Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

MRI Shows Lung Perfusion Changes after Vaping and Smoking

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Conflicts of interest are listed at the end of this article.

See also the editorial by Kligerman in this issue.

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Background: Evidence regarding short-term effects of electronic nicotine delivery systems (ENDS) and tobacco smoke on lung ventilation and perfusion is limited.

Purpose: To examine the immediate effect of ENDS exposure and tobacco smoke on lung ventilation and perfusion by functional MRI and lung function tests.

Materials and Methods: This prospective observational pilot study was conducted from November 2019 to September 2021 (substudy of randomized controlled trial NCT03589989). Included were 44 healthy adult participants (10 control participants, nine former tobacco smokers, 13 ENDS users, and 12 active tobacco smokers; mean age, 41 years ± 12 [SD]; 28 men) who underwent noncontrast-enhanced matrix pencil MRI and lung function tests before and immediately after the exposure to ENDS products or tobacco smoke. Baseline measurements were acquired after 2 hours of substance abstinence. Postexposure measurements were performed immediately after the exposure. MRI showed semiquantitative measured impairment of lung perfusion (R_Q) and fractional ventilation (R_{FV}) impairment as percentages of affected lung volume. Lung clearance index (LCI) was assessed by nitrogen multiple-breath washout to capture ventilation inhomogeneity and spirometry to assess airflow limitation. Absolute differences were calculated with paired Wilcoxon signed-rank test and differences between groups with unpaired Mann-Whitney test. Healthy control participants underwent two consecutive MRI measurements to assess MRI reproducibility.

Results: MRI was performed and lung function measurement was acquired in tobacco smokers and ENDS users before and after exposure. MRI showed a decrease of perfusion after exposure (R_Q, 8.6% [IQR, 7.2%–10.0%] to 9.1% [IQR, 7.8%–10.7%]; $P = .03$) and no systematic change in R_{FV} ($P = .31$) among tobacco smokers. Perfusion increased in participants who used ENDS after exposure (R_Q, 9.7% [IQR, 7.1%–10.9%] to 9.0% [IQR, 6.9%–10.0%]; $P = .01$). R_{FV} did not change ($P = .38$). Only in tobacco smokers was LCI elevated after smoking ($P = .02$). Spirometry indexes did not change in any participants.

Conclusion: MRI showed a decrease of lung perfusion after exposure to tobacco smoke and an increase of lung perfusion after use of electronic nicotine delivery systems.

Online supplemental material is available for this article.

In recent years, electronic nicotine delivery systems (ENDS; also known as vaping) have been established as substitutes for traditional cigarettes and are promoted as facilitating smoking cessation by replacing tobacco smoking. Randomized control trials suggest that ENDS can effectively support smoking cessation (1,2). Contrary to nicotine replacement therapy, a higher proportion of smokers who successfully quit tobacco smoking and were supported by ENDS continue to use ENDS beyond the point of successful smoking cessation (2). Although the use of ENDS is increasing on a global scale, there are limited data regarding the short- and long-term effects of ENDS usage on the lung. In laboratory analyses, ENDS is associated with a safer risk profile than conventional cigarettes (3). However, vaping increases heart rate and blood pressure similarly to conventional tobacco smoking (4). Previous in-vitro studies showed that electronic cigarette, or e-cigarette, exposure

Abbreviations

ENDS = electronic nicotine delivery system, ESTxENDS = Efficacy, Safety and Toxicology of Electronic Nicotine Delivery Systems, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ICC = intraclass correlation coefficient, LCI = lung clearance index, R_{FV} = measured impairment of fractional ventilation, R_Q = measured impairment of lung perfusion

Summary

MRI showed a regional decrease of lung perfusion after exposure to tobacco smoke and a local increase of lung perfusion after electronic nicotine delivery systems use.

Key Results

- In tobacco smokers, a regional decrease of lung perfusion at functional MRI was shown following a single smoking session compared with the baseline measurement.
- In participants who used an electronic nicotine delivery system, a local increase of lung perfusion was shown after exposure.
- In healthy control participants, the mean difference between both measurements for perfusion impairment was −0.1% (95% CI: 1.4, −1.7).

induces inflammation and oxidative stress in pulmonary endothelium and stem cells (5,6). Different studies assessed ENDS short-term effects on lung function (7,8). Five minutes of use of ENDS reduces the fraction of exhaled nitric oxide, a volatile molecule indicating airway inflammation, and increased airway resistance (8). One study used MRI to show that inhaling nicotine-free e-cigarette aerosol transiently affected endothelial function in healthy nonsmokers (9).

Compared with lung function tests, noninvasive MRI techniques have shown a high sensitivity and reproducibility in detecting local lung perfusion and ventilation impairment, in addition to helping assess structural changes in the lung parenchyma (10,11). Several reports suggested that functional MRI of the lungs could be a sensitive marker of parenchymal alteration, depicting early changes in ventilation and perfusion not detectable with traditional lung function parameters (11,12). Functional MRI in the lungs could be a sensitive marker to help assess early changes in ventilation and perfusion that are not detectable with traditional lung functional assessment.

The aim of our study is to investigate the short-term responsiveness of ventilation and perfusion changes to vaping and tobacco smoking exposure by using nitrogen multiple-breath washout, spirometry, and functional MRI. We hypothesize that use of ENDS and tobacco smoking variably affect lung perfusion and ventilation in comparison to a healthy control group.

