AIRWAY DISEASE AND EMPHYSEMA ON CT – NOT JUST PHENOTYPES OF LUNG PATHOLOGY

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In this issue of the Journal Martinez et al (1) examined the relationships between quantitative Computed Tomography (QCT) parameters of emphysema, airway wall remodeling and airway narrowing to composite clinical and physiological indices of COPD, the BODE index (2) and the St George’s Respiratory Questionnaire (SGRQ) (3). BODE stands for Body mass index, airflow Obstruction, Dypnea, and Exercise capacity.

Not surprisingly these QCT estimates of pathological changes were related to measures of clinical impact. More interestingly, the authors found that there were differences in the strength of the associations between measures of emphysema and airway disease and the composite indices. Measures of emphysema were more closely related to the BODE index while the airway wall abnormalities were better predictors of the SGRQ.

While it has long been recognized that there is a spectrum of changes in the airways and parenchyma in COPD (4) the separation of the airway predominant phenotype from the parenchymal predominant phenotype was largely limited to the autopsy room until the advent of CT. CT has confirmed that some patients have airflow obstruction with little emphysema while others have predominant emphysema with little airway disease (bracketing a large group who have various combinations) (5). In addition there is evidence that the predominant pattern is to some extent familial (6) and is associated with different rates of decline of lung function (7).
The presence of airway disease and emphysema on CT can be assessed qualitatively or quantitatively. The power of the quantitative indices, as used in the present study, is that they are completely reproducible provided that similar scanners, imaging parameters and software are used. The hope is that the separate mechanisms that lead to these pathological changes in COPD can be individually targeted by specific therapy and followed noninvasively with repeat imaging. Since CT allows a measure of anatomic derangement its validation has largely been by comparison with pathological estimates of emphysema and airway disease. Many studies have shown that CT provides an accurate estimate of the extent and severity of emphysema (8-11) although only a few have compared CT measures of airway lumen narrowing and wall remodeling to pathological changes (12).

More recently there have been a number of studies in which quantitative estimates of CT phenotypes have been compared to clinical phenotypes; measures of lung function and symptoms (13-19). The reasoning is that, in the absence of a structural gold standard, lung function and symptoms can act as a surrogate to test validity. If CT can accurately assess anatomic derangement of lung structure and if structural damage correlates with lung function and symptoms, then there should be good relationships between the CT measures and these clinical features. In general the results of these studies have been reasonably robust, supporting the idea that CT can be used to grade the clinical as well as the pathological severity of COPD. Martinez et al (1) have added a new dimension to the puzzle. By comparing the CT measures of emphysema and airway disease to the SGRQ and the BODE index they have found that specific “pathological” features are more closely related to certain combinations of clinical features.

To understand their results more fully we need to examine what goes into determining the SGRQ and BODE scores. The SGRQ (http://www.healthstatus.sgul.ac.uk/sgrq-downloads/sgrq-c-downloads) is a 50 item questionnaire that assesses respiratory symptoms, physical activity and psychosocial well being. In addition to providing a total score, scores for the 3 domains can be determined independently. The SGRQ correlates significantly with other measures of disease activity such as cough, dyspnea, 6-min walk distance (6MWD) and FEV1 as well as measures of general health status such as the SF36. The BODE index is more complex and was developed to predict risk of death in COPD. It is derived from the combination of a measure of nutritional status (body mass index –BMI), the degree of airflow obstruction (FEV1 % predicted), the
severity of dyspnea (modified Medical Research Council (MMRC) dyspnea scale), and the 6-MWD.

