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# Scientific Newsletter

## Summer 2018


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# 1 Strong evidence supporting the use of LLN instead of fixed FEV1/FVC ratio

*A recent study published in the European respiratory Journal, Dr. Yunus Çolack and his collaborators confirmed a link between the under-diagnosed airflow obstruction based on fixed FEV1/FVC ratio and worst outcomes including severe COPD exacerbations and mortality.*

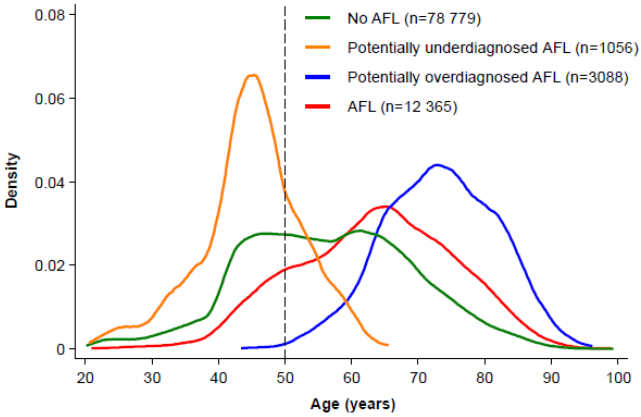



*Figure 1: Contrary to expectations, most of under-diagnosed patients were younger than 50 years old.*

## Main findings

1 Overall, the potential under or over diagnosis occurred in only 1% and 3%, respectively. However, as a huge population of 95,288 people were considered, the actual number of misdiagnosed patients is remarkable: about 3000 healthy subjects might have been falsely classified as airflow obstruction, whilst another 1000 patients might not benefit from treatment only because their FEV1/FVC wasn't below 0.7 .

2 In addition, most of potentially underdiagnosed subjects were young and middle aged (20-50 years), indicating that a disagreement was not exclusive in children and old people as we always expect.

3 Further analysis consisted of a 6 to 11 years follow-up. During this period, it was found that individuals with potentially underdiagnosed airflow limitation had a higher prevalence of asthma, respiratory symptoms and airway medication usage. Most of those individuals (80%) did develop a mild obstruction despite a FEV1 still above 80% of the predicted value.

4 The potentially underdiagnosed patients also had a higher risk of pneumonias, heart failure or ischemic heart disease compared to healthy individuals. Those results have been adjusted for smoking status.

5 Among individuals without airflow limitation, those in the 1st quartile (0.83 to 1) of FEV1/FVC ratio still had a high risk of exacerbation of obstructive lung disease and all-cause mortality compared to those in the 4th quartile (0.7 to 0.76). This suggests an association of reduced lung function with poor outcome, even within the range of normal lung function.

More than 95,000 subjects aged 20-100 years were recruited for this study. Based on 4 possible combinations between fixed threshold (i.e. 0.7 for FEV1/FVC) and limits of normal (LLN/ULN) criteria, the individuals were assigned into exclusive sub-groups:

**Group 1**: No airflow limitation, as confirmed by both FEV1/FVC ≥ 0.7 AND ≥ LLN

**Group 2**: Potentially underdiagnosed airflow limitation, as FEV1/FVC is below LLN but still ≥ 0.7

**Group 3**: Potentially over-diagnosed airflow limitation, as FEV1/FVC is above LLN but below 0.7

**Group 4**: Airflow limitation, confirmed by both criteria

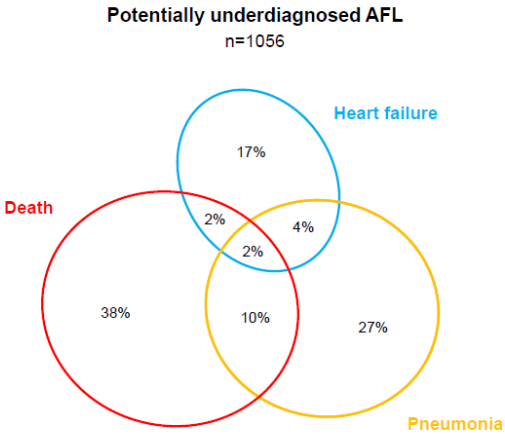



*Figure 2: Subsequent morbidity and mortality risks among potentially underdiagnosed patients*

## Comments

Even with a well standardized and accurate measurement, lung function test outcomes are useless without appropriate interpretation criteria. There is a never-ending debate among clinicians about what criteria should be chosen between lower limit of normal (as recommended by ATS-ERS) and fixed ratio (supported by GOLD and other local guidelines), to assess airflow limitation.