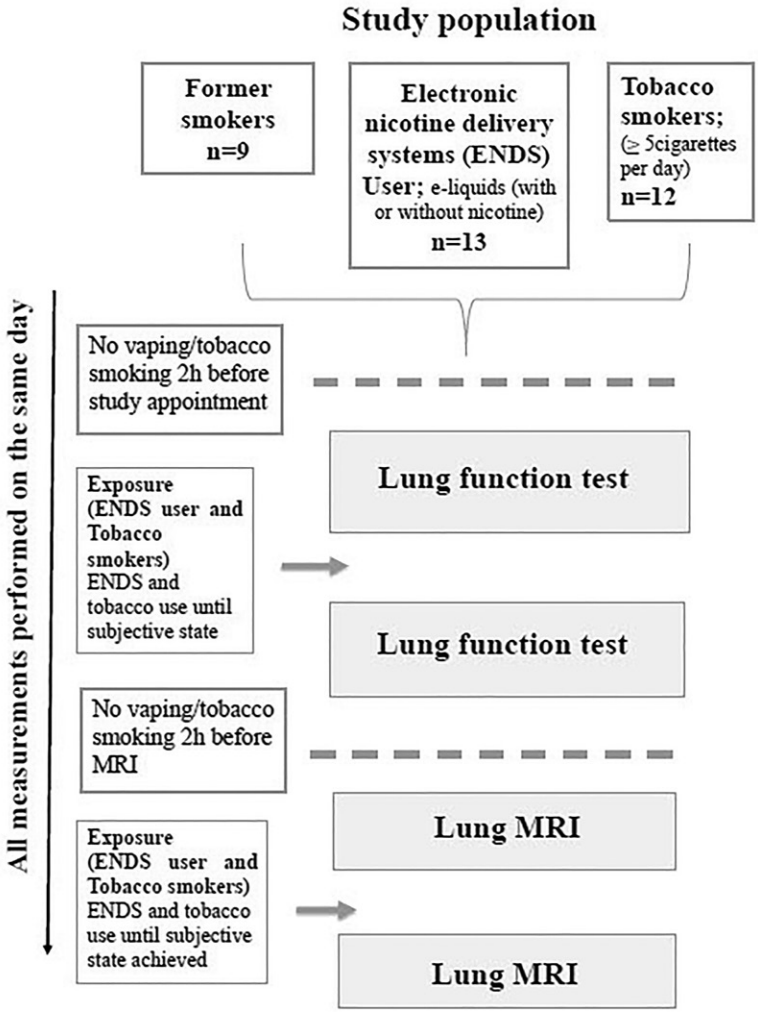

Figure 1: Study flowchart. ENDS = electronic nicotine delivery system.

Materials and Methods

Study Design and Population

This pilot study is a prospective observational study performed at the Bern University Hospital conducted between November 2019 and September 2021 and represents a substudy of the ongoing Efficacy, Safety and Toxicology of Electronic Nicotine Delivery Systems (ESTxENDS), which is a randomized controlled trial (NCT03589989). In ESTxENDS, active adult smokers consuming at least five cigarettes per day who are willing to make a serious quit attempt are randomized into usual care (control group) or usual care with ENDS and e-liquids for 6 months. Participants in the ESTxENDS trial in Bern were scheduled for their 6-month follow-up visit with the following smoking and/or use of ENDS status: former smokers (recent quitters for a maximum of 6 months and no current use of ENDS), ENDS users, and tobacco smokers. A healthy control group of never-smokers was included in Basel to assess the reproducibility of the MRI measurements. This study was approved by the local ethics committees at Bern and Basel (2017–02332 and 2018–00079, respectively). Written informed consent from all participants was obtained prior to study inclusion. All measurements in each individual participant were performed on the same day (Fig 1).

Lung Function Tests

Baseline measurements (nitrogen multiple-breath washout, spirometry, carbon monoxide diffusion capacity) in tobacco smokers and ENDS users were acquired after 2 hours of substance abstinence; 2 hours was chosen because that is the approximate plasma half-life of nicotine (13,14). Following the baseline measurements, tobacco smokers and ENDS users were instructed to smoke and vape, respectively. Immediately thereafter, study participants performed the same lung function tests again (nitrogen multiple-breath washout, spirometry, carbon monoxide diffusion capacity) to capture short-term effects. Former smokers performed repeated baseline measurements without smoking exposure.

Table 1: Parameters of Steady-State Free Precession Pulse Sequence for MRI

Parameter	Value
Repetition time (msec)	1.52
Echo time (msec)	0.68
TA per image (msec)	109
T_{int} (msec)	191
Acquisition rate (images/sec)	3.33
Flip angle α (degrees)	65
Bandwidth (Hz/pixel)	2056
Section thickness (mm)	12
Field of view (mm)	450 × 450
Matrix	128 × 128
GRAPPA factor	2

Note.— GRAPPA = generalized auto calibrating partially parallel acquisitions, TA = acquisition time, T_{int} = interval between image acquisition blocks.

MRI Measurements

Following the lung function assessment (before and after tobacco smoke or ENDS exposure), participants had to adhere to another 2-hour abstinence interval (no smoking or use of ENDS). The first MRI examination was performed in tobacco smokers and ENDS users. After undergoing MRI, participants were instructed again to smoke or vape until a subjective state of satisfaction was achieved. Immediately following this second exposure to tobacco smoke or ENDS, a second MRI examination was performed. Former smokers and healthy volunteers were measured without previous exposure.

MRI Data Acquisition

MRI examinations were performed with a 1.5-T whole-body MRI scanner (Magnetom Aera; Siemens Healthineers) by using a 12-channel thorax and a 24-channel spine receiver coil array. Functional imaging was performed by using the matrix

Table 2: General Characteristics of Study Participants

Characteristics	Healthy Control Participants (*n* = 10)	Former Smokers (*n* = 9)	ENDS Users (*n* = 13)	Tobacco Smokers (*n* = 12)
Age (y)	40 ± 9	43 ± 12	41 ± 12	42 ± 14
Sex				
No. of male participants	6	5	9	8
No. of female participants	4	4	4	4
Height (cm)	174.1 ± 8.9	171.8 ± 7.8	178.5 ± 11	176.3 ± 9.1
Weight (kg)	71.9 ± 12.4	83.3 ± 29.8	88.2 ± 20	75.5 ± 13.5
BMI (kg/m^2)	23.6 ± 2.4	27.7 ± 7.5	27.4 ± 4.6	24.4 ± 4.3
Questionnaire before measurement				
No. of cigarettes smoked per day	NA	NA	NA*	12.2 ± 7.9
No. of vaping puffs per day				
<1–5 puffs	NA	NA	0 (0)	NA*
6–50 puffs			5 (38)	
>50 puffs			8 (62)	
Participants vaping with nicotine per day				
Yes	NA	NA	9 (69)	NA
No			4 (31)	
Vaping with flavor/day				
Yes	NA	NA	9 (69)	NA
No	NA		4 (31)	
Questionnaire after exposure				
Length of exposure (min)	NA	NA	4.9 ± 1.1	6.8 ± 3.6
No. of vaping puffs or cigarettes	NA	NA	19 ± 13	1.6 ± 1.2

Note.—Mean data are ± standard deviation; data in parentheses are percentages. BMI = body mass index, ENDS = electronic nicotine delivery system, NA = not applicable.

