Epithelial Resurfacing: The Bronchial Skin Peel

Chronic bronchitis (defined as a chronic cough and sputum production on most days for 3 mo/yr for 2 consecutive years), or chronic mucus hypersecretion, has for decades been a neglected area for therapeutic intervention, with limited drug therapies available aside from antibiotics for infective exacerbations and mucolytics. However, the importance of chronic bronchitis has been well recognized, and previous studies have demonstrated that it appears to increase the risk of exacerbations (1), hospitalization (2) and mortality (3). Furthermore, the longer the duration of chronic mucus hypersecretion, the greater the degree of decline in FEV_1 (4).

In this issue of the *Journal*, Valipour and colleagues (pp. 681–689) have evaluated the safety and feasibility of bronchial rheoplasty (5). This is a novel procedure that utilizes a bronchoscopic catheter–based procedure to apply high energy–pulsed electrical fields to the bronchial epithelium. This has been purported to induce cell death to a depth of 0.4 mm without disrupting the extracellular matrix, thus allowing the regeneration of the airway epithelium. The hypothesis is that the regenerated bronchial epithelium of patients with chronic bronchitis secondary to cigarette smoking will have less of the inflammatory changes, metaplasia, and goblet cell hyperplasia than is seen at baseline.

There is some merit in this approach, and parallels can be drawn with the field of dermatology. Skin peels have been extensively used in dermatology for the treatment of numerous skin conditions (acne, melasma, dyschromias, photodamage, actinic keratoses, multiple solar keratoses, superficial scars, severe photoaging, deep wrinkles, and scars) and also as a way for skin rejuvenation (6). Chemical skin peels can be calibrated to different skin depths to achieve varying effects, depending on the chemical utilized. Superficial skin peels have an effect on the epidermis and dermal-epidermal interface, with epithelial regeneration accompanied by a decrease in corneocyte adhesion and an increase in dermal collagen. The net effect of this is to rejuvenate the epidermis and the upper-dermal layers of the skin. Deeper skin peels denature the surface keratin and other proteins down to the reticular dermis and may even have a role in treating precancerous skin lesions (7). On the assumption that the bronchial epithelium will behave in a similar manner to skin resurfacing, the potential benefit of regenerating the bronchial epithelium in patients with chronic bronchitis may be a reduction in epithelial abnormality or aberrancy.

In chronic bronchitis, the normal mechanisms of wound healing are interrupted, with cigarette-induced oxidative stress resulting in an epithelial phenotype shift, the disruption of epithelial junctions, and epithelial-to-mesenchymal transition, a process whereby the epithelium dedifferentiates toward a fibroblast-type mesenchymal cell phenotype (8). In conjuncture, basal progenitor squamous metaplasia results in goblet cell hyperplasia with glycosylated mucin protein expression, a key component of lung-derived mucus, upregulated (9). These processes, combined with disrupted mucociliary clearance and inappropriate leukocyte recruitment, perpetuate airways inflammation, leading to the persistent mucosal abnormalities demonstrated in former smokers (10). Resetting this epithelial aberrancy through a "bronchial peel" may turn the clock back on the damage caused by smoking, with the effects judged through indices such as a reduction in the absolute number and/or size of the mucous-producing hyperplastic goblet cells.

One of the early methods of bronchial epithelial resurfacing was described by Karakoca, who used a resector balloon (Enbio Corp.) to essentially abrade the epithelium in ten patients with chronic obstructive pulmonary disease (COPD) (11). The device used was a balloon covered with a hexagonal mesh of polyurethane/Lycra fibers that were approximately 0.2–0.3 mm thick. The resector balloon was inserted into the bronchial segments and repeatedly inflated and deflated while being maneuvered through the bronchial tree. In this small early study, there were some improvements in oxygenation and spirometric values and a relative decrease in goblet cells after the procedure. A further cohort of 188 patients with COPD who were treated and followed up for 1 month demonstrated similar improvements (12). However, this approach has only been evaluated in uncontrolled studies at a single center.

Applying a controlled amount of liquid nitrogen cryospray (RejuvenAir system; CSA Medical, Inc.) that flash freezes and ablates the epithelium to a depth of 0.1–0.5 mm without affecting the extracellular matrix is a further method of achieving epithelial resurfacing (13). A multicenter safety study has treated and followed up 35 patients with chronic bronchitis (COPD Global Initiative for Chronic Obstructive Lung Disease stage 1–3 for 12 mo) (14). The approach was safe and feasible, and it demonstrated significant improvements in patient-reported outcomes (quality-of-life measures, including the COPD Assessment Test [CAT] and the Leicester Cough Questionnaire).

Valipour and colleagues have stitched together two small open-label trials with similar protocols, conducted in three continents and involving 30 patients treated in five centers. The protocol was adapted through the trial, and the final approach was to enroll patients with an FEV_1 greater than 30% predicted with a CAT score greater than 10 who scored at least seven points on the questions related to cough. The study has demonstrated that the procedure is both safe and technically feasible, with only few adverse events of note (one subject with pneumonia 2 d after the procedure, one subject who developed atrial fibrillation approximately 1 wk after the procedure, and a few exacerbations of COPD).

The large reductions in the Saint George's Respiratory Questionnaire (mean reductions of 14.6 in the total score at 6 mo and 15.2 at 12 mo) and CAT scores (mean reductions of 7.9 in the total score at 6 mo and 7.0 at 12 mo) observed after treatment may draw a lot of attention. However, in an open-label study, such patient-reported outcomes should be interpreted with caution. Such incredible results are unlikely to be reproduced in sham-controlled randomized studies, and the large changes observed may be driven by just a few individual subjects. Although on initial inspection the improvements appear to be sustained, the large standard error and interquartile ranges (data available in the online supplement) suggest variable responses in the patients treated over the study period.

Despite the open-label nature of this study, one of its strength is the systematic approach to obtaining biopsies using the endobronchial

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cryobiopsy technique (15) before treatment and 3 months after treatment. The hematoxylin and eosin– and periodic acid–Schiff–stained slides were evaluated by a pathologist and graded. The example provided in the manuscript is visually very compelling, with a remarkable reduction in goblet cell density and the amount of mucin staining. There was a reduction in the goblet cell hyperplasia score from 1.48 (SE, 0.91) at baseline to 0.91 (SE, 0.81) after treatment. There are some caveats that hamper such histological studies, including the following: the biopsy process itself may affect subsequent findings because of the scarring and healing effect of the biopsy; sampling errors are possible; the scoring process is not validated; the scoring is done with a qualitative approach; and the scoring was performed by a single pathologist. Nevertheless, this key piece of evidence supports the concept of epithelial resurfacing correcting some of the abnormalities observed in chronic bronchitis, and the approach merits further evaluation. ■

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Computed Tomography Vascular Tree-in-Bud: A Novel Prognostic Imaging Biomarker in COVID-19?

As of July 14, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease (COVID-19), has infected more than 13 million and killed nearly 600,000 individuals worldwide (1). The predominant mode of morbidity and mortality in COVID-19 is respiratory failure related to acute lung injury and hypoxia (2, 3). Although the histopathological features in the airways and parenchyma of COVID-19 lungs are largely indistinguishable from those of other viral pneumonias, including influenza, there is mounting evidence to suggest that SARS-CoV-2 infection causes significant vascular damage, leading to pulmonary angiopathy (2, 4, 5). Consistent with this notion, many patients present to medical attention with hypoxemia that is out of proportion to the severity of patient symptoms, leading in some cases to "silent hypoxia." Though

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