World Journal of Respirology

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World J Respirol 2017 March 28; 7(1): 1-16

DOI: 10.5320/wjr.v7.i1.1

ISSN 2218-6255 (online)

REVIEW

Phenotyping emphysema and airways disease: Clinical value of quantitative radiological techniques

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Author contributions: Turner A designed the review question; Turner A and Subramanian D reviewed the main text; Crossley D wrote the paper.

Conflict-of-interest statement: None.

Manuscript source: Invited manuscript

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Received: August 31, 2016
Peer-review started: September 1, 2016
First decision: November 10, 2016
Revised: December 20, 2016
Accepted: January 11, 2017
Article in press: January 14, 2017
Published online: March 28, 2017

Abstract

The pathophysiology of chronic obstructive pulmonary disease (COPD) and Alpha one antitrypsin deficiency is increasingly recognised as complex such that lung function alone is insufficient for early detection, clinical categorisation and dictating management. Quantitative imaging techniques can detect disease earlier and more accurately, and provide an objective tool to help phenotype patients into predominant airways disease or emphysema. Computed tomography provides detailed information relating to structural and anatomical changes seen in COPD, and magnetic resonance imaging/nuclear imaging gives functional and regional information with regards to ventilation and perfusion. It is likely imaging will become part of routine clinical practice, and an understanding of the implications of the data is essential. This review discusses technical and clinical aspects of quantitative imaging in obstructive airways disease.

Key words: Chronic obstructive pulmonary disease; Alpha one antitrypsin deficiency; Computed tomography; Densitometry; Phenotype; Spirometry; Magnetic resonance imaging

Core tip: Phenotyping emphysematous patients radiologically allow physicians to diagnose and deliver tailored and targeted therapies that are not possible with spirometry. When patients are divided into chronic bronchitis or emphysema on computed tomography (CT), they have significantly different clinical features and spirometry, demonstrating its ability to characterise phenotypic differences. CT offers accurate mapping and measurement of emphysema whereas magnetic resonance imaging (MRI) can provide functional information relating to ventilation and perfusion. This unique feature of MRI can help prognosticate patients in whom surgery is being considered. CT and MRI have both been sufficiently validated clinically and pathologically.

Crossley D, Turner A, Subramanian D. Phenotyping emphysema

and airways disease: Clinical value of quantitative radiological techniques. *World J Respirol* 2017; 7(1): 1-16 Available from: URL: http://www.wjgnet.com/2218-6255/full/v7/i1/1.htm DOI: http://dx.doi.org/10.5320/wjr.v7.i1.1

INTRODUCTION

The pathophysiology of chronic obstructive pulmonary disease (COPD) and Alpha one antitrypsin deficiency (AATD) is increasingly recognised as complex and lung function alone is insufficient for early detection, categorising and dictating management. Up to one third of the lung can be destroyed before respiratory impairment is detected by spirometry[1], meaning those with early disease may remain undiagnosed. Patients with emphysema and airways disease have significant clinical and physiological differences[2,3] and therefore phenotyping radiologically should allow for more individualised treatment with outcomes that are more meaningful to the patient.

The typical clinical phenotype of the patient with emphysema is that of significant breathlessness, hyperinflation and low body mass index. By contrast, the phenotype associated with predominant airways disease, *i.e.*, chronic cough and infective exacerbations, has a different clinical spectrum within the umbrella term of COPD and requires separate recognition. Severity of symptoms and exacerbation rates are factors that directly impact patient's quality of life, and therefore diagnosing and tailoring treatment early on will have the best outcome for symptom resolution and slowing disease progression.

Quantitative imaging techniques can phenotype patients into predominant airways disease or emphysema, providing an objective tool to detect disease earlier and more accurately. This is of increasing significance as targeted treatments beyond inhaled therapy (such as endobronchial valves and alpha one augmentation therapy) become available, which require careful patient selection. Computed tomography (CT) provides detailed information relating to structural and anatomical changes seen in COPD, whereas MRI/nuclear imaging gives functional and regional information with regards to ventilation and perfusion. Optical coherence tomography (OCT) gives microscopic detail of the airway wall where differences in the contribution of active inflammation and airway remodelling could be a useful biomarker and drug target.