Fortunately Martinez et al (1), in their supplementary data, also report the relationship between QCT measures and the components of the SGRQ and BODE index so that we can appreciate which were primary drivers for the relationships. Interestingly all of the measures which contribute to the BODE index were significantly related (by univariate Spearman correlation) to both emphysema score and Pi10 as a marker of airway remodeling. However the most important contributor to the BODE’s stronger relationship with emphysema is the correlation between quantitative emphysema and FEV1 percent predicted ($r = -0.54 – p <0.001$). Nakano et al (5) compared QCT measures of emphysema and airway wall remodeling to FEV1% predicted and also found that there was a substantially better correlation with emphysema than with airway wall parameters. CT emphysema was also significantly related to BMI with lower BMI in subjects who had worse emphysema ($r = -0.27 – p <0.001$). It is well known that for equal degrees of airflow obstruction, individuals who have worse emphysema have lower BMI (or persons with low BMI have worse emphysema – the direction of this relationship is unclear) (20). Thus the stronger relationship of BODE with QCT emphysema could be driven by these two factors. However the BODE index also related to the other two components of the BODE, the 6MWD and the MMRC dyspnea index. Diaz et al (18) have examined the relationship between 6MWD and QCT-defined measures of emphysema and airway disease and found that emphysema was better correlated with 6MWD than with airway remodeling parameters. In the present study the strength of the association, as assessed by r values was slightly stronger for Pi10 ($r = 0.33 – P < 0.001$) than for emphysema ($r=0.24 – p<0.001$). Interestingly the factor that substantially disrupts the robustness of the relationship of the BODE index with airway scores is the completely opposite, but significant, relationship between BMI and airway remodeling (Pi10). Individuals who have thicker/smaller airways have significantly greater BMI ($r=0.17 – P<0.001$). This positive relationship between measures of airway wall remodeling and body mass index has been previously reported by Lee al (19) but it’s cause and significance is unknown.

More surprising to us was the closer relationship of airway wall parameters to respiratory health status as measured by the SGRQ. Why would respiratory health status measures be more closely
related to airway pathology than emphysema? Previous studies have reported an association of measures of altered airway dimensions with *symptoms* such as cough, sputum, wheeze and dyspnea. For example, Lee et al (19) reported that CT-measured wall area and wall area percent correlated with dyspnea as measured with the MMRC, whereas the CT measure of emphysema did not. In supplementary table 2 Martinez et al (1) used a multivariate analysis to dissect out the independent contribution of the 3 SGRQ domains to the relationships with airway remodeling and emphysema. All three domains, symptoms, impacts and activity were significantly associated with airway wall remodeling (Pi10). On the other hand the quantitative emphysema score was only associated with the activity score and unrelated to symptoms and impacts. It is be understandable that the symptoms of cough, sputum and wheeze are more closely related to airway morphology than to emphysema. The relationship of emphysema to activity is also logical since dynamic hyperinflation during exercise is an expected consequence of the loss of lung recoil that is characteristic of emphysema. What is unclear is why the impacts domain, which measures psychosocial impacts of COPD (including questions on panic during symptoms, or feeling one is a burden to friends or family), relates to airway disease measures but not to emphysema measures. We are unaware of any study that has probed the relationships between phenotypes of COPD and psychosocial functioning, but if the relationship between the airway measurements and the SGRQ impacts component can be confirmed, this could lead to an intriguing area of study.

It is especially impressive that airway measurements related so well to the SGRQ since the airways that are assessed using HRCT are the relatively large airways which are not the site of major airway resistance in COPD. The fact that large airway dimensions are related to respiratory health status as measured by the SGRQ supports the suggestion that airway wall remodeling in large airways is a reflection of generalized airway narrowing and/or obliteration as has been suggested by Nakano et al (12). McDonaugh et al (21) have recently shown that an early lesion in COPD is the loss of terminal bronchioles. Perhaps there is a relationship between this obliterative process in the smallest of the conducting airways and the inflammatory/fibrotic process that thickens and narrows the larger airways that are visible on CT.

In summary the results of Martinez et al (1) raise important questions about the relationship between structural changes in the lung, abnormalities of lung function and respiratory related
symptoms, physical activity and psychosocial impacts. It is somewhat paradoxical that the authors chose to compare more precise morphological features of COPD with composite measures of function and symptoms since the COPD community is striving to separate sub-phenotypes of COPD based on pathogenetic mechanism and structural changes. However by providing the relationships between these CT features and the components of the composite scores the authors have allowed us to tease apart the functional and symptomatic parameters to more precisely determine their relationship to CT features and in so doing have raised important issues.

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