The current study provides strong evidence toward the application of inferior and superior limits of normal (LLN, ULN) in making the diagnosis of airflow limitation, as this approach would give the physicians a better chance to identify a vulnerable population with subsequent high morbidity and mortality.

*Ref: Yunus Çolak et al. European Respiratory Journal 2018; DOI: 10.1183/13993003.02681-2017*

# 2 Longitudinal lung function trajectories in male smokers

*Forced spirometry testing plays a central role in the diagnosis and staging of COPD. Besides the reference values that determine clinical interpretation of a specific individual, lung function decline patterns are helpful for understanding the effect of different pathological factors on lung functions, such as cigarette smoking over time.*

The study began with a hypothesis that longitudinal data from unrelated but demographically similar cohorts (historical epidemiological surveys) could be used to identify the trajectories of FEV1 decline. These rules could then be applied to assign new participants to trajectories for better characterization of COPD heterogeneity.

The study implies two large, separate datasets: The first one established since 1963 (Normative Aging study: NAS, including 1006 male smokers with a very long follow up period from their early adulthood to late life) was used for determining the FEV1 trajectories.

The authors adopted a new Bayesian nonparametric modeling framework, introduced by Jame Ross et al. in 2016 (PMID:28060702) to identify the most plausible sub-types among all FEV1 over time changing patterns. Then, the COPDGene dataset (5 year follow-up on 1802 male patients, with extensive radiologic and genetic information) was used to evaluate the outcomes when assigning patients to those trajectories.

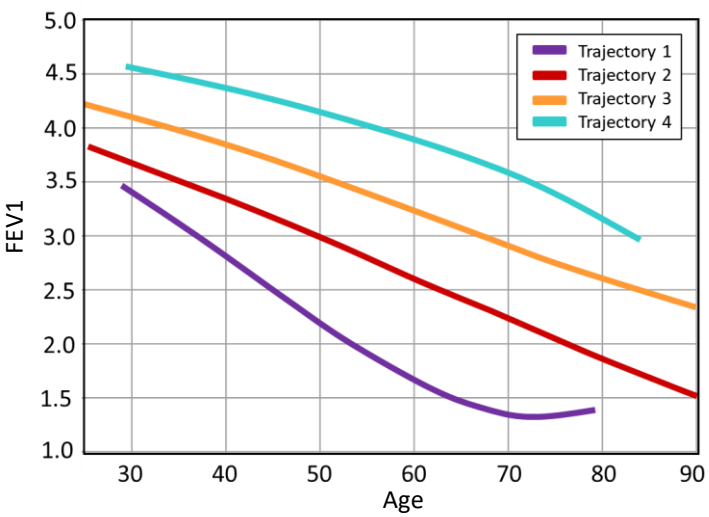



*Figure: Four distinct trajectories of FEV1 with differing levels of maximum lung function and rate of decline.*

Those findings provided novel insights into the natural history of COPD and COPD phenotypic heterogeneity. The 4 identified trajectories were associated with different risk levels of developing COPD and distinct COPD-related phenotypic manifestations, suggesting that a rapid decline in FEV1 contributes to COPD risks.

## Main findings

1 Four distinct FEV1 trajectories were identified based on two quartic polynomial functions for Age and Packyear. The 1st trajectory appeared to represent those with the lowest peak lung function and the most rapid decline in FEV1, while the trajectories 2 to 4 represent the subjects with incrementally higher peak lung health but relatively similar rate of decline in lung function.

2 When new COPD patients from COPDgene study were assigned to the appropriate trajectories, the following characteristics could be observed:

The patients that belong to Trajectory 1 present the largest radiologic burden of disease (the most emphysema, more severe airway wall thickening and worse small airway function).

In Trajectory 2, the subjects had thicker bronchial walls compared to those in trajectories 3 and 4 and a higher emphysema rate with increasing age.

The subjects assigned to trajectory 3 and 4 did not develop appreciable emphysema observed on the CT scan despite their average cigarette consumption up to pack years. Within trajectory 3, only the oldest subjects present airway remodeling.

According to the findings, trajectory 1 is characterized by the worst outcome. The patients in trajectory 2 develop airway wall thickening in advance of emphysema. In contrast, the trajectory 3 is airway-predominant as the members would develop only airway thickening but not emphysema throughout the entire observation period.

