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Lung Fissural Integrity: It's Written in the Genes

The field of interventional pulmonology is currently a-buzz with innovations in endobronchial procedures that challenge the traditional place of surgery in managing severe emphysema with hyperinflation. Leading one of the charges in this field is the practice of deploying endobronchial valves (EBV), which, backed now by close to 20 years of research, compares favorably with standard medical care in improving lung function and exercise capacity (1–3), quality of life (4), and survival (5) in selected cohorts.

The criteria for EBV deployment have been derived from the National Emphysema Treatment Trial of lung volume reduction surgery (6): inclusion and exclusion criteria were governed by extent and regional distributions of emphysema, but distinctions between heterogeneous versus homogeneous or upper versus lower zone disease are not now considered barriers to such treatment (7, 8). Indeed, both the Food and Drug Administration in the United States and the National Institute for Health and Care Excellence in the United Kingdom have approved EBV therapy in eligible patients. However, there is an important caveat in patient selection, namely, the "leaky fissure"; an intact barrier between "treated" and "untreated" lobes, preventing exchange of gases, is a mandatory predictor of success (9). Accordingly, a key feature of assessment prior to EBV treatment is determining fissural integrity on high-resolution computed tomography (HRCT), a surrogate for absent interlobar collateral ventilation.

Fissural integrity varies between lobes, and the minor fissure is the most frequently incomplete: the average completeness of the two major fissures is an estimated 82%, whereas the minor fissure averages 62% (10). Visual inspection of fissural integrity lacks precision and is increasingly being supplanted by automated methods (11). A fissural integrity "score" >95% is generally regarded the threshold for achieving at least 350 ml target lobe volume reduction, with completeness <80% usually warranting referral for alternative procedures including lung volume reduction surgery or investigational treatments such as vapor or coils (12). Those with intermediate scores (i.e., 80–95% complete) generally undergo a Chartis test of collateral ventilation in which the diffusion of gases into a target lobe, with its airway occluded, is detected (12). The consequences, for example, for participants in two randomized controlled trials of EBV treatment were exclusions on account of collateral ventilation of 16.5% (1) and 9.2% (2). There is no mainstream remedy at present.

Differences in fissural integrity have been appreciated since 1947 (13), and a number of cadaveric studies in diverse populations, despite the potential confounding effects of methodological heterogeneity, have suggested a possible link to ethnicity (14). However, the determinants and natural course of fissural integrity are unclear. For example, it is presently unknown whether fissural completeness decreases as emphysema severity increases. The study by van der Molen and colleagues (pp. 807–816) in this issue of the *Journal* is a welcome contribution to the field (15). The authors collected data of just under 10,000 participants from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study (16); the study population comprised African American and non-Hispanic White individuals aged 45–80 years at enrollment, with

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and without chronic obstructive pulmonary disease. Fissural completeness was assessed on volumetric CT images at baseline and at 5 years. The genetic and environmental factors contributing to fissural integrity were explored. For the CT analyses, Thirona's platform, LungQ, calculated fissure completeness and the lobar percentage emphysema extent using a density threshold of less than −950 Hounsfield Units. Genome-wide association analyses were undertaken separately for each racial group.

The study investigators make a case for a genetic role in fissure integrity. African Americans had significantly higher median fissure integrities than non-Hispanic White individuals for all three fissures ($P < 0.001$) and especially for right major and minor. Relevant genome-wide loci were identified on two chromosomes, numbers 5 and 14, for African Americans and on no fewer than six (numbers 2, 3, 5, 12, 14, and 17) for non-Hispanic White individuals. Importantly, rs2173623, rs7209556, and rs6504172 are known to influence expression of WNT5A and HOXB cluster antisense RNA, which, in turn, are regulators of embryonic development (17, 18).

Intriguingly, pack-year history predicted integrity of the right minor fissure only (79.3% never-smokers vs. 71.9% former smokers; $P < 0.001$). There were weak associations between the percentage emphysematous destruction and fissural completeness, not thought to have a clinically relevant impact on integrity, reaffirming the conclusions of earlier but smaller studies (10, 19). It is tempting to speculate that the right minor fissure is vulnerable to the effects of cigarette smoke by virtue of the comparatively smaller volume of the right middle lobe. Age, sex, exacerbation frequency, and maternal smoking during pregnancy had no influence.

The novelty of the data lies in the impressive longitudinal follow up and the finding that fissure integrity did not change over the 5-year study period. The investigators conclude that differences are genetically determined, involving multiple loci, presumably established at birth and are stable (subject to confirmation with longer studies).

