CHEST

CT-Assessed Dysanapsis and Airflow Obstruction in Early and Mid Adulthood

To the Editor:

Dysanapsis refers to an anthropometric mismatch of airway tree caliber that was initially inferred from maximal expiratory airflow variation among healthy adults.[1] CT-assessed dysanapsis among older adults is a major risk factor for COPD independent of standard risk factors (ie, tobacco exposures, air pollutants, asthma).[2] Although the mechanisms of dysanapsis are uncertain, factors that affect airway tree growth early in life[1,3] and factors that affect airway tree homeostasis later in life have been implicated.[4,5]

The present study tested the hypothesis that dysanapsis that is assessed directly by CT and its association with airflow obstruction are established by early adulthood, thus providing evidence that CT-assessed dysanapsis, at least in part, is due to early life factors.

Participants and Methods

We conducted a cross-sectional study that included men and women aged 20 to 60 years old who were enrolled from the community at the University of Iowa. Exclusion criteria included participants who reported ever smoking (≥20 cigarettes in their lifetime), any diagnosed lung disease ever or medication for breathing, contraindication to spirometry or CT, or chest CT within 1 year. All procedures were approved by ethics committees of the University of Iowa and Columbia University. All participants provided written informed consent.

CT Assessment of Dysanapsis

Participants underwent inspiratory full-lung CT[6] according to a standardized protocol (Siemens SOMATOM Force scanner: 36 milliampere-seconds, 120 kilovoltage peak, thickness 0.75 mm, CareDose, [mean ± SD radiation dose, 1.04 ± 0.22 millisievert], advanced modeled iterative reconstruction kernel; Siemens Healthineers). Cross-sectional airway lumen diameters at 19 standard anatomic locations (trachea-to-subsegments) and total lung volume were measured from CT images with the use of Apollo software (VIDA Diagnostics).[2]

Dysanapsis was quantified for each participant as the mean of airway lumen diameters in centimeters measured at 19 standard anatomic locations divided by the cube-root of total lung volume in cubic centimeters (airway-to-lung ratio). Lower values of airway-to-lung ratio indicate smaller airway tree caliber relative to lung size.

Spirometry

Spirometry was performed according to American Thoracic Society standards.[7] Postbronchodilator spirometry was not performed. Airflow obstruction was quantified as the FEV_1 divided by FVC. FEV_1/FVC *z*-score was calculated with the Global Lung Initiative equation as an alternate approach to account for age, height, and sex differences in FEV_1/FVC.[8]

Other Variables

Age, sex, and race/ethnicity were self-reported. Body height and weight were measured with the use of a standardized protocol; BMI was calculated as weight in kilograms divided by height in square meters. CT-assessed emphysema was quantified as the percent lung volume ≤950 Hounsfield units (HU) and the lower 15th percentile of cumulative lung density distribution.

Statistical Analysis

The association between airway-to-lung ratio and FEV_1/FVC was assessed by fitting a regression model adjusted for age, age squared, sex, height and height squared. Sensitivity analyses included models unadjusted, adjusted additionally for BMI, race/ethnicity, and emphysema measures, replacement of FEV_1/FVC with $FEV_1/FVC_{z\text{-score}}$, addition of an age x airway-to-lung ratio interaction term, and restriction of the sample to the 20- to 30-year age range (early adulthood).

To quantify the proportion of variation in FEV_1/FVC explained by airway-to-lung ratio, the adjusted R^2 was calculated from a regression model incrementally adjusted for age, age squared, height, height squared, sex, and airway-to-lung ratio.

Analyses were performed with the use of SAS software (version 9.4; SAS Institute Inc). A two-sided probability value of $<.05$ was considered statistically significant.

Results

Among 101 participants (Table 1), the mean ± SD age was 41 ± 13 years (20 to 30 years old: n = 30); 56% were women; the mean FEV_1/FVC was 0.80 ± 0.05, and airway-to-lung ratio was 0.031 ± 0.003.