3 Patients with lower lung function trajectories were also associated with lower exercise capacity, higher BODE index and more severe dyspnea over the previous year.

4 With genetic contribution of 51%, the heritability of Trajectory 1 was higher compared to other trajectories. Subjects in trajectories 1 and 2 had greater self-reported parental histories of emphysema, COPD, chronic bronchitis and asthma.

*Reference: Ross JC et al. Am J Respir Crit Care Med. 2018 Apr 19. doi: 10.1164/rccm.201707-1405OC.*

# 3 Acute effect of bronchodilators on alveolar nitric oxide level

*In this randomised clinical trial, Dr. Pierachille Santus and his collaborators (Milan, Italy) demonstrated a significant effect of two inhaled long-acting bronchodilators on the nitric oxide concentration derived from alveolar airspace.*

*The main outcome (CANO) was evaluated using a Medisoft' FeNO+, the only electrochemical based NO analyzer that supports the multiflow NO analysis. For the first time, the acute and beneficial effects of bronchodilators on different aspects of pulmonary function can be investigated. These include the improvement mechanics of ventilation, static volume, diffusing capacity, ventilation distribution and dynamics of nitric-oxide within the lungs.*

This study aimed to evaluate the bronchodilation effects by formoterol and salmeterol on FENO50 and alveolar NO concentration (CANO) in 45 patients with stable COPD (These two bronchodilators are different in terms of intrinsic efficacy, pharmacokinetics and deposition ability). The authors also attempt to verify the association between CANO and other lung function parameters.

The study protocol implied comprehensive pulmonary function testing for each visit, that included blood gas, multi-flow FENO, body plethysmography, SB-DLCO, N2 washout test and spirometry.

## Main findings

1. The baseline lung function level was similar between the two groups. The studied population was characterized by a ventilation inhomogeneity, considerable impairment in KCO, desaturation and stable airflow obstruction.

2. The patients showed moderate to high FENO values at all 3 flowrate levels. The averaged CANO was high in both groups (above 9 ppb), suggesting an inflammation within their peripheral airways, however CANO was found varying in a large scale (SD=7.97 and 8.33 ppb).

3. The administration of either formoterol or salmeterol did cause progressive reduction of FENO at every flowrate. A negative effect was also observed for CANO but only reached a statistical significance after 180 minutes.

4. Acute change in CANO from the baseline level was correlated with changes in spirometric lung volume, hyperinflation (RV/TLC) and alveolar volume but not with the reversibility level of Forced expiratory flow (FEV1).

5. Both bronchodilators seem to have the same effect on lung function. Improvements were achieved 180 minutes after administration for plethysmographic airway resistance and VA but not for TLC. As VA increased, so did DLCO.

*Reference: Sanctus P et al. Pharmacol Res. 2018 May 23;133:160-169. doi: 10.1016/j.phrs.2018.05.010.*

## Comments

It's greatly appreciated that a standard sampling protocol for multi-flow NO analysis using Medisoft's device was well described in their paper, particularly the fact that only flows above 50 ml/s should be used for CANO estimation.

Increased baseline CANO might suggest an active inflammation in small airways (A LLN of 5 ppb has been suggested for CANO). Unfortunately, the diagnostic value of CANO is still unclear, as most lung disease is associated to an inflammation process, including the early phase of interstitial lung disease, systemic autoimmune diseases, asthma and COPD. It seems that the baseline CANO measurement alone does not allow us to specify a target disease like COPD. However, in the current study, consistently high FENO at every expiratory flowrate and significant correlations with other lung function parameters were observed, indicating an association between CANO and COPD.

Previously, FENO dynamics in response to bronchodilation have been studied in asthma, but data in COPD is still limited and most of previous studies showed only a negative or insignificant effect. The acute reduction in CANO was only documented once.

An acute reduction in CANO in response to bronchodilators could be explained by different mechanisms:

(1) As there was lung volume recruitment, CANO might decrease simply by a dilution effect;

(2) As CANO reflects a dynamic equilibrium between the NO production rate and NO uptake by lung capillary blood, an improvement in diffusing capacity would reduce the available quantity of NO within alveolar air space, however given the minor change in DLCO, this hypothesis should be unlikely;

(3) In their article, the authors suggested another hypothesis that CANO reduction may be secondary to a direct inhibition of NO synthase enzymes within the epithelial cells, as have been demonstrated experimentally before;

(4) Another hypothesis is that by removing the extent of dynamic stress on small airway may exert an indirect effect on the mechanical component of the inflammatory cycle.

