed by the nasal potential difference (PD) measurement, in the pathogenesis of the bronchiectatic phenotype, focusing on the role of abnormal cystic fibrosis transmembrane regulator (CFTR) function in governing ion transport rates. Thus, a combination of nasal PD measurements, molecular assessments of *CFTR* mutation status, sweat Cl^- concentrations, and clinical indices, including bacterial colonization and FEV_1, were measured and correlated. The groups were broken down into subjects with bronchiectasis exhibiting no *CFTR* mutations or sequence variants (DB0, 85 subjects), those with a single *CFTR* mutation or sequence variant (DB1, 22 subjects), and patients with two *CFTR* mutations or variants (DB2, 15 patients).

As a group, the subjects with bronchiectasis had evidence of abnormal ion transport. The degree of abnormality correlated with the number of *CFTR* mutations or sequence variants, that is, 0, 1, or 2. Although still subject to debate, there appears to be an emerging consensus that the abnormal ion transport defects in CF reflect abnormalities in both the Na^+ absorptive and Cl^- secretory processes that regulate airway surface hydration (2). It appears that abnormal airway surface hydration in CF leads to collapse of the periciliary layer, adhesion of a concentrated mucus layer to airway surfaces, persistent mucus, bacterial infection, inflammation, and lung damage, including diffuse bronchiectasis. Several key physiological concepts have emerged to explain certain clinical features of CF, including the long periods of relative health during basal states and the profound effects of acute exacerbations on lung function. The first concept is that CF lung disease indeed reflects a vulnerability to exogenous insults that trigger intercurrent exacerbations rather than a persistent failure of lung defense (3). A second concept is that the vulnerability to transient losses of lung defense is a function of (*1*) the severity of the *CFTR* mutations, and (*2*) modifier genes and environmental influences, both socioeconomic and viral/inhaled pollutant exposures (4, 5). Analyses of both the severity of *CFTR* mutations and potential modifier gene/environmental influences are instructive in identifying mechanisms relating the postulated continuum of ion transport dysfunction to disease phenotype in the Bienvenu and colleagues bronchiectasis cohort.

The patients described with two *CFTR* mutations or sequence variants (DB2 patients) as a group had intermediate sweat Cl^- values and nasal PD values just outside the range diagnostic for CF, and 11 of 15 had bacterial colonization with organisms typical of CF. Thus, these patients were likely correctly assigned to a "CF" or "CF-related disease" category, and the relatively mild phenotype likely reflected the mild nature of the *CFTR* mutations or sequence variants per se and potentially contributions of modifier genes and/or environmental influences.

The DB1 subjects with bronchiectasis, with a single genetically identified *CFTR* mutation or sequence variant, exhibited nasal ion transport defects intermediate between those of patients with bronchiectasis with two versus no *CFTR* mutations/variants, and importantly, bioelectric properties different from those of phenotypically "normal" *CFTR* obligate heterozygotes. Because the entire *CFTR* gene was not sequenced in this study, some of these DB1 subjects indeed may have had an unrecognized second *CFTR* mutation to account for the differences in nasal PDs from obligate *CFTR* heterozygotes. In parallel, modifier genes, including mutations in the epithelial sodium channel gene (*ENaC*), and environmental influences, for example, respiratory viruses and acid reflux, may play a role in producing the bioelectric and clinical phenotype characteristic of this subgroup.

The most interesting patient population was that of the bronchiectatic patients who exhibited no defined mutations in *CFTR* and nasal PD patterns consistent with abnormal Na^+ transport but normal Cl^- transport (DB0 patients). It is possible that the raised Na^+ transport rates were an acquired phenotype in response to chronic inflammation and infection, although the typical pattern is for reduced Na^+ transport rates in this setting (6). Consequently, it is possible that in these patients, genetic abnormalities in ENaC-mediated Na^+ transport may contribute to disease pathogenesis, as has been previously suggested by Fajac and colleagues (7). As the trend in this bronchiectatic subpopulation is for raised nasal PDs and raised amiloride-sensitive PDs (Δamiloride PDs), the *ENaC* mutations presumably reflect a gain-of-function phenotype. Lessons from another gain-of-function *ENaC* mutation, that is, that associated with Liddle's syndrome, suggest that this mutation produces a phenotype in which the Liddle's ENaC hyperfunction expressed in the kidney is suppressed by CFTR in the respiratory tract, likely explaining the absence of a respiratory phenotype in patients with Liddle's syndrome (8, 9). Thus, disease-causing *ENaC* mutations in this bronchiectasis subpopulation might be predicted to be ones that escape CFTR regulation. It should be noted that the abnormality in ENaC associated with CF lung disease is not the absolute rate of ENaC-mediated Na^+ transport, but the failure of ENaC-mediated Na^+ absorption to slow as the airway surface becomes dehydrated (volume depleted). This observation suggests that airway surface liquid volume measurements may best assess *ENaC* mutations in the context of causing airway disease (2).