This review article discusses these three imaging modalities, how they can be used to phenotype patients radiologically into emphysema and airways disease, and therefore individualise management. The clinical and pathological validation of each is demonstrated as well as the methods of quantification. Their individual merits and how they compare against one another is discussed, and trials that have used imaging as an outcome measure for treatments in COPD already are highlighted. It is the strengths of these techniques make it likely imaging will become part of clinical practice, and an understanding of the implications of the data is therefore essential for healthcare workers.

CT

Phenotyping using CT

Spirometry measures such as the forced expiratory volume in 1 second (FEV1) alone are insensitive to early emphysematous change, and only moderately correlate to quality of life measures[4]. Therefore using symptoms and exacerbations alongside FEV1 to categorise COPD seems logical, which led to adoption of these methods in the most recent GOLD guidelines[5]. However this is not the only conceivable way in which severity could be described; CT scanning has potential to delineate additional phenotypes complementing GOLD severity stage.

Studies have shown measures of airways disease on CT such as increased wall thickening are distinct from those of low density and parenchymal destruction seen in emphysema and therefore can be used to subdivide COPD patients into phenotypes[3,6]. When patients have been classified by CT into emphysema or airways predominant phenotypes, there are significant differences between the groups for lung function, symptoms and exacerbation rates. Table 1 lists relevant trials that have divided patients radiologically and the clinically different variables between the groups. Han *et al*[7] demonstrated differences in the rate of exacerbations between the emphysema and airway predominant phenotypes, and that the risks were independent between the two groups. This adds evidence to the increasing recognition that the two disease states are separate and the driving pathology behind them may be different.

Table 2 summarises the current treatment recommendations from BTS and GOLD once patients have been phenotyped. There is of course overlap between the groups, with those patients with an emphysematous predominant phenotype experiencing more frequent exacerbations, and patients should continue to be evaluated individually. This overlap is highlighted in the table.

Disease distribution

Emphysema as a result of smoking/inhalation of noxious gases most frequently results in the centrilobular distribution of emphysema which begins in the upper zones. However, their relative high V/Q ratio means they contribute significantly less to the overall PFT result and therefore in usual COPD isolated to purely the upper zones, the PFTs may seem relatively normal earlier on. Nakano *et al*[16] showed accordingly that the correlation between FEV1 and %LAA was weakest in the upper zones, but as the emphysema often begins in the upper zones, there is a higher association for DLCO here and centrally rather than peripherally. Similar

Table 1 Summary of studies dividing patients as HRCT defined phenotypes and their significant differences clinical and physiological ($P < 0.05$)

Ref.	HRCT defined phenotypes	Variables studied	Significant variable difference
Kitaguchi *et al*[8], 2006	A: Little or none of either emphysema or BWT E: Emphysema but no BWT M: Emphysema and BWT	Gas exchange Gas transfer Lung function Response to beta-agonist Response to treatment with ICS Sputum cell differentiation	A: ↑ BMI ↑DLCO ↓ hyperinflation ↑ reversibility ↑response to ICS ↑ % of sputum eosinophils E: No response to ICS M: ↑ response to ICS ↑ % of sputum eosinophils
Fujimoto *et al*[9], 2006	A: Little or none of either emphysema or BWT E: Emphysema but no BWT M: Emphysema and BWT	Exacerbation rates Gas exchange Gas transfer Hospital admissions Lung function Response to beta-agonist Symptoms	M: ↑ volume of sputum, exacerbation rate and admission to hospital
Pistolesi *et al*[10], 2008	From derivation set, created new validation set Group A and B	CT parameters Gas exchange Gas transfer Lung function	A: ↓ FEV1, ↑ TLC ↓ DLCO. ↑ pixel index (threshold -950HU) B: ↑ BMI purulent sputum worse bronchial wall thickening
Han *et al*[7], 2011	Emphysema predominant or Airway predominant	BWT Exacerbation rates lung function % emphysema	Emphysema Predominant (> 35% -950HU): ↓ FEV1 and 6MWD ↑ SGRQ and MRC grade For every 5% ↑ in emphysema, 1.18 fold ↑ exacerbation frequency Airways predominant: For 1 mm ↑ in segmental BWT 1.84 fold ↑ in exacerbation frequency
Subramanian *et al*[3], 2016	Emphysema dominant, airways disease dominant, mixed pathology and mild disease	Blood parameters CT parameters Gas exchange Gas transfer Lung volumes Spirometry	Compared with airway disease dominant group, emphysema dominant group had ↑ lung volumes, ↓ gas transfer ↓ pO_2 + pCO_2 ↓BMI ↑Hb No difference between age, and smoking history between the groups
Da Silva *et al*[2], 2016	Emphysema or airways disease	Clinical + functional evaluation HRCT	Emphysema group: ↑ airflow obstruction ↓ BMI ↓ 6MWD