# 4 Increased airway responsiveness is a risk factor for COPD

*Hyper-responsiveness is a pathological behavior of the airways that increase the intensity of their constriction in response to a lower level of physical or chemical stimulations, compared to healthy individuals. The most frequently used method for assessing the airway responsiveness is the bronchial provocation test with methacholine. While the utility of this technique is well established in asthma, the association between positive methacholine challenge test and pathological aspects of COPD is still unclear.*

In this study, the authors aimed to justify whether increased airway responsiveness is a risk factor for COPD. Data analysis was based on a large multi-centric cohort of 4025 COPD patients from 10 European countries.

The main outcomes include the COPD incidence as defined by LLN at the third examination, and FEV1 decline during a 10 year follow-up.

## Main findings

1. Analyses showed an accelerated FEV1 decline for increasing responsiveness relative to the baseline level, but not in absolute terms. The decline rate was estimated from 1.04 to 1.17% per year.

2. There is a clear dose-response relationship between airway responsiveness and the risk of developing COPD, with the incidence rate ranging between 0.6 to 5.3 per thousand/year. A positive result of the methacholine test is associated with 1.79 to 8.91 times higher risk of developing COPD.

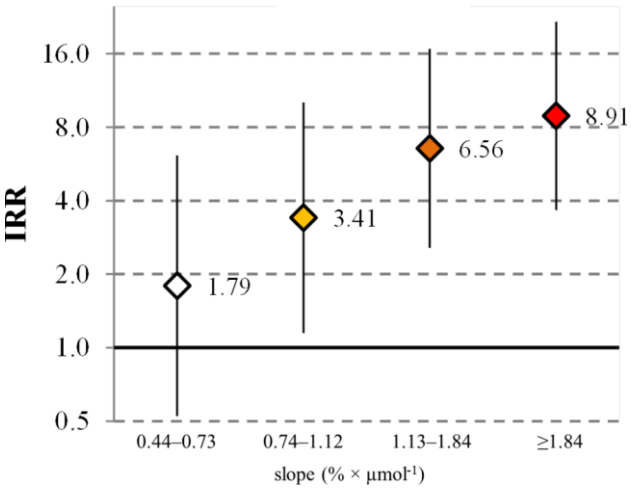



*Figure 1: The severity of AHR, reflected by the slope of dose-response curve is associated to a higher risk (Incidence rate ratio: IRR) of subsequent COPD diagnosis.*

The current study suggests that airway hyper-responsiveness could be interpreted as an independent risk factor for COPD, even at a moderate slope level.

Baseline or recurrent methacholine tests are helpful not only for the differential purpose but also in identifying a group of patients at higher risk for COPD. Further investigation could be considered to verify whether early intervention on these patients would slow down their disease progression toward COPD.

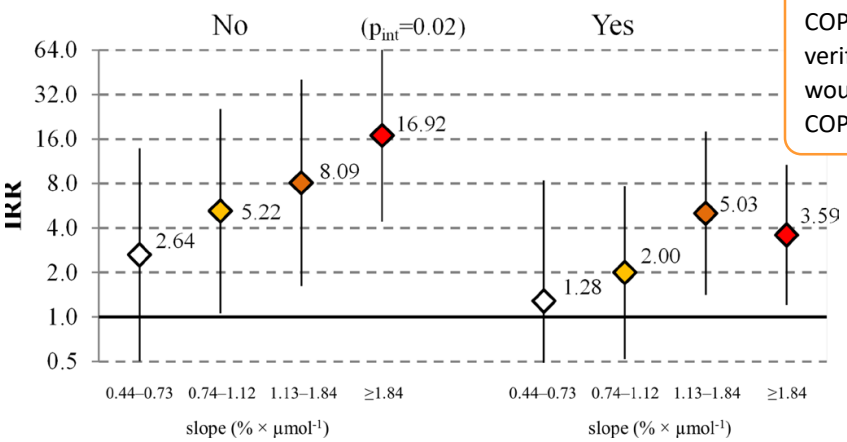



Figure 2: Incidence rate ratios (IRRs) with 95% CIs estimated for the association between AHR and development of COPD, stratified by history of asthma-like symptoms.

