hoc test odds would be 0.076 [0.25 × 0.303] and corresponding to a *post hoc* test probability of 7.6% [0.076/(1 + 0.076)]) (8).

We designed the classifier to assess organ quality for donor pool expansion strategies, to identify organs for possible rehabilitation on *ex vivo* lung perfusion, and to identify potential targets for directed therapies in clinical trials. The validation of the pathways identified in this transcript panel highlights the importance of the innate immune system in the development of PGD and identifies its constituent genes as potential therapeutic targets. This work builds on previous work identifying associated pathways and developing clinical predictors important in PGD to assess risk prior to procurement to facilitate decision making for potential therapeutics and advanced surgical therapies (3, 4, 7).

Although these results are promising, there are limitations to consider. The cohort sample size was small, therefore reducing overall power. Nonetheless, this study represents a temporal validation in tissue of prior findings in blood and BAL using a conventional machine learning approach. Tissue biopsy is an invasive procedure with associated risks. We validated our classifier in tissue to ensure that all lung compartments were sampled (endothelial, epithelial, and lymphoid), and we acknowledge that further refinement will be necessary to scale to clinical practice. Additionally, translating gene expression prediction to the bedside will require development of point-of-care technologies using abbreviated gene sets, such as those using microfluidics (9). As this study cohort did not overlap with our prior cohorts, we were unable to assess interactions between blood, BAL, and tissue compartments. Although this work is supported by several other studies that show association (3, 4, 10), additional validation will be necessary to confirm discriminant and diagnostic validity and generalizability.

In summary, we have demonstrated that transcript analysis of donor lung tissue, using an innate immunity pathway classifier, can be used in conjunction with clinical variables to predict PGD with excellent discrimination and precision. With the ability to identify organ risk, this panel has the potential to alter future PGD clinical trial designs and lead to the development of precision medical approaches. As PGD drives morbidity and mortality associated with lung transplant, further research in this area has the potential to improve outcomes following transplantation. ∎

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Smoking Pattern in Men and Women: A Possible Contributor to Sex Differences in Smoke-related Lung Diseases

To the Editor:

Chronic obstructive pulmonary disease (COPD) due to cigarette smoking is a major cause of morbidity and mortality worldwide. Given

Table 1. Baseline Characteristics of the Study Population

Variable	Women (n = 14)	Men (n = 14)	P Value
Age, yr	46 ± 11	41 ± 9	0.182
Height, m	167 ± 5	167 ± 5	0.944
Weight, kg	67 ± 7	70 ± 8	0.381
BMI, kg/m^2	24 ± 3	25 ± 3	0.420
Pack-years	23 ± 8	25 ± 9	0.464
FEV_1, % pred.	101 ± 9	104 ± 8	0.371
FVC, % pred.	107 ± 8	103 ± 7	0.232
FEV_1/FVC, % pred.	107 ± 0.2	112 ± 0.2	0.533
ITGV, % pred.	118 ± 11	112 ± 19	0.244
TLC, % pred.	106 ± 14	99 ± 10	0.142
SmoV, % VC	24 ± 3	25 ± 3	0.352
SmoIT, s	1.0 ± 0.2	1.1 ± 0.2	0.533

Definition of abbreviations: BMI = body mass index; ITGV = inspiratory thoracic gas volume; pred. = predicted; SmoIT = smoking inhalation time; SmoV = smoking volume.
Statistical analyses included one-way ANOVA tests for continuous variables, followed by pairwise comparisons using Student's *t* tests or Mann-Whitney *U* tests. Pairwise comparisons showed no significant differences in the percentage of men, ages, pack-years, pulmonary function, and anthropometric data, between men and women. Data are presented as mean ± SD.

the same amount of exposure to tobacco smoke, women are more likely to develop more severe airflow limitation at an earlier age than men (1). Importantly, at all stages of COPD severity, men have more severe computed tomography–defined emphysema than women (2). Also, the prevalence odds ratio for screen-detectable lung cancer (conditional on age and smoking history) indicates that women have an increased susceptibility to tobacco carcinogens but have a lower rate of fatal outcome of lung cancer compared with men (3).

So far, the reasons why women differ from men in cigarette smoking susceptibility and the pathological and clinical expressions of COPD remain largely unknown. Higher levels of cigarette smoke metabolites, such as polycyclic aromatic hydrocarbons adducts, have been previously found in the lungs of women smokers compared with men (4). Thus, we hypothesize that the differences in the way women and men inhale smoke from cigarettes may, at least in part, contribute to the different clinical and pathological COPD phenotypes between sexes. Using optoelectronic plethysmography (OEP), a noninvasive motion capture method to measure chest wall movements and estimate lung volumes, we assessed the smoking pattern of a matched woman and man population.