A: Airways; E: Emphysema; M: Mixed; BWT: Bronchial wall thickening; 6MWD: 6 minute walk distance; CT: Computed tomography; BWT: Bronchial wall thickness; DLCO: Transfer factor for carbon monoxide; ICS: Inhaled corticosteroid; FEV1: Forced Expiratory Volume in 1 second; TLC: Total lung capacity; HU: Hounsfield units; SGRQ: St Georges Respiratory Questionnaire; MRC: Medical reseach council; HRCT: High resolution computed tomography.

findings were demonstrated by Parr *et al*[17] in AATD patients that basal distribution is associated with greater impairment of FEV1 ($P = 0.002$), but less impairment of gas exchange ($P = 0.016$), and Aa gradient ($P = 0.007$). Given the lung function variation between different lung regions the authors warn of using a single physiological parameter as a measure of severity as it may introduce bias.

Castaldi *et al*[18] found that panlobular rather than centrilobular distribution was associated with stronger associations with lung function and QoL than CT lung density, demonstrating that the distribution of disease has an independent effect on severity. AATD typically occurs in a panlobular distribution with basal predominance, and Dawkins *et al*[19] showed that for these patients, basal distribution carried a higher mortality risk. Finally, in patients randomised to the medical arm of the National Emphysema Treatment Trial, the authors demonstrated that a greater proportion of emphysema in the lower lung zone *vs* upper lung zone was predictive of mortality ($P = 0.005$)[20].

Lung volume reduction surgery: Using CT measurements both visually and quantitatively allow for more careful selection of COPD patients when considering lung volume reduction surgery (LVRS). Selecting patients appropriately to either medical or surgical treatments can reduce the associated mortality. The National Emphysema Treatment Trial randomised 1218 severe emphysema patients to either LVRS or medical management[21]. They visually scored the CT scans of patients as being either predominantly upper lobe or lower lobe, and assessed exercise capacity. They found that in a carefully selected population of those with upper lobe emphysema and a low exercise capacity, those in the surgical treatment arm had a significantly lower mortality (RR for death 0.47, $P = 0.005$). However, in those with predominantly lower lobe emphysema but a

Table 2 Treatment of chronic obstructive pulmonary disease as defined by computed tomography phenotypes

CT phenotype	CT defining features	Clinical features	Findings	Treatments	Ref.
Emphysema	↓ Perc15 Emphysema Centrilobular Panlobular Paraseptal Bullous	Health status	↓ BMI[2] ↑ SGRQ + MRC[7]	Rehabilitation Nutritional support Palliative care	GOLD 2016[5]
		Exercise tolerance	↓ 6MWD[2] ↓ pO_2 ↓ pCO_2[3]	Rehabilitation Maintenance of physical activity Oxygen	GOLD 2016[5]
		Lung function	↑ TLC ↓ KCO ↓ FEV1/FVC	LAMA/LABA LVRS/BVLS Transplant Bullectomy[11] LVRS[11]	GOLD 2016[5] NICE 2010[11]
		Symptoms	↑ Hb[3] No significant response to ICS[8]	Theophylline Rehabilitation typically MRC > 3	GOLD 2016[5] NICE 2010[11]
Airways disease		Exacerbation frequency/ severity	↑ Exacerbations hospital admissions[7]	LABA/phosphodiesterase-4 inhibitor LAMA/phosphodiesterase-4 inhibitor Mucolytics Add in ICS Prophylactic antibiotics	GOLD 2016[5] NICE 2010[11] Brown *et al*[12], 2007 Fabbri *et al*[13], 2009 Calverley *et al*[14], 2009 Herath *et al*[15], 2013
	Lower wall area/body Surface area ratio (WA/BSA) Lower luminal area/BSA Higher %WA	Symptoms	Significant response to ICS+ Significantly higher % of sputum eosinophils[8] Peribronchial thickening[10] Air trapping	Physiotherapy and active breathing techniques Mucolytics Roflumilast Bronchodilators	NICE 2010[11]