*Reference: Marcon A, et al. Thorax 2018;0:1-8. doi:10.1136/thoraxjnl-2017-211289*

# 5 A novel technology aiming to quantify morphometric changes of the alveolo-capillary membrane

*At the ATS 2018 congress last month, we discovered this interesting pilot study conducted by Dr. Martinot JB and his partners. Authors introduced a novel technique allowing the estimation of both the inner lung surface area and the alveolo-capillary membrane thickness. Validation data on 3 sub-groups of patients with emphysema, lung fibrosis and healthy individuals demonstrated a very good sensitivity and specificity of these morphologic parameters.*

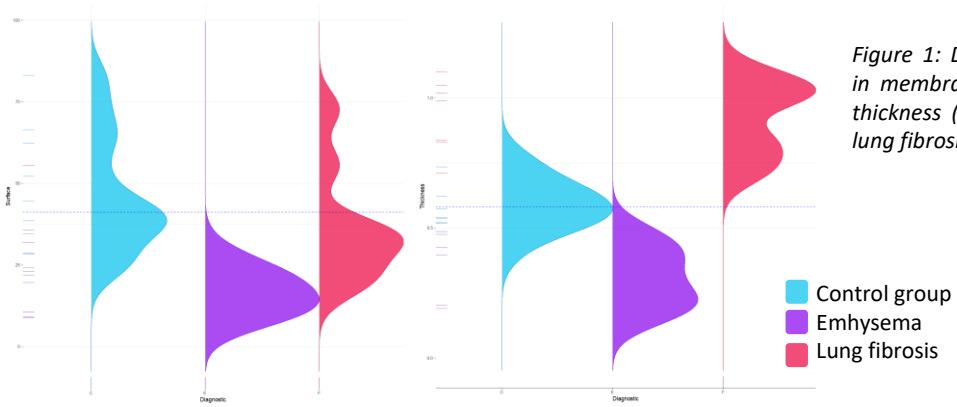



*Figure 1: Distributions and morphologic changes in membrane surface area (left) and membrane thickness (right) in patients with emphysema or lung fibrosis, compared with healthy patients.*

This morphologic study consists of combining a measurement of double diffusing capacities (DLNO and DLCO) (Hervé Guénard, 1988) using Medisoft'HypAir system and an estimation of the alveolar dimension based on the changes in the exhaled and inhaled concentrations of micronized particles (Brand P, 1999).

The aerosol derived morphometry testing aims to measure the alveolar gas sheet thickness that allows estimation of the alveolar surface using Weibel's model. The double diffusion measurement provides conductance of alveolar membrane for CO (DmCO), which is proportional to alveolar surface and inversely proportional to the mean harmonic membrane thickness (Fick law).

Data were obtained in patients with high resolution-CT proved emphysema or interstitial fibrosis and in healthy non-smoking individuals.

## Main findings

1. Neither alveolar volume (VA), nor membrane conductance (DmCO) was sensitive enough to distinguish the patients with lung fibrosis or emphysema from healthy subjects.

2. There was a clear and significant contrast in effective alveolar membrane surface between the patients with emphysema and two other groups, as this parameter is significantly reduced in lung emphysema. However, membrane surface does not allow to rule in lung fibrosis compared to the control group.

3. Alveolar membrane thickness showed a significant changes due to Emphysema and lung fibrosis. The patients with Emphysema presented a thinner membrane (mean = 0.307, CI: 0.245 to 0.37; p<0.0001), whilst the lung fibrosis represent a significant membrane thickening (Mean=0.923, CI: 0.845 to 1.001; p<0.0001), compared to that in healthy subjects (Mean = 0.591, CI: 0.531 to 0.651).

The findings indicate that even a sophisticated pulmonary function test like DLNO-CO cannot work alone in making the diagnosis of emphysema or lung fibrosis. A combination of DLNO-CO measurement and aerosol-derived lung surface allows the estimation of membrane thickness which sensitively reflects the alveolar destruction in emphysema or membrane thickening due to lung fibrosis.