Perhaps equally interesting is the fact that many of the DB0 patients have nasal Na^+ transport and Δamiloride PDs that overlap the normal range, raising a question concerning why normal subjects in this range did not exhibit disease. This question raises the possibility that "multiple hits" in lung defense are required to produce disease in this subpopulation as well as others. For example, it has been reported that βENaC mice (mice expressing a βENaC transgene), exhibiting a gain of function in airway Na^+ transport and a pulmonary disease phenotype that resembles CF, do not exhibit a spontaneous airway bacterial infection in adulthood (10). However, when βENaC mice are bred with mice that have a second genetic defect in lung defense that also does not produce spontaneous bacterial infection, for example, a genetic deletion of the MyD88 signaling molecule that couples bacterial LPS production to airway luminal neutrophilia, a persistent bacterial infection results in double-mutant mice (11). Thus, it may be instructive in the DB0 patient population to look specifically for modifier genes/second genetic mutations in pathways that are complementary to the mucus clearance pathway in keeping the airway free of bacterial pathogens.

The article by Bienvenu and colleagues also raises three other questions regarding patients with bronchiectasis.

First, are nasal PDs diagnostically useful in this disease group? As the authors argue, although nasal PDs are not part of the currently designated diagnostic workup for CF (12), they appear to be useful in this patient population, including both individual Na^+ versus Cl^- transport parameters and combined indices. Indeed, both Bienvenu and colleagues (1) and Wilschanski and colleagues (13) use diagnostic indices that include the Δamiloride response as the index of Na^+ transport, and indices of Cl^- transport that include the Δisoproterenol PD (Δiso) and ΔCl^- free PD/Δiso response, respectively. However, it should noted that the Δamiloride response measures not only the inhibition of Na^+ transport by amiloride but also the capacity of the epithelium to increase Cl^- secretion in response to the hyperpolarization of the cell interior caused by the amiloride block of ENaC (14). Consequently, the Δamiloride response is somewhat redundant for measuring Cl^- transport with 0 Cl^-/0 Cl^- Δiso measurements. Indeed, the basal PD is perhaps a better index of Na^+ transport rates alone (14), so perhaps a combination of the basal PD plus the total Cl^- permeability response, as revealed by the sum of the Δ0 Cl^- and ΔIso responses, may be even more discriminative.

Second, is chronic bacterial infection a typical feature of bronchiectasis? The DB2 patients had a relatively high incidence of bacterial colonization (11 of 15), but the DB1 patients (6 of 22) and the DB0 patients had a relatively low incidence of culture-defined bacterial colonization. This result suggests two quite different possibilities. It is possible that this failure to identify bacterial pathogens reflects the relative insensitivity of classic bacterial hospital cultures to detect the spectrum of bacteria that chronically infect the abnormal lung, as suggested by comparisons of cultures with culture-independent 16S profiling in CF (15). Alternatively, this result could suggest that our current under-

standing of the pathogenesis of bronchiectasis is poor and that processes that directly damage the airway wall may be more important in the bronchiectatic phenotype than chronic infection. Certainly, the results of culture-independent molecular profiling of bacterial species in bronchiectatic patient populations will be important, both for research and for clinical applications.

Finally, are we treating our patients with bronchiectasis optimally? As noted previously, an accurate description of the microbiological communities that may inhabit the bronchiectatic lung will be important to tailor antibiotics. From a broader view, the notion that abnormal ion transport produces a dehydrated airway surface in bronchiectasis, with chronic mucus adhesion and infection, suggests that agents that restore hydration to airway surfaces may be rational for this patient population. Indeed, "hydrating" agents such as inhaled hypertonic saline and other osmolytes appear to be efficacious in subjects with CF (16, 17). Thus, studies of the pathogenesis of bronchiectasis, based on principles of electrolyte transport abnormalities and the spectrum of microbial infections gleaned from CF, may spur a new wave of therapies for bronchiectatic patients that may be more effective in controlling bronchiectatic symptoms and, we hope, eradicating the progression of this disease.

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