Methods

Twenty-eight active smokers, 14 men and 14 women, matched by anthropometric data and smoking habit, and free of pulmonary and other relevant diseases and not under chronic medical treatment, were recruited (*see* Table 1). First, the breathing pattern during 10 consecutive tidal breaths was assessed. Then, the subjects were invited to puff a cigarette with filter mimicking the way they usually smoke, including the depth of the puff (puff volume), the duration of the puff, and the interval between puffs. To standardize the procedure of data collection, after ignition of the cigarette, the first five puffs were excluded to allow the subject to stabilize his/her puffing pattern. Then, the volume of the following five puffs was measured by OEP. Moreover, to standardize the breathing frequency and to avoid confounding effects on total and compartmental V_T, we excluded the subjects with a smoking puff time longer than 1.5 seconds with a smoking volume >30% of the VC. A dedicated software computed the enclosed volume and its variations during breathing with high accuracy, providing a measurement of the three-dimensional micromovement of the points belonging to the chest wall to compute volume variations of the whole chest wall and the different compartments (5): pulmonary rib cage (RCp), abdominal rib cage (RCa), and the abdomen (Abd). The measurement of the volumes of each hemithorax was provided by midline sensors (anteriorly, along the sternum and continuing caudally below the xiphoid through the umbilicus, and posteriorly, along the spinous processes of the vertebral column).

The software takes into account three main factors: *1)* the lung- and diaphragm-apposed parts of the rib cage (RCp and RCa, respectively) are exposed to substantially different pressures on their inner surface during inspiration; *2)* the diaphragm acts directly only on RCa; and *3)*

	Anterior View	Lateral View	Posterior View		Males	Females	P Value

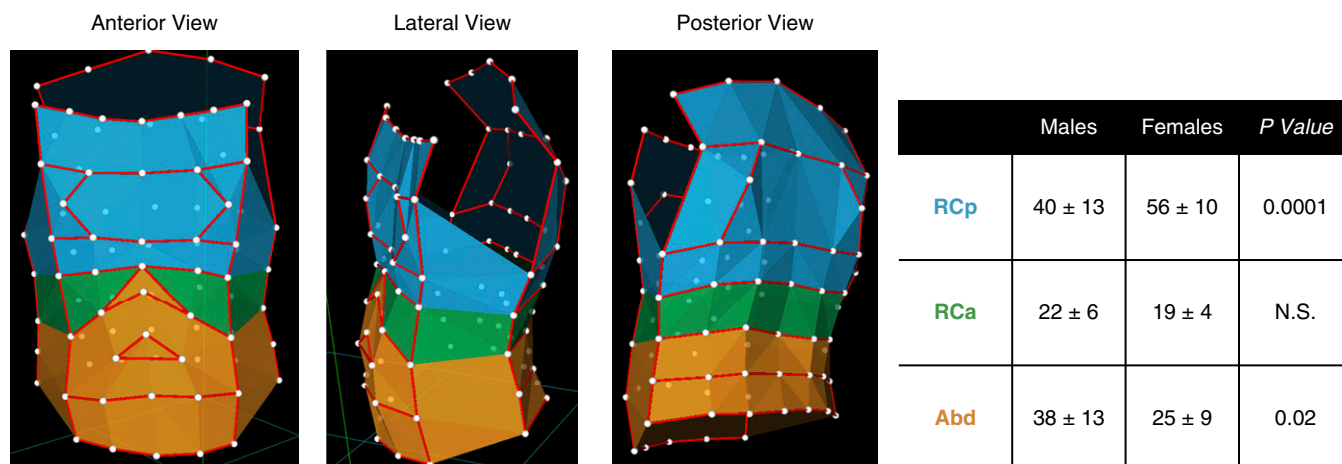|	Males	Females	*P Value*
RCp	40 ± 13	56 ± 10	0.0001
RCa	22 ± 6	19 ± 4	N.S.
Abd	38 ± 13	25 ± 9	0.02

Figure 1. Optoelectronic plethysmography configuration of infrared-reflective markers identifying three main compartments associated with breathing: blue = pulmonary rib cage; green = abdominal rib cage; and orange = abdomen. The left microphotograph shows the anterior view, the middle microphotograph shows the lateral view, and the right microphotograph shows the posterior view. The table shows pairwise comparison (Student's *t* test) of the total smoking volume distribution in men and women in the three thoracic compartments. Abd = abdomen; N.S. = not significant; RCa = abdominal rib cage; RCp = pulmonary rib cage.

Table 2. Differences in the Smoking Volume Distributions between Right and Left Hemithoraces in Men and Women

	Within Men			Within Women		
Compartment	% SmoV Right Side	% SmoV Left Side	*P* Value	% SmoV Right Side	% SmoV Left Side	*P* Value
RCp	21 ± 7	20 ± 7	0.62	30 ± 6	26 ± 6	0.15
RCa	10 ± 4	11 ± 3	0.40	9 ± 2	10 ± 4	0.80
Abd	19 ± 6	19 ± 8	0.87	12 ± 6	13 ± 7	0.68
Total		100			100	

Definition of abbreviations: Abd = abdomen; RCa = abdominal rib cage; RCp = pulmonary rib cage; SmoV = smoking volume.
Differences are expressed as percentage of the total smoking volume puff (% SmoV), in each compartment, between right and left side in women and men.

nondiaphragmatic inspiratory muscles act largely on RCp. Abd volume change is defined as the volume swept by the abdominal wall (Figure 1).