* Five electronic nicotine delivery system users were dual users regularly vaping and occasionally smoking (fewer than two cigarettes per day); and two tobacco smokers were dual users regularly smoking and occasionally vaping (fewer than two puffs per day); for details, see Appendix E1 (online).

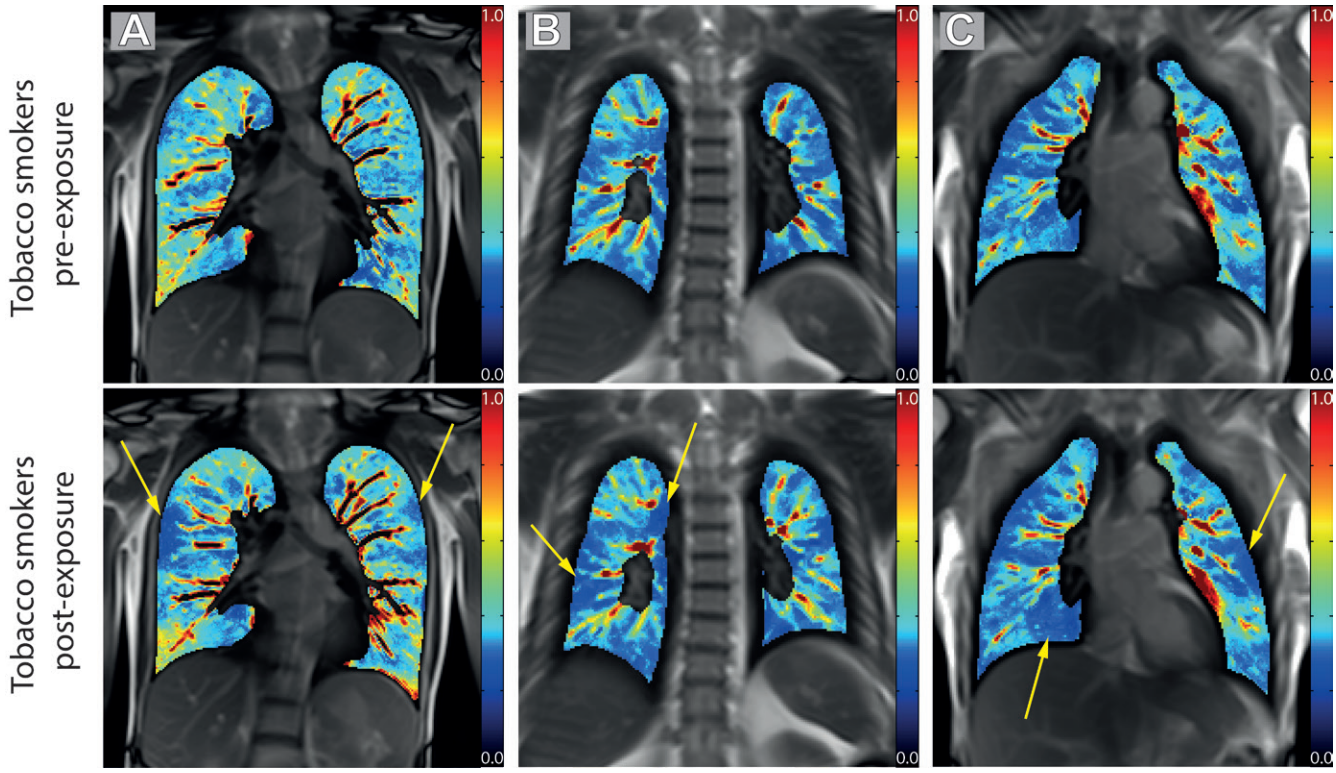

Figure 2: **(A–C)** Example of pulmonary perfusion images obtained by using noncontrast-enhanced matrix pencil MRI in three different tobacco smokers before exposure (pre-exposure) and after exposure (post-exposure). The images before and after exposure were acquired at corresponding coronal section locations. Arrows indicate lung regions with decreased regional perfusion after the exposure to nicotine. Red corresponds to high values of ventilation amplitude and perfusion amplitude, whereas blue corresponds to low values.

pencil decomposition free-breathing MRI technique without contrast agent administration (15,16). The matrix pencil MRI relies on dynamic free-breathing ultrafast balanced steady-state free precession lung image acquisitions and provides regional ventilation and perfusion information from a single acquisition series (17). Main parameters of the ultrafast balanced steady-state free precession pulse sequence are given in Table 1. The segmented areas are processed voxelwise by using a matrix pencil decomposition method in combination with a linear least square analysis to generate fractional ventilation and perfusion maps. Fractional ventilation maps reflect changes of the lung parenchyma density during respiration, whereas the perfusion maps reflect the amplitude of signal modulation caused by the pulsatile blood flow. For each subject, the lungs were automatically segmented on the calculated fractional ventilation and perfusion maps by using an artificial neural network (18,19). MRI postprocessing was fully automatized and required no manual interaction. The robustness of the automatized segmentation versus manual segmentation was recently assessed (17). Detailed information about MRI data evaluation is described in Appendix E1 (online). Software and protocols were the same at both sites.

MRI Data Evaluation

Voxel distributions of the segmented lung regions in fractional ventilation and perfusion maps were used to estimate threshold values indicating a functional impairment (20). Primary outcomes were percentage of the lung volume with impaired fractional ventilation (R_{FV}) and measured impairment of lung perfusion (R_Q). Morphologic scans were chosen on the basis of published standard MRI protocols for chest examinations (21). Structural changes in the lung parenchyma were assessed on the proton MRI images by two independent reviewers; discrepancies were resolved by consensus. Observers were blinded to the participants' groups.

Lung Function Assessment

Nitrogen multiple-breath washout was performed with a commercially available device (Exhalyzer D; Eco Medics) according to consensus guidelines (22). The primary outcome was the lung clearance index (LCI). Spirometry (Jaeger MasterScreen; CareFusion) was conducted according to the official clinical practice guideline of the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Society (23). Primary outcomes were forced expiratory volume in 1 second (FEV_1) and the FEV_1-to–forced vital capacity (FVC) ratio. Diffusion capacity of the lungs for carbon monoxide was assessed as recommended (24–26).