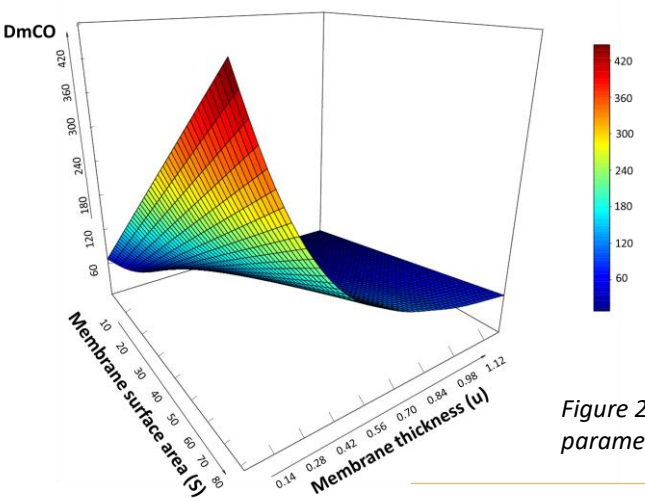



*Figure 2: The relationship between DmCO and two morphologic parameters: effective membrane surface (S) and membrane thickness (u)*

*Reference: Martinot JB et al. American Journal of Respiratory and Critical Care Medicine 2018;197:A5833*

# 6 Overtime evolution of nasal NO in healthy infants

*For the first time, natural evolution of nasal NO during the first 2 years of life can be described. This remarkable study was conducted in Denmark with over 200 nasal NO (nNO) measurements in 44 healthy infants from birth until 2 years age. Data were also compared with those in 7 children with primary ciliary dyskinesia (PCD) .*

All measurements implied an online, tidal breath sampling protocol at flowrate of 330 mL/min on a chemiluminescence analyzer (CLD-88). Nasal NO was averaged from the 3 highest, distinct peaks obtained within 30 sec.

## Main findings

1 There was a very high success rate of nasal NO measurement (99.6%) in healthy infants. This could be done easily in newborns from 2 weeks to 4 months during sleep. The measurement is more difficult in infants older than 4 months but this problem could be resolved by repeated measurements.

2 In newborns under 2 weeks, nasal NO is very low (upper IQR was only 69 ppb or 22.8 nl/min), but it would increase progressively with age. At the age of 2 yrs, the nNO level in healthy children was about 203 to 389 ppb (equivalent to a nNO production rate of 67 to 128 nl/min).

3 From 2 weeks of age, a linear association could be expected between log-transformed nNO and age: nNO would increase by 5.4% per month (3.7 to 7%).

4 nNO might drop by 78.9% in the occurrence of respiratory tract infection, but the true value could be recovered within 2 months after infection.

5 Compared to the natural trend of nNO in healthy children, 7 infants with PCD showed a very low historical nNO values within the first 2 years of life. Their nNO levels were similar to that observed in healthy infants during respiratory infection.

6 Even in absence of infection, overlapping was found between the two groups up to the ae of 12 months. Later, follow up measurements in childhood showed consistently low nNO level in PCD patients. At 2 years, most of the healthy infants (94%) represent a nNO level above the previously established threshold of 158 ppb.

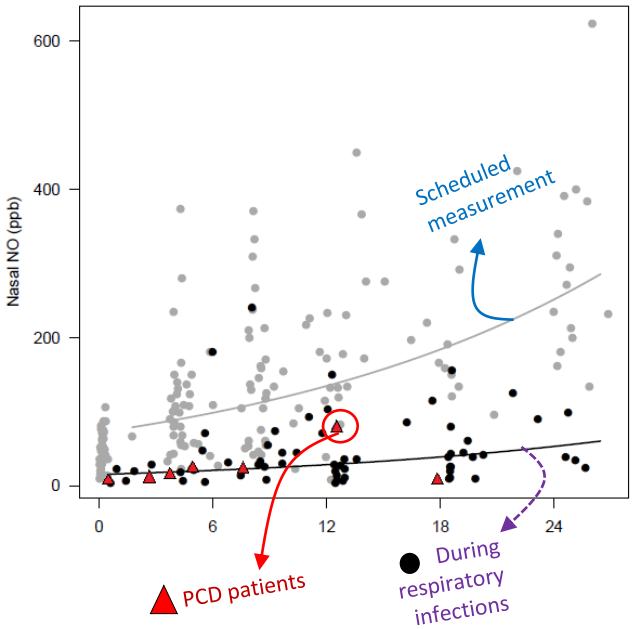



*Figure: Natural evolution of nasal NO from birth until age 2 years (grey curve/dots). Respiratory tract infection periods cause a temporary and net reduction in nasal NO (black curve/dots), indistinguishable from infant with PCD (red points).*

This is the first longitudinal study ever conducted to describe the natural development of nNO in healthy infants.