6MWD: 6 minute walk distance; CT: Computed tomography; ICS: Inhaled corticosteroid; FEV1/FVC: Forced expiratory volume in 1 second/forced vital capacity; TLC: Total lung capacity; HU: Hounsfield units; SGRQ: St georges respiratory questionnaire; MRC: Medical reseach council; HRCT: High resolution computed tomography; Perc15: 15th percentile point; KCO: Gas transfer co-efficient; LVRS: Lung volume reduction surgery; LAMA: Long acting muscarinic antagonist.

high exercise capacity, those randomised to the surgical arm did worse (RR for death 2.06, P = 0.02). Therefore, LVRS confers a survival advantage in carefully selected patients, but there is associated higher mortality with no significant increase in functional status in those with non-upper zone predominant disease. Gierada *et al*[22] have also demonstrated that those upper lobe predominant emphysema, in a heterogeneous have a two-fold or more average increase in FEV1 following LVRS.

Predicting post-operative FEV1: CT density masking to quantify the severity of emphysema is linked to favourable post-operative outcomes. Sverzellati *et al*[23] applied a density mask to 9 COPD patients awaiting lobectomy for lung cancer, along with spirometry. With specific equations, they predicted the post-operative FEV1 using both values and found quantitative CT was superior to lung function (r = 0.9). Gierada *et al*[24] used various LAA measurements and determined that a 75% LAA or greater for -900HU threshold, or 25% at -950HU were associated with improved outcomes post-operatively including a > 50% improvement in FEV1 and 2 fold increased six minute walk distance.

Finally the ratio of upper to lower lobe emphysema is of particular importance in assessing predicted post-operative FEV1 following bilateral LVRS. Consistent with the fact that upper lobe predominance is associated with better outcomes, Flaherty *et al*[25] found that the CT emphysema ratio (CTR) was the best single predictor of a successful 12% increase in FEV1 (absolute value 200 mL). Importantly, the highest CTR scores (> 2.5) were associated with a greater than 90% specificity at each time point up to 36 mo, although the sensitivity was low. The positive predictive value of this threshold was at least 75% up to 36 mo after surgery. The negative predictive value remained moderate at all thresholds throughout 36 mo of follow-up.

Quantification of emphysema

CT densitometry is the method of quantifying the severity of emphysema using dedicated software. Figure 1 demonstrates how the CT images are digitally produced. X-rays are emitted and passed through the subject and received by detectors that calculate how much the intensity has been reduced by the tissue. These attenuation co-efficients are then converted into a digital image in the form of a matrix consisting of many small data sets. Each small square in the matrix is a pixel, and in 3D with volume adjustment is a voxel. Each pixel is assigned a value in hounsfield units (HU) from -1000 representing the least possible density/ attenuation, *i.e.*, air and 1000 representing the highest,