The solution offered for broadening EBV eligibility is to focus on modalities to increase fissure completeness, such as biological or synthetic sealant (NCT04256408 and NCT04559464). EBVs are clinically effective, minimally invasive, safe, and easily removable or replaced and have a favorable cost-effectiveness profile well justifying this strategy.

The authors are to be congratulated on their resourcefulness in exploiting a large and well-phenotyped database of individuals with CT chest imaging out to 5 years. They acknowledge the limitations of their study of individuals aged between 45 and 80 years and who had likely accrued various environmental exposures; ideally, imaging surveillance would be conducted from youth to old age, although the practicalities and ethical requirements for minimizing radiation exposure would understandably prove challenging. They accept the results may not necessarily be extrapolated to other ethnic populations. Nevertheless, the insights afforded by this study are considerable, and it would be of great interest to see if the results can be replicated with other large retrospective data sets, such as MESA (Multi-Ethnic Study of Atherosclerosis) and FHS (Framingham Heart Study). We must wish these investigators success in their endeavor to expand the accessibility of this very promising device. ■

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Ambient Air Pollution and Lung Cancer: Nature and Nurture

During a typical day, the average adult inhales about 10,000 L of air. Consequently, even the carcinogens present in the air at low concentrations are of concern as a risk factor for lung cancer in large populations. Outdoor (ambient) air can contain a number of hazardous agents, and many of these are generated by the combustion of fossil fuels, including carcinogens such as polycylic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium. Depending on the pollution sources, the constituents of "air pollution" vary by locale and over time. Particulate matter (PM), which has multiple sources in urban air, has been studied the most as a potential lung cancer risk factor, and studies from around the world are generally consistent in finding increased cancer risk with increased exposure to PM $\leqslant$2.5 μm in aerodynamic diameter. In 2013, the International Agency for Research on Cancer classified ambient air pollution as a Group 1 carcinogenic to humans (1). PM, a major component of air pollution, was evaluated separately and also classified as a Group 1 carcinogen—a strong signal to the international community to take immediate action to reduce exposures.

There is also growing evidence for heritable susceptibility to lung cancer. A meta-analysis of all multiple 28 case-control and 17 cohort studies found an approximately twofold increased risk of lung cancer associated with family history (2). Risk was generally higher for relatives of people in whom lung cancer was diagnosed at a young age and when multiple family members were affected.

Studies of risk for lung cancer among relatives of never-smokers are limited. Those studies do find some increased risk, but the association is usually weaker than among smokers. Germline mutations in the TP53 gene cause the inherited Li-Fraumeni syndrome. Individuals with this syndrome are at increased risk for many cancers, including lung cancers.

Studies of families with multiple relatives affected by lung cancer identified a region on chromosome 6q23-25 harboring a susceptibility region in families that had four or more affected relatives in two or more generations (3). Haplotype studies indicate that light or heavy smoking conferred high risk, demonstrating that the individuals in these families are particularly sensitive to tobacco exposure. Rare deleterious cancer risk variants have also been described recently to significantly impact lung cancer risk (4).

As for common genetic variants and lung cancer risk, the region identified in early genome-wide association studies studies included a neuronal nicotinic acetylcholine receptor gene cluster comprising *cholinergic receptor nicotine* α *5 CHRNA5*, *CHRNA3*, and *CHRNB4* subunits. Since the 2008 studies, 51 susceptibility loci have been found for lung cancer among a variety of populations and ethnicities, each one accounting for a small to moderate proportion of risk, in smokers (5). Polygenic or genetic risk score (GRS) is a parameter that summarizes the estimated effect of many genetic variants on a person's phenotype, typically calculated as a weighted sum of disease-associated alleles. Recent evidence suggests that an individual's genetic background may inform the optimal lung cancer low-dose computed tomography screening strategy (6). To date, however, there is little information on the combined effect of genetic risk factors and environmental factors, such as ambient air pollution, while accounting for smoking.

In this issue of the *Journal*, Huang and colleagues (pp. 817–825) conducted a study using the UK Biobank cohort of over 455,000 participants, 95% of whom are of European descent (7). The study has the advantage of a large size, increasing the power to examine both main effects and gene–environment interactions while adjusting for multiple comparisons. Data on exposure to common air pollutants were available as well as data on covariates and potential confounders such as smoking and obesity. In addition to recapitulating the association between air pollution and lung cancer, the authors calculated a polygenic risk score utilizing 18 single-nucleotide polymorphisms. The higher exposure category of pollution was associated with a 63% increased risk of lung cancer and the higher GRS with a 50% increased risk. More importantly, the air pollution–lung

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