The longitudinal approach provides a more accurate reference for PCD detection than an averaged, fixed cut-off. This is because the data recaptured either baseline trend as well as confounding effects such as upper airway infections which can minimize the risk of false positive diagnosis.

The study also suggests that nasal NO measurement is feasible in all age group including the newborn babies using tidal breath sampling technique.

*Reference: J.K. Marthin et al. European Respiratory Journal 2018; DOI: 10.1183/13993003.02503-2017*

# 7 Abnormal RV/TLC ratio is associated to higher risk for airway obstruction due to secondhand tobacco smoke exposure

*In this study, the authors attempt to verify whether static lung volume measurements are sensitive enough to reflect the respiratory morbidity in 256 subjects who were exposed to second hand tobacco smoke but having a preserved spirometric lung function.*

Pulmonary function testing data were explored using Pearson correlation analysis. Then, the RV/TLC was treated as a target predictor in linear models for examining its association with the extent of gas trapping on lung CT imaging, exercise capacity and the presence of respiratory symptoms. The diagnostic ability of RV/TLC for respiratory symptom was then compared with that in stand-alone spirometry.

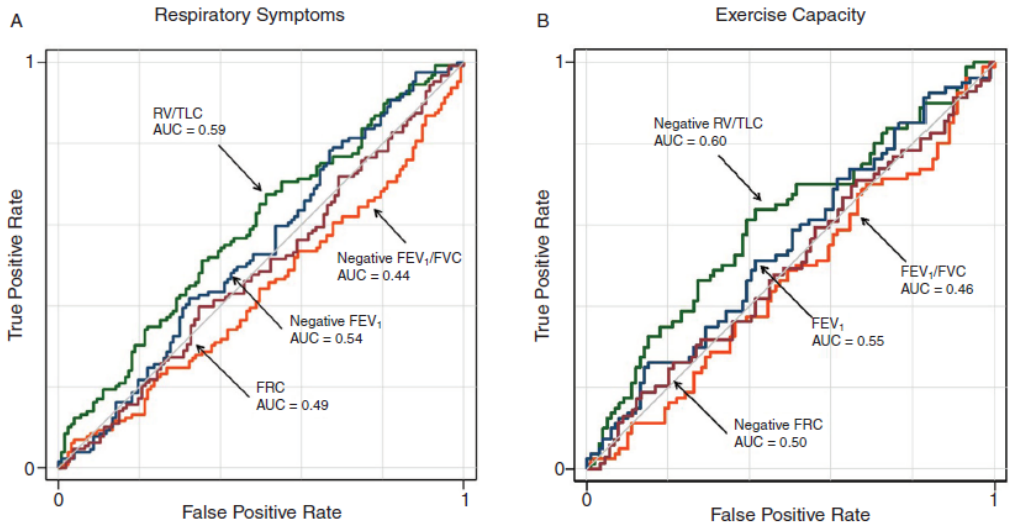



Figure:

## Main findings

1. As a target predictor, RV/TLC showed a large variance distribution and was completely independent to FEV1/FVC ratio.

2. Increased RV/TLC ratio was significantly associated with higher risk of respiratory symptom manifestation: for each 1% increase in RV/TLC ratio, this risk would increase by 9%. Combination of both FEV1/FVC and RV/TLC did not affect their independent effects on the respiratory symptom.

3. Stand-alone RV/TLC presents a slightly better diagnostic performance than both FEV1 and FEV1/FVC (AUC=0.59 versus 0.54 and 0.44, respectively). The optimized threshold was 90% and a subject having RV/TLC above this level is 92% more likely to develop respiratory symptoms.

4. High RV/TLC was also associated with lower maximum exercise capacity in subjects with preserved spirometry. This ratio was inversely correlated to the maximum achieved work rate. Each 1% increase in RV/TLC is associated with a decrease in VO2max by -16 mL/min and -1.4 W in maximum workrate. RV/TLC was also better than any spirometric indices for detecting the ones who were not able to achieve maximal predicted VO2max (AUC=0.6).

In a population at risk of obstructive lung disease due to their prolonged secondhand cigarette smoke exposure, higher RV/TLC could be an additional risk of manifesting clinical symptoms and reduced exercise capacity, regardless their preserved spirometric lung function.