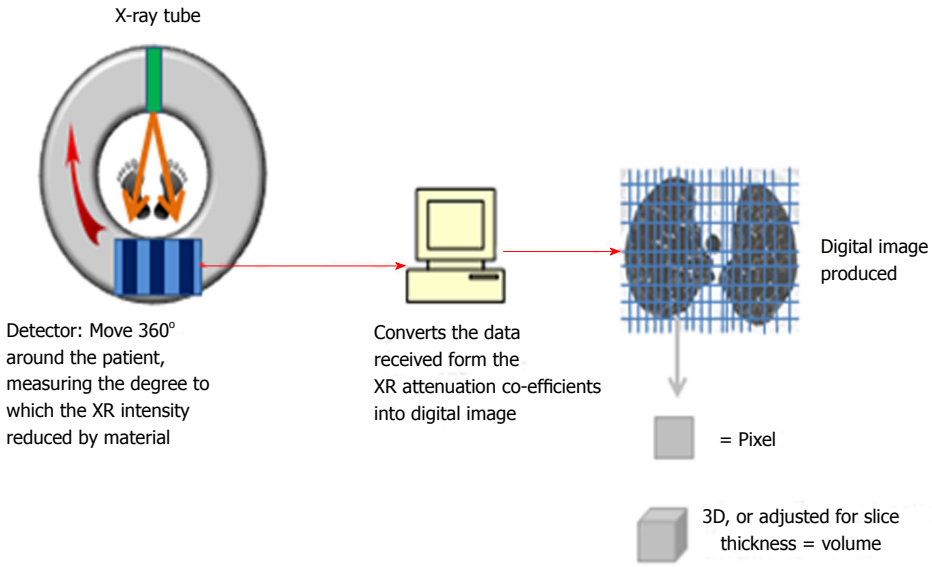

Figure 1 The process of computed tomography scanning. X-rays are passed from the source through the subject laid on the table, and received by the detectors that rotate 360° around the patient. The reduction of the intensity of the XR beam passed through the subject is calculated as an attenuation co-efficient, which from all the slices is reformatted into a digital image.

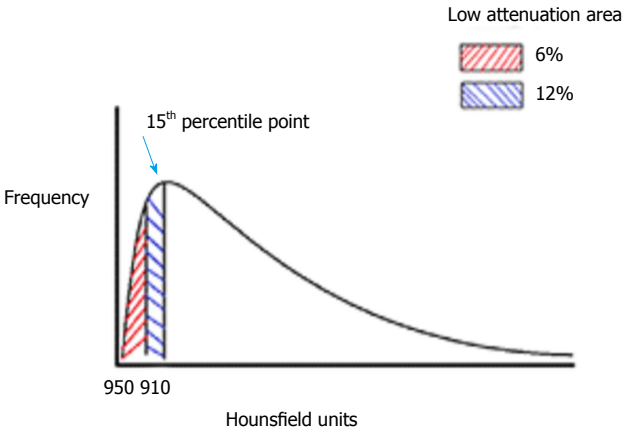

Figure 2 Calculation of densitometric indices. Example of a density histogram, and how the area under the curve at a given threshold is calculated. In this figure, with a threshold of -910HU, 12% of the pixels are between -910 and -1000HU.

Table 3 Table to summarise studies performed in alpha one antitrypsin deficiency and chronic obstructive pulmonary disease directly comparing the most accurate measure of computed tomography density

Condition	Type of study	910	950	Perc15	Conclusion of superior measure	Ref.
Alpha one	RCT	x	x		950	Parr *et al*[29]
	RCT		x	x	950 and Perc15	Parr *et al*[30]
	RCT	x	x	x	Perc15	Parr *et al*[26]
	Review	x	x	x	Perc15	Hogg *et al*[28]
Chronic obstructive pulmonary disease	RCT	x	x	x	Perc15	Shaker *et al*[31]
	Review	x		x	Perc15	Dirksen *et al*[27]
	RCT		x	x	950	Chong *et al*[32]

Variables tested, type of study and conclusion of the most superior measure shown. RCT: Randomised controlled trial.

i.e., solids. These pixels or voxels can be plotted on a histogram as shown in Figure 2. There are two ways of reading the severity from this histogram. The first is the value of where the 15th percentile point lies on the curve (Perc15) and is the most preferred value in trials quoting density, as it is most accurate and sensitive to change[17,26-28]. The second method is to calculate the percentage under the curve that represents the low attenuation area for a selected threshold, *e.g.*, -910HU or -950HU. These and other values are used in studies quoting density, and Table 3 demonstrates trials that have sought to ascertain the most valid method in both AATD and COPD.

Validation

Pathological correlations: The ability of density analysis to accurately assess the degree of emphysema has been validated on pathological studies. Müller *et al*[33] in 1988 showed a strong correlation between density mask results and an assigned emphysema pathology score (1 to 100) in 28 patients who had undergone lobar resection for a lung tumour (r = 0.83, P < 0.001). In a larger group of patients who had undergone resection for similar reasons, Gould *et al*[34] also demonstrated a strong correlation between emphysema measures quantitatively on imaging and that on resected specimens (r = 0.77)[35,36].

Clinical correlations: Numerous studies have shown significant correlations between CT measures of emphysema (Perc15 and %LAA 950) and FEV1 and DLCO[37-40], as well as measures of exercise tolerance, *e.g.*, MRC grade and 6 min walk distance (6MWD)[41-45]. There are also significant correlations with frequency