Statistical Analysis

Continuous variables were skewed and described by using nonparametric estimates. Differences between measurements were compared with paired Wilcoxon signed-rank test, and differences between groups were compared with unpaired Mann-Whitney test. Participants who used ENDS were stratified in groups of those who used nicotine-containing e-liquids and those who used nicotine-free e-liquids. Post hoc analysis was

Table 3: Functional MRI Imaging Values of Study Participants Before and After Exposure

Parameter	Measurement 1	Measurement 2	*P* Value
Healthy control participants (*n* = 10)			
Impairment of perfusion (%)	8.4 (7–9.6)	8.2 (7.8–9.8)	.50
Impairment of ventilation (%)	11.2 (9.1–12.6)	11.2 (10.1–13.9)	.80
Former smokers* (*n* = 9)			
Impairment of perfusion (%)	7.9 (7–9.7)	8.1 (7.6–9.4)	.44
Impairment of ventilation (%)	12.9 (11.9–13.6)	12.5 (12.2–13.6)	.37
ENDS users (*n* = 13)			
Impairment of perfusion (%)	9.7 (7.1–10.9)	9.0 (6.9–10)	.01
Impairment of ventilation (%)	11.8 (11.3–13.4)	12.7 (11.4–13.3)	.38
Tobacco smokers (*n* = 12)			
Impairment of perfusion (%)	8.6 (7.2–10)	9.1 (7.8–10.7)	.03
Impairment of ventilation (%)	11.9 (9.9–14.2)	12.2 (10.3–13.7)	.31

Note.—Data are presented as medians; data in parentheses are IQRs. Measurement 1 is before exposure; measurement 2 is after exposure. Continuous variables between the measurements were compared with Wilcoxon signed rank test.

* Healthy control participants (never smokers) and former smokers performed all measurements without exposure.

performed by comparing LCI before exposure (based on all nitrogen multiple-breath washout tests with the LCI from the first nitrogen multiple-breath washout test) and directly after exposure. Associations between functional indexes from MRI and lung function before and after exposure were examined graphically and were quantified by using the Spearman correlation coefficient. The agreement over two measurements was assessed by using intraclass correlation (ICC) coefficients and Bland Altman plot. ICC is defined as very good (ICC, >0.8), good (ICC, 0.6–0.8) and moderate (ICC, 0.4–0.6) (27). Upper limit of normal LCI was calculated with published data for healthy adults (ie, mean + 1.6 × SD) (28). *P* values less than .05 were considered to indicate statistical significance. Analyses were performed by using software (StataTM Stata Statistical Software, release 13, StataCorp; Matlab 2012b, MathWorks; and GraphPad Prism, GraphPad Software).

Results

Study Population

A total of 44 adult participants (28 men; mean age, 41 years ± 12 [SD]) were enrolled. Seven tobacco smokers consumed more than 10 cigarettes per day. Eight ENDS users vaped more than 50 puffs per day. Nine ENDS users were using the ENDS device provided to participants at the ESTxENDS trial and four participants (30.7%) were not vaping nicotine-containing e-liquids (Table E1 [online]). Characteristics of study participants are given in Table 2.

All 44 participants were able to perform functional MRI at both points. Functional lung MRI was performed for an average of 6.3 minutes (range, 5.3–9.8 minutes). All morphologic scans and functional measurements were of good diagnostic image quality. Morphologic imaging included an ultrashort echo time sequence without depiction of extensive parenchymal abnormalities (eg, lung fibrosis).

Exposure

Exposure duration was set for the minimum time required to smoke at least one cigarette or use an ENDS product (ie, use of nicotine-containing e-liquids and nicotine-free e-liquids). On average, 1.6 cigarettes ± 1.2 were smoked for 6.8 minutes ± 3.6. In the ENDS users' group, 19 ± 13 puffs were vaped for 4.9 minutes ± 1.1 (Table 2). Measurements were performed directly afterward. Common symptoms after exposure were dry mouth (*n* = 6; 24%) and cough (*n* = 5; 20%).

Lung Function Changes at MRI and Lung Functional Assessment in All Groups

Local perfusion decreased in tobacco smokers after exposure (R_Q, 8.6% [IQR, 7.2%–10.0%] to 9.1% [IQR, 7.8%–10.7%]; *P* = .03 compared with the baseline measurement) (Fig 2, Table 3). However, local perfusion increased in participants who used ENDS after exposure (R_Q, 9.7% [IQR, 7.1%–10.9%] to 9.0% [IQR, 6.9%–10.0%]; *P* = .01) (Figs 3, 4). Subsequently, we stratified participants in the following groups: participants who used nicotine-containing e-liquids (*n* = 9; 69%) and participants who used nicotine-free e-liquids (*n* = 4; 31%). Local perfusion increased after exposure in participants who used ENDS with nicotine containing e-liquids (R_Q, 9.7% [IQR, 8.4%–10.7%] to 8.0% [IQR, 7.3%–9.9%]; *P* = .01). No change in perfusion was detected in the group of participants who used nicotine-free e-liquids (8.3% [IQR, 5.2%–11.9%] to 7.8% [IQR, 5.2%–10.5%]; *P* = .5; Fig E1 [online]). R_{FV} did not change in any group (Fig E2 [online]).

The LCI was elevated in five of nine former smokers (56%), five of 13 ENDS users (38%), and six of 12 tobacco smokers (50%) before exposure (Table 4). Spirometry and diffusion capacity of the lungs for carbon monoxide indexes did not show any obstructive lung disease, abnormal dynamic volumes according to *z*-scores, or other impairment in tobacco smokers and ENDS users. No change in lung function compared with baseline was observed in the stratified participants who used nicotine-containing e-liquids and who used nicotine-free e-liquids (Table E2 [online]). After exposure, the mean of the LCI (on the basis of the sum of repeated nitrogen multiple-breath washout measurements) did not change for any group. However, the post hoc analysis showed that the initial first LCI measurement directly after exposure increased in tobacco smokers from 8.3 (IQR, 8.0–8.8) to 9.5 (IQR, 8.3–11.3) (*P* = .02) (Fig 5),