Those findings, along with previous clinical studies, suggest to add RV/TLC as an index for air-trapping, that could be easily measured with body-plethysmography or N2washout techniques to the conventional spirometry test in the subjects who are at risk of COPD due to either direct smoking or exposure to second hand smoking and air pollution.

*Reference: Arjomandi M et al. BMJ Open Resp Res 2018;5 :e000284. doi:10.1136/bmjresp-2018-000284*

# 8 KCO better reflects emphysematous dysfunction than DLCO

*It has been suggested that the measurement of DLCO could be useful for distinguishing COPD from asthma. In this study, the authors from Hokkaido (Japan) indicate that the transfer coefficient KCO might better reflect emphysematous changes than DLCO. The study targeted 3 sub-types of obstructive lung disease, including: non-smoker with asthma (AS.NS), smokers with asthma (AS.SM) and COPD.*

## Main findings

1. As expected, AS.NS patients have better ventilation function and diffusing capacity (KCO) compared to AS.SM group. Only KCO but not DLCO did show a significant correlation with FEV1.

2. Despite an adjustment for airflow limitation, the diffusing capacity (DLCO) was still significantly lower in patients with COPD than two Asthma sub-groups. However, no difference in DLCO could be found between two smoking status among asthmatics.

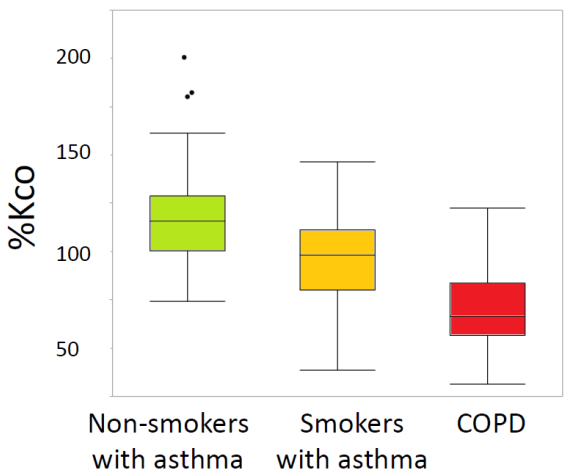
3. KCO is the only index that showed a clear contrast pattern among 3 sub-groups, as this parameter was highest in non-smokers, then significantly reduced in asthmatics who smoke. It was lowest in COPD patients.

4. Compared to DLCO, KCO also showed stronger correlations with the extent of emphysema on CT scan, as measured by low attenuation volume fraction and percentage cross sectional area of small pulmonary vessels.

Together, those findings clearly indicate that KCO is more sensitive than spirometry and even DLCO, in reflecting the pathology of structural changes and pulmonary vasoconstriction in COPD. KCO alone allows us to distinguish the COPD patients from asthmatic patients, regardless their smoking status.

These results are also consistent with previous studies that provide evidences in favor of adding the single breath DLCO measurement to the routine pulmonary function check-up for patients suspected of having obstructive lung diseases.

*Figure: Clear contrast pattern in KCO level among 3 sub-groups.*




## Comments

It has been 4 years since the study of Marc Decramer et al (2014) showing that combining a SB-DLCO measurement to spirometry could enhance the accuracy of diagnosis 54% more. This technique is simple yet very helpful for an early detection of structural changes in alveolar-capillary membrane due to lung diseases. A SB-DLCO is available in most of multifunction PFT systems. Recently, a global reference value for DLCO and KCO was developed by Global lung function initiatives (GLI), making the interpretation of these outcomes even more efficient.

However, the physiological meaning of KCO is often misunderstood. Some clinicians still consider KCO as an adjustment of DLCO for lung volume or an averaged diffusing capacity per lung volume unit. In fact, KCO is the true measurement of the carbon monoxide uptake rate during breath holding.

Despite that in most situations, KCO could give better information than the DLCO, however, a stand-alone KCO does not provide the precise anwser for every clinical questions.

KCO can change due to different causes. A reduced KCO might suggest abnormality in either perfusion factor, membrane thickening or a decreased efficient membrane surface. Increased KCO can be due to a destruction of alveolar units or ventilation-perfusion mismatching (KCO is still dependent on lung volume).

Advanced methods such as double-diffusion (DLNO-CO) or techniques that directly target the morphometric characteristics of alveolar membrane structure could be even more useful than KCO.

*Reference: Shimizu et al. J Appl Physiol (1985). 2018 Apr 12. doi: 10.1152/japplphysiol.01062.2017.*

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