Results

Men and women had similar anthropometric data and pulmonary function (Table 1). During tidal breathing, both men and women mainly recruited the RCp compartment, to a lesser extent the Abd, and minimally the RCa. The inhaled cigarette smoke volume (25 ± 3% VC in men and 24 ± 3% VC in women; $P = 0.352$) and the smoke inhalation time (1.1 ± 0.2 s in men and 1.0 ± 0.2 s in women; $P = 0.533$) were similar between men and women. The compartmental distributions of the smoking volume in the three compartments (pRC, aRC, and Abd) between right versus left hemithoraces within women and men and between women versus men are shown in Tables 2 and 3.

Instead, the smoke inhalation volume, in each right and left hemithoraces, was mainly concentrating in the RCp and Abd compartments in men. In women, 58% and 54% (right and left side, respectively) of the total smoke inhalation volume was concentrated in the RCp, whereas the remaining volume was distributed between RCa and Abd. This difference in distribution between men and women was emphasized by averaging up both hemithoraces. In men, RCp and Abd shared almost 80% of the smoke inhalation volume (RCp vs. RCa: $P < 0.0001$; Abd vs. RCa: $P < 0.001$; RCp vs. Abd: nonsignificant), whereas in women the smoke inhalation volume was mainly collected in RCp (RCp vs. RCa: $P < 0.0001$; RCp vs. Abd: $P < 0.0001$; Abd vs. RCa: $P < 0.05$). The smoking volume collected in RCp and Abd was significantly different between men and women (table within Figure 1).

Discussion

We show for the first time that, while smoking, women preferentially recruit the rib cage with lesser contribution of the abdomen, whereas men preferentially recruit the abdominal compartment. This may be one potential mechanism contributing to the different cigarette smoke susceptibility, and the incidence of lung cancer and COPD, observed between women and men.

Women smokers develop more airflow limitation and more severe COPD, despite lower exposure to tobacco (2), and have a more rapid annual decline in FEV_1 than men smokers, even when they smoke fewer cigarettes (6). Furthermore, women with severe COPD have a higher risk of hospitalization and death from respiratory failure and comorbidities (7). However, the underlying reasons are largely unknown.

The different susceptibility to tobacco smoke could reflect a sex difference in the metabolism of cigarette smoke or in the inflammatory response to cigarette smoking owing to hormonal effects (8). We are now adding another mechanism potentially associated with the increased susceptibility to cigarette smoke observed in women: how cigarette smoke is inhaled and distributed throughout the lung.

At birth, the lungs of women are on average smaller than those of men and have fewer respiratory bronchioles. The airways in women are relatively smaller than those in men for the same lung volume, which might induce a higher concentration of tobacco smoke per unit area (9). During growth, the development of new lung parenchyma and airways and the loss of lung elastic recoil occur in women earlier than men (10). However, this maturation process occurs homogeneously throughout the lung and it is unlikely associated with the difference in the smoking pattern that we observe between men and women.

One possible explanation to our findings is that during the biological evolution of the human species, an adaptation of the respiratory system anatomy in women occurred, to allow the gravid uterus to grow the fetus. This possible adaptation might underlie the predominant recruits of the upper areas of the thorax in women while enhanced breathing (smoking). As our data are observational, we cannot provide evidence to support mechanisms underlying the sex differences in the smoking pattern observed in our study. However, it is important to note that in our case study there were not only women who had had at least one pregnancy but also women who had never given birth, and the compartmental smoking distribution between them was similar.

To our knowledge, there are no other described physiological conditions where women use the rib cage compartment more than men. Interestingly, it has been previously demonstrated, by using chest radiographs, that women exhibit a greater inspiratory rib cage muscle contribution and volume expansion during resting breathing than men, presumably reflecting an improved mechanical advantage conferred to these muscles by the greater inclination of ribs (11).

Table 3. Differences in Percentage of the Total Smoking Volume Puff Distribution in Each Compartment in the Right and Left Sides between Women and Men

	Men vs. Women	
Compartment	% SmoV Right Sides	% SmoV Left Sides
RCp	**0.001**	**0.010**
RCa	0.473	0.201
Abd	**0.001**	**0.038**

For definition of abbreviations, *see* Table 2.
Data are presented as *P* values. Bold indicates *P* values < 0.05.

Limitations of the study include the observational nature of the study and the fact that we did not confirm the spatial distribution of the inhaled cigarette smoke by using a tracer. However, OEP is an excellent noninvasive tool to determine compartmental displacement during breathing accurately and has the advantage of allowing accurate observation without complex instrument interference.

To conclude, we show for the first time that, while smoking, women mainly engage the pulmonary ribcage, whereas men mainly engage the abdominal compartment. These findings may help explain the increased susceptibility to cigarette smoke in women versus men, which underlies the increased risk of developing COPD, severe emphysema, and lung cancer in the female population. ∎

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Five-Year Follow-up after Mesenchymal Stromal Cell–based Treatment of Severe Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by uncontrolled bilateral inflammatory