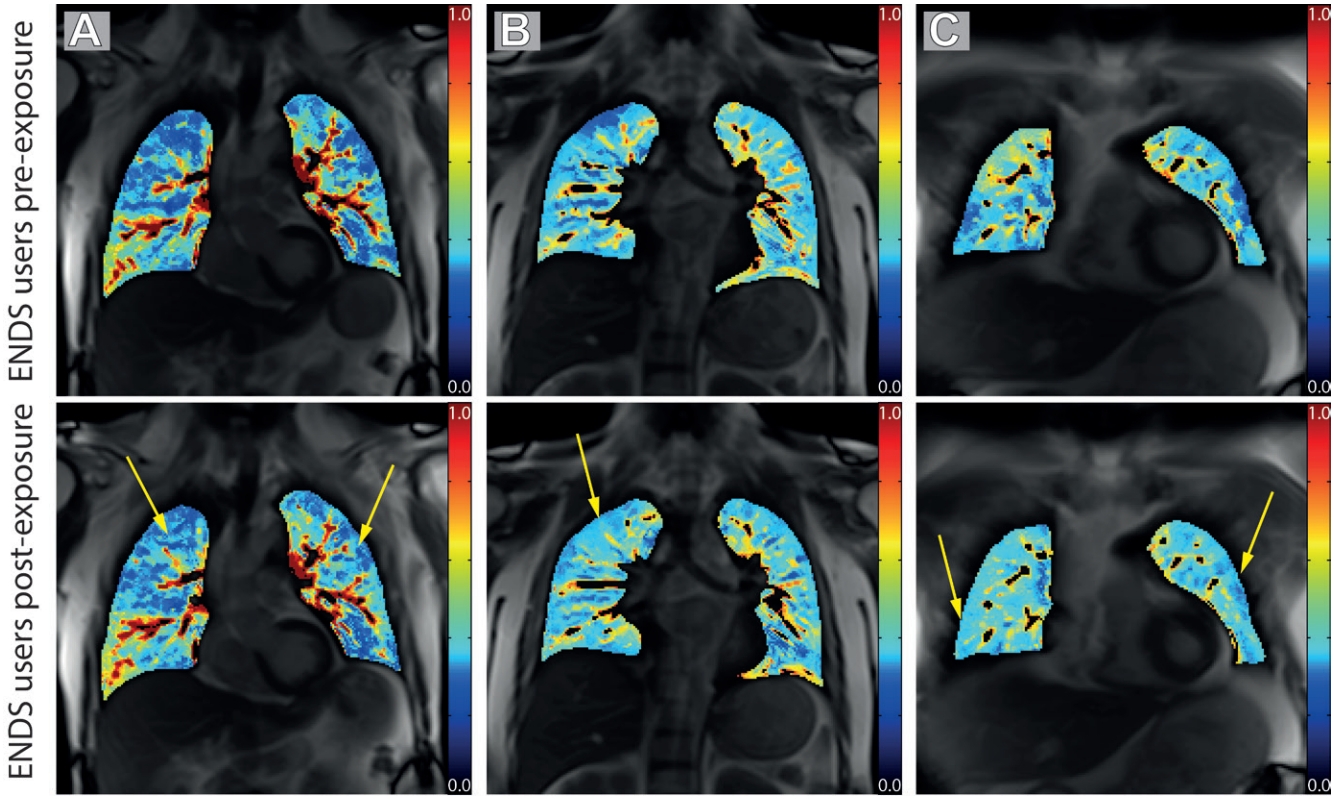

Figure 3: **(A–C)** Example of pulmonary perfusion images obtained by using noncontrast matrix pencil MRI in three electronic nicotine delivery system (ENDS) users before exposure (pre-exposure) and after exposure (post-exposure). The images before and after exposure were acquired at corresponding coronal section locations. The arrows indicate lung regions with increased regional perfusion after the exposure. Red corresponds to high values of ventilation amplitude and perfusion amplitude, whereas the blue color corresponds to low values.

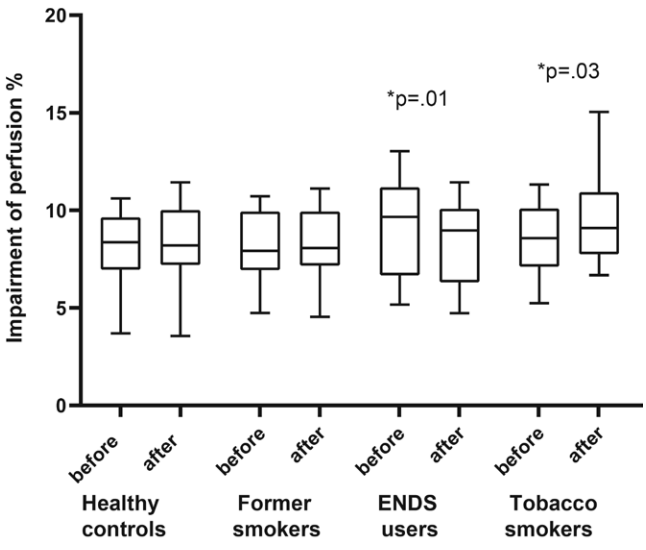

Figure 4: Box and whisker plot of impairment of perfusion in all participants. Electronic nicotine delivery system (ENDS) users and tobacco smokers performed measurements before and after exposure. Former smokers and healthy control participants performed measurements at MRI without exposure. * = Significant *P* value.

indicating increased global ventilation inhomogeneity. In all groups, there were no systematic changes in spirometry and diffusion capacity of the lungs for carbon monoxide indexes between both measurements (Table 4).

Correlation between Functional MRI and Lung Function

In tobacco smokers and ENDS users, the extent of R_Q was between 5% and 13.0% before exposure and 5% and 15.0% after exposure, respectively. In tobacco smokers, we suggested a correlation between R_Q and LCI after exposure (r = 0.65; P = .02) (Fig 6). The extent of impaired ventilation relative to lung volume (ie, R_{FV}) in tobacco smokers and ENDS users ranged between 7% and 18% before exposure and 6% and 17% after exposure, respectively. R_{FV} showed no correlation with LCI after exposure in in tobacco smokers and ENDS users (r = 0.35, P = .27; and r = 0.37, P = .21, respectively). We found no correlation between FEV_1 or FEV_1-to-FVC ratio and functional MRI indexes in any group.

Reproducibility of MRI Measurements

Agreement measured by ICC in former smokers ranged between very good and good for lung function and MRI indexes. The ICC for R_{FV} between two measurements in the same individual was very good in former smokers (ICC, 0.9). The ICC for R_Q was good in former smokers (ICC, 0.6). The ICC for LCI was very good in former smokers (ICC, 0.9). In healthy control participants, the ICC was very good for MRI indexes. The ICC for R_{FV} and R_Q between two measurements in the same participant was very good (ICC, 0.9). In healthy control participants, the mean difference between both measurements for perfusion impairment was −0.1% (95% CI: 1.4, −1.7). For ventilation impairment, the mean difference was −0.02% (95% CI: 1.9, −2.0) (Fig 7).