Smaller airway-to-lung ratio was associated with significantly lower FEV_1/FVC independent of age, age squared, sex, height, and height squared (mean difference per 1-SD decrement in airway-to-lung ratio, -0.03; 95% CI, -0.04 to -0.02; $P < .0001$). Similar associations were observed in analyses unadjusted ($P = .003$); with additional adjustment for BMI ($P < .0001$); race/ethnicity ($P < .0001$); emphysema measures (percent lung volume ≤950 Hounsfield units, $P < .0001$; the lower 15th percentile of cumulative lung density distribution,

TABLE 1] Participant Characteristics

Characteristic	Measure
Participants, No.	101
Participants by age range, No.	
20-30 y	30
31-40 y	16
41-50 y	22
51-60 y	33
Age, mean ± SD, y	41 ± 13
Sex, No. (%)	
Female	56 (55)
Male	45 (45)
Height, mean ± SD, cm	171 ± 9
BMI, mean ± SD, kg/m^2	26 ± 4
Race/ethnicity, No. (%)	
Non-Hispanic White	83 (82)
Non-Hispanic Black	3 (3)
Hispanic	6 (6)
Asian	9 (9)
Spirometry, mean ± SD	
FEV_1/FVC	0.80 ± 0.05
$FEV_1/FVC_{z\text{-score}}$	−0.84 ± 0.99
CT measures	
Airway-to-lung ratio,[a] mean ± SD	0.031 ± 0.003
Percent lung volume ≤950 Hounsfield units,[b] median (interquartile range), Hounsfield units	0.04 (0.02 to 0.13)
Lower 15th percentile of cumulative lung density distribution, mean ± SD, Hounsfield units[b]	−758 ± 63

[a]Airway-to-lung ratio was quantified as the geometric mean of airway lumen diameters in centimeters measured at 19 standard locations divided by to cube root of lung volume in cubic centimeters.
[b]Percent lung volume below −950 Hounsfield units and the 15th percentile of cumulative lung density distribution are quantitative CT measures of emphysema-like lung.

$P < .0001$); restricted to participants 20 to 30 years old ($P < .001$), and $FEV_1/FVC_{z\text{-score}}$ ($P < .0001$). Age did not modify the association between airway-to-lung ratio and FEV_1/FVC (P-interaction = .17).

The combination of age and age squared accounted for 15% of the variation in FEV_1/FVC; height and height squared explained an additional 6%, and sex explained an additional 1%. The airway-to-lung ratio, when added to the aforementioned factors, explained an additional 20% of the variation in FEV_1/FVC.

Discussion

Dysanapsis quantified directly by CT as the airway-to-lung ratio was evident among non-smoking adults free of clinical lung disease aged 20 to 60 years and was associated with FEV_1/FVC independent of age, sex, and body size. Moreover, this association was evident among young adults (aged 20 to 30 years old) and did not differ by age from early-to-mid adulthood. These findings provide empiric evidence that CT-assessed dysanapsis among adults and its association with airflow obstruction, at least in part, are due to factors that occur at or before early adulthood.

The variation in airway-to-lung ratio that was observed in early-to-mid adulthood (airway-to-lung-ratio SD, 0.003) was similar to that reported in two community-based samples of older adults (the Canadian Cohort of Obstructive Lung Disease [airway-to-lung ratio SD, 0.003] and the Multi-Ethnic Study of Atherosclerosis Lung study [airway-to-lung ratio SD, 0.004]).[2] Moreover, the proportion of variation in FEV_1/FVC explained by airway-to-lung ratio in the present study (adjusted R^2, 20%) is consistent with that observed in older adult community-based samples (Canadian Cohort of Obstructive Lung Disease, 19%; Multi-Ethnic Study of Atherosclerosis Lung study, 17%).[2] The findings are also consistent with a previous lung function trajectory study that showed that a substantial proportion of older adults with COPD manifest low lung function in early adulthood[9] and that dysanapsis inferred from spirometry is evident in childhood.[3]

The present study did not assess mechanism. Although direct observation of dysanapsis among young adults in the absence of smoking or clinical lung disease implies that etiologic factors must be present at or before early adulthood,[1,3] they do not exclude subsequent contributions by factors related to airway homeostasis/injury later in life.[4,5]

Dysanapsis was initially inferred among healthy individuals with the use of spirometry,[1,3] which is a safe and reproducible procedure. In clinical populations, however, various pathophysiologies may impair maximum expiratory flow (eg, emphysema, small airways disease, dysanapsis). Imaging may facilitate clinical endotyping[2,10] by quantifying the extent of each these abnormalities in the setting of obstructive lung disease.