Table 4: Lung Function Values of Study Participants

Parameter	Measurement 1	Measurement 2	*P* Value
Former smokers (n = 9)*			
LCI lung turnover	8.3 (7.3–10.4)	9.5 (7.3–10.2)	.59
LCI lung turnover one test†	8.3 (7.3–10.4)	9.6 (7.3–10.2)	.81
FEV_1			
Percent predicted	95 (86–95)	94 (85–96)	.43
Z score	−0.5 (−0.96 to −0.42)	−0.5 (−1 to −0.4)	.51
FEV_1-to-FVC ratio			
Percent predicted	93 (88–101)	93 (93–103)	.95
Z score	−0.4 (−0.9 to 0.3)	−1.0 (−1.0 to 0.4)	.26
DLco percent predicted	96 (86–100)	94 (90–101)	.43
ENDS users (n = 13)			
LCI lung turnover	7.4 (7.1–8.6)	8.0 (7.7–8.7)	.75
LCI lung turnover one test†	7.4 (7.1–8.6)	8.1 (7.5–8.5)	.22
FEV_1			
Percent predicted	102 (92–106)	101 (89–106)	.97
Z score	0.1 (−0.7 to 0.4)	0.1 (−0.9 to 0.4)	.92
FEV_1-to-FVC ratio			
Percent predicted	97 (92–102)	95 (95–100)	.42
Z score	−0.4 (−1 to 0.3)	−0.6 (−0.7 to 0.04)	.46
DLco percent predicted	97 (82–104)	93 (92–104)	.23
Tobacco smokers (n = 12)			
LCI lung turnover	8.3 (8.0–8.8)	8.8 (7.9–9.3)	.53
LCI lung turnover one test†	8.3 (8.0–8.8)	9.5 (8.3–11.3)	.02
FEV_1			
Percent predicted	96 (86.5–108.5)	95 (87.5–106)	.2
Z score	−0.3 (−1.1 to 0.7)	−0.4 (−1.0–0.5)	.24
FEV_1-to-FVC ratio			
Percent predicted	96 (92.5–99.5)	97 (94–98.5)	.30
Z score	−0.5 (−0.9 to −0.04)	−0.3 (−0.8 to −0.1)	.24
DLco percent predicted	97 (93–105.50)	99 (89.5–106)	.6

Note.—Data are presented as medians; data in parentheses are IQRs. Continuous variables between the measurements were compared with Wilcoxon signed rank test. Measurement 1 is before exposure; measurement 2 is after exposure. DLco = diffusion capacity of the lungs for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LCI = lung clearance index.

* Former smokers performed all measurements without exposure. Of note, healthy control participants performed only two consecutive MRI measurements.

† Comparison of the mean LCI from measurement 1 with the first LCI test from measurement 2.

Discussion

We examined the intra-individual short-term responsiveness of lung perfusion and ventilation after the use of electronic nicotine delivery systems (ENDS) and tobacco smoking assessed by using a matrix pencil MRI technique and lung function tests. By using noncontrast-enhanced functional lung MRI, perfusion decreased in tobacco smokers after exposure (measured impairment of lung perfusion [R_Q], 8.6% [IQR, 7.2%–10.0%] to 9.1% [IQR, 7.8%–10.7%]; P = .03) compared with the baseline measurement. However, perfusion increased after exposure in participants who used ENDS (R_Q, 9.7% [IQR, 7.1%–10.9%] to 9.0% [IQR, 6.9%–10.0%]; P = .01). Among participants who used nicotine-free e-liquids, no systematic change in R_Q was detected (R_Q, 8.3% [IQR, 5.2%–11.9%] to 7.8% [IQR, 5.2%–10.5%]; P = .5). In healthy control participants, the intervisit reproducibility for measured impairment of fractional ventilation and R_Q was very good, and the relatively small systematic changes detected in our study were considered reliable. Spirometry-derived forced expiratory volume in 1 second–to–forced vital capacity ratio *z*-scores did not systematically change after exposure and was normal at the baseline in tobacco smoker and ENDS users. However, lung clearance index from the nitrogen multiple-breath washout was elevated in five of nine former smokers (56%), five of 13 ENDS users (38%), and six of 12 tobacco smokers (50%) at baseline. This indicated increased ventilation inhomogeneity related to the small airways disease, potentially caused by smoking exposure.

After exposure, the mean LCI (based on the sum of repeated nitrogen multiple-breath washout measurements) did not change for any group. However, the post hoc analysis showed that the initial first LCI measurement directly after exposure increased (higher ventilation inhomogeneity) in tobacco smokers (LCI, 8.3 [IQR, 8.0–8.8] and 9.5 [IQR, 8.3–11.3], respectively; P = .02). Overall, the correlation between perfusion impairment and LCI in tobacco smoking suggested that tobacco smoking induces a short-term change in lung function. This finding was not confirmed by the R_{FV} at MRI. This could be attributable to the MRI method itself, where the ventilation maps are an extrapolation from the changes of signal intensities from the perfusion maps.

Our results indicated opposite effects of tobacco smoke and ENDS aerosol on perfusion impairment assessed at functional MRI. We demonstrated a decrease of local perfusion after tobacco smoking. This agrees with previous studies, showing ventilation and perfusion mismatch in response to smoking one cigarette by measuring the blood flow in the pulmonary capillaries (29). In tobacco smoking products, nicotine is one major constituent that is a strong alkaloid (30). As a result, peripheral vasoconstriction, tachycardia, and elevated blood pressure may be observed after nicotine intake (31). Another study demonstrated acute vasoconstriction of the epicardial coronary

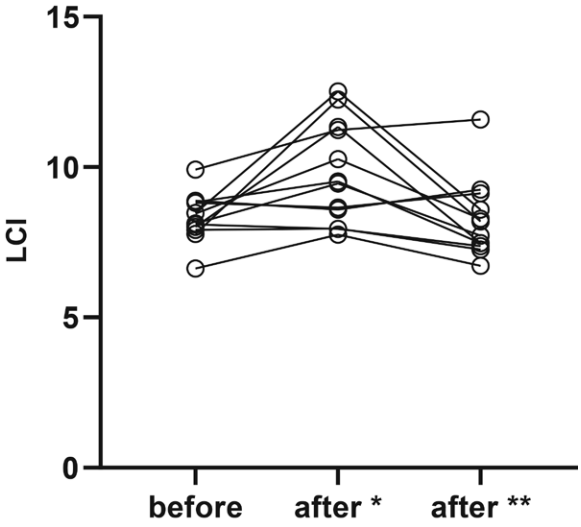

Figure 5: Graph of short-term change of lung clearance index (LCI) before and after tobacco smoking. LCI was assessed at nitrogen multiple-breath washout to capture ventilation inhomogeneity and spirometry to assess airflow limitation. After exposure, the mean LCI did not change in participants after they smoked tobacco. However, the post hoc analysis showed that LCI from the first initial nitrogen multiple-breath washout measurement after exposure ($P = .02$) increased, indicating increased global ventilation inhomogeneit y. * = First initial nitrogen multiple-breath washout measurement after exposure. ** = Mean of all nitrogen multiple-breath washout measurements.