The cross-sectional design is a limitation, though we note that (1) longitudinal CT imaging among young adults free of clinical disease has radiation risk and (2)

the main inference that dysanapsis and its association with airflow obstruction are manifest in early adulthood does not require longitudinal design.

In summary, CT-assessed dysanapsis and its association with FEV_1/FVC are evident from early adulthood. These findings provide empiric evidence that dysanapsis and its association with airflow obstruction, at least in part, are due to factors that occur at or before early adulthood.

Motahareh Vameghestahbanati, MD
Montreal, QC, Canada
Grant T. Hiura, MPH
R. Graham Barr, MD, DrPH
New York, NY
Jessica C. Sieren, PhD
Iowa City, IA
Benjamin M. Smith, MD
Eric A. Hoffman, PhD
Iowa City, IA

AFFILIATIONS: From the Department of Medicine (M. Vameghestahbanati and B.M. Smith), McGill University; the Department of Medicine (G.T. Hiura, R.G. Barr, and B.M. Smith), Columbia University Irving Medical Center; the Departments of Radiology (J.C. Sierene and E.A. Hoffman) and Internal Medicine (E. Hoffman), University of Iowa Carver College of Medicine; and the Department of Biomedical Engineering (J.C. Sieren and E.A. Hoffman), University of Iowa.

FUNDING/SUPPORT: Supported, in part, by National Institutes of Health grants: R01-HL112986, R01-HL130506, R01-HL077612, and S10-OD018526. M. Vameghestahbanati was supported by Vanier Canada Graduate Scholarship.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: M. V. does not declare any conflict of interest. G. T. H. reports receiving grants from the National Institutes of Health (NIH). R. G. B. reports receiving grants from NIH and COPD Foundation. J. C. S. reports receiving grants from Children's Tumor foundation, Myokardia, and Noah's Hope and consulting fees from VIDA Diagnostics Inc. J. C. S.'s spouse is a former full-time employee, current paid consultant for VIDA diagnostics and has stock options in the company. She also reports receiving Honorarium & travel payment from NIH grant review and St Michaels Hospital, Canada. B. M. S. reports receiving grants from NIH, Canadian Institutes of Health (CIHR), Quebec Health Research Fund – Respiratory Health Network, the Research Institute of the McGill University Health Centre, and the Quebec Lung Association. E. A. H. reports receiving grants from the NIH; being a founder and shareholder of VIDA Diagnostics.

CORRESPONDENCE TO: Benjamin M. Smith; email: benjamin.m.smith@mcgill.ca

DOI: https://doi.org/10.1016/j.chest.2021.08.038

Acknowledgment

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Green M, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol*. 1974;37(1):67-74.
2. Smith BM, Kirby M, Hoffman EA, et al. Association of dysanapsis with chronic obstructive pulmonary disease among older adults. *JAMA*. 2020;323(22):2268-2280.
3. Martin TR, Feldman HA, Fredberg JJ, Castile RG, Mead J, Wohl ME. Relationship between maximal expiratory flows and lung volumes in growing humans. *J Appl Physiol*. 1988;65(2):822-828.
4. Rawlins EL, Okubo T, Xue Y, et al. The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium. *Cell Stem Cell*. 2009;4(6):525-534.
5. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest*. 2009;135(1):173-180.
6. Hammond E, Sloan C, Newell JD Jr, et al. Comparison of low- and ultralow-dose computed tomography protocols for quantitative lung and airway assessment. *Med Phys*. 2017;44(9):4747-4757.
7. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
8. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
9. Lange P, Celli B, Agusti A. Lung-function trajectories and chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373(16):1575.
10. Galban CJ, Han MK, Boes JL, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med*. 2012;18(11):1711-1715.