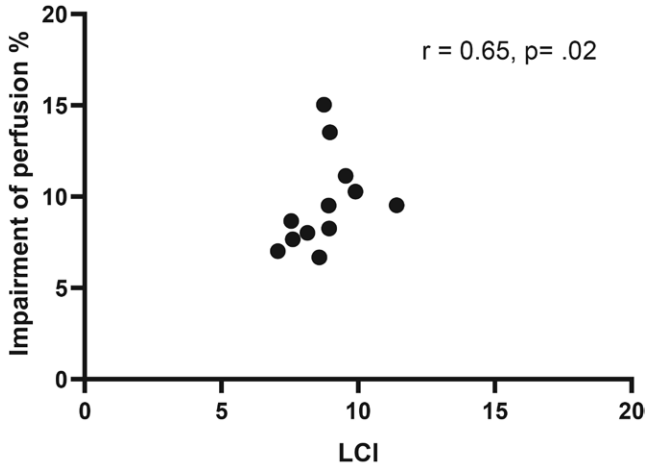

Figure 6: Plot of correlation between lung clearance index (LCI) and perfusion impairment of the lung in percentage. LCI was assessed at nitrogen multiple-breath washout to capture ventilation inhomogeneity and spirometry to assess airflow limitation. Participants were tobacco smokers, and the correlation was determined after exposure. In tobacco smokers, we suggest a correlation between perfusion and LCI after exposure ($r = 0.65$; $P = .02$).

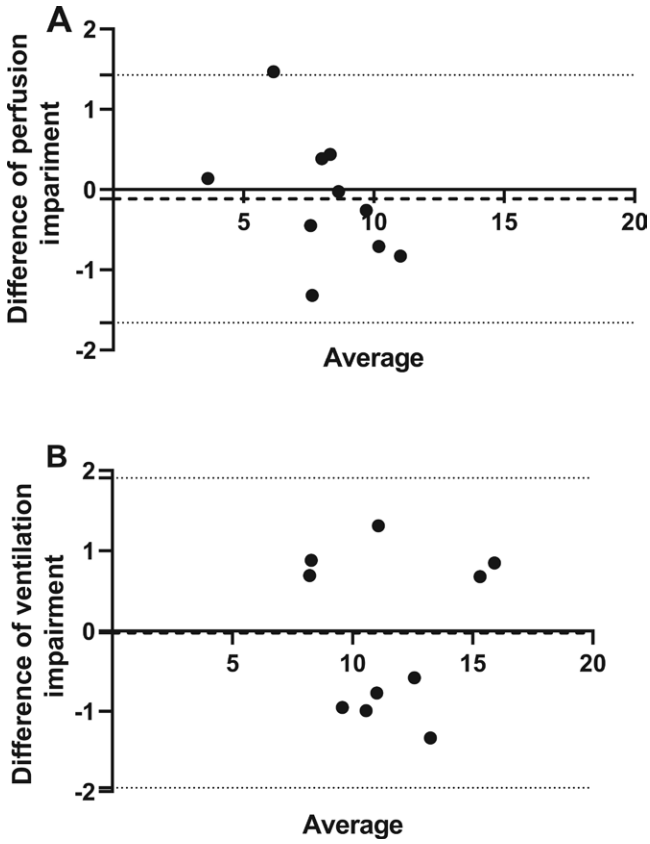

Figure 7: Bland-Altman plots for intertest agreement of two consecutive MRI measurements, the **(A)** perfusion impairment and **(B)** ventilation impairment, in healthy control participants (never-smokers; $n = 10$). Ninety-five percent limits of agreement are shown as dotted lines and mean differences are displayed as dashed lines.

arteries and reduced coronary flow reserve after smoking (32). However, we found an increase of local perfusion with functional MRI after exposure to ENDS products. We stratified a priori the participants into two groups: one who used nicotine-containing e-liquids and the other group who used e-liquids without nicotine. In participants who used nicotine-containing e-liquids, we observed an increase of local perfusion impairment in functional MRI. Flavorings can alter airway responsiveness in murine models (33). Sixty-nine percent of participants in our study had different flavors in their e-liquids. Whether short-term perfusion changes in the ENDS users in our study is caused by additives remains unexplored and requires further investigation. To our knowledge, long-term consequences of perfusion changes in healthy individuals are unknown and should be investigated.

With findings that were different than what we found in our data, Caporale et al (9) found a decrease in luminal flow-mediated dilation and reactive hyperemia peak velocity after vaping in the thigh arterial vasculature, which is a different perfusion territory that serves the skeletal muscle and has a high resistive index with biphasic flow at rest. Measurements were on the basis of the peripheral vascular reactivity (femoral artery). In our study, we used a dynamic free-breathing multisection ultrafast balanced steady-state free precession acquisition in the whole lung, providing regional fractional ventilation and perfusion maps. It remains unclear why different effects on the vessels were observed on pulmonary compared with peripheral vessels in the lungs. Similar to our study, a recent study found increased ventilation and perfusion mismatch in people who vape. Kizhakke et al (34) used oxygen-enhanced MRI and had results that were comparable to ours but in a study population of younger participants. Instead of the oxygen-enhanced MRI method, we used the matrix pencil MRI technique, which did not require any gas

or contrast media application. Both techniques indicated that ENDS liquids and their constituents affect lung perfusion.

This is a small sample size, and these data need to be confirmed in a larger study. Our study design allowed for an observation period that was created to noninvasively standardize the study protocol while also allowing participants to enlist without concerns of nicotine deprivation. Considering the relatively short half-live of nicotine (approximately 2 hours), this approach guaranteed complete adherence to the protocol by all participants. A critical point is the overlap of the results in the intergroup comparison. However, our aim was to detect intraindividual changes of lung perfusion and ventilation, yielding significant results. In addition, differences in the outcome values could be influenced by a large number of variables (eg, age, sex, weight, degree of emphysema, and heart disease).

In conclusion, short-term perfusion changes after use of electronic nicotine delivery systems and tobacco smoke exposure can be sensitively detected by functional MRI. Perfusion impairment at MRI did correlate with ventilation inhomogeneity (lung clearance index) and was altered after tobacco smoking. Lung ventilation at MRI showed no changes after exposure to nicotine. These preliminary results suggest that MRI indexes may be considered as a noninvasive test to complement pulmonary function testing in this setting.

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References

1. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2020;10(10):CD010216.
2. Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med 2019;380(7):629–637.
3. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf 2014;5(2):67–86.
4. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. J Am Coll Cardiol 2016;67(23):2802–2803.
5. Kuntic M, Oelze M, Steven S, et al. Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2). Eur Heart J 2020;41(26):2472–2483.
6. Schweitzer KS, Chen SX, Law S, et al. Endothelial disruptive proinflammatory effects of nicotine and e-cigarette vapor exposures. Am J Physiol Lung Cell Mol Physiol 2015;309(2):L175–L187.
7. Kotoulas SC, Pataka A, Domvri K, et al. Acute effects of e-cigarette vaping on pulmonary function and airway inflammation in healthy individuals and in patients with asthma. Respirology 2020;25(10):1037–1045.
8. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest 2012;141(6):1400–1406.
9. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli FW. Acute Effects of Electronic Cigarette Aerosol Inhalation on Vascular Function Detected at Quantitative MRI. Radiology 2019;293(1):97–106.
10. Nyilas S, Bauman G, Pusterla O, et al. Structural and functional lung impairment in primary ciliary dyskinesia. Assessment with magnetic resonance imaging and multiple breath washout in comparison to spirometry. Ann Am Thorac Soc 2018;15(12):1434–1442.
11. Nyilas S, Bauman G, Pusterla O, et al. Ventilation and perfusion assessed by functional MRI in children with CF: reproducibility in comparison to lung function. J Cyst Fibros 2019;18(4):543–550.
12. Ebner L, Kammerman J, Driehuys B, Schiebler ML, Cadman RV, Fain SB. The role of hyperpolarized ^{129}xenon in MR imaging of pulmonary function. Eur J Radiol 2017;86:343–352.
13. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 2009;49(1):57–71.
14. Chaumont M, van de Borne P, Bernard A, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. Am J Physiol Lung Cell Mol Physiol 2019;316(5):L705–L719.
15. Bauman G, Puderbach M, Deimling M, et al. Non-contrast-enhanced perfusion and ventilation assessment of the human lung by means of fourier decomposition in proton MRI. Magn Reson Med 2009;62(3):656–664.
16. Bauman G, Bieri O. Matrix pencil decomposition of time-resolved proton MRI for robust and improved assessment of pulmonary ventilation and perfusion. Magn Reson Med 2017;77(1):336–342.
17. Bauman G, Pusterla O, Bieri O. Ultra-fast Steady-State Free Precession Pulse Sequence for Fourier Decomposition Pulmonary MRI. Magn Reson Med 2016;75(4):1647–1653.
18. Andermatt S, Pezold S, Cattin P. Multi-dimensional Gated Recurrent Units for the Segmentation of Biomedical 3D-Data. In: Carneiro G, Mateus D, Peter L, et al, eds. Deep Learning and Data Labeling for Medical Applications. DLMIA 2016, LABELS 2016. Lecture Notes in Computer Science, vol 10008. Cham, Switzerland: Springer, 2016; 142–151.
19. Willers C, Bauman G, Andermatt S, et al. The impact of segmentation on whole-lung functional MRI quantification: Repeatability and reproducibility from multiple human observers and an artificial neural network. Magn Reson Med 2021;85(2):1079–1092.
20. Nyilas S, Bauman G, Sommer G, et al. Novel magnetic resonance technique for functional imaging of cystic fibrosis lung disease. Eur Respir J 2017;50(6):1701464.
21. Puderbach M, Hintze C, Ley S, Eichinger M, Kauczor HU, Biederer J. MR imaging of the chest: a practical approach at 1.5T. Eur J Radiol 2007;64(3):345–355.
22. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J 2013;41(3):507–522.
23. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319–338.
24. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49(1):1600016 [Published correction appears in Eur Respir J 2018;52(5):1650016.].
25. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26(3):511–522.
26. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and Euro-

pean Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019;200(8):e70–e88.
27. Portney L, Watkins M. Foundations of clinical research: application to practice. Stamford, Conn: Appleton & Lange, 1993.
28. Nyilas S, Schreder T, Singer F, et al. Multiple breath washout: A new and promising lung function test for patients with idiopathic pulmonary fibrosis. Respirology 2018;23(8):764–770.
29. Rieben FW. Acute ventilation-perfusion mismatching resulting from inhalative smoking of the first cigarette in the morning. Clin Investig 1992;70(3-4):328–334.
30. Langone JJ, Gjika HB, Van Vunakis H. Nicotine and its metabolites. Radioimmunoassays for nicotine and cotinine. Biochemistry 1973;12(24):5025–5030https://doi.org/10.1021/bi00748a032.
31. Narkiewicz K, van de Borne PJ, Hausberg M, et al. Cigarette smoking increases sympathetic outflow in humans. Circulation 1998;98(6):528–534.
32. Quillen JE, Rossen JD, Oskarsson HJ, Minor RL Jr, Lopez AG, Winniford MD. Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. J Am Coll Cardiol 1993;22(3):642–647.
33. Chapman DG, Casey DT, Ather JL, et al. The Effect of Flavored E-cigarettes on Murine Allergic Airways Disease. Sci Rep 2019;9(1):13671.
34. Kizhakke Puliyakote AS, Elliott AR, Sá RC, Anderson KM, Crotty Alexander LE, Hopkins SR. Vaping disrupts ventilation-perfusion matching in asymptomatic users. J Appl Physiol (1985) 2021;130(2):308–317.
35. Sandkühler R, Jud C, Pezold S, Cattin PC. Adaptive graph diffusion regularisation for discontinuity preserving image registration. In: Klein S, Staring M, Durrleman S, Sommer S, eds. Biomedical Image Registration. WBIR 2018. Lecture Notes in Computer Science, vol 10883. Cham, Switzerland: Springer, 2018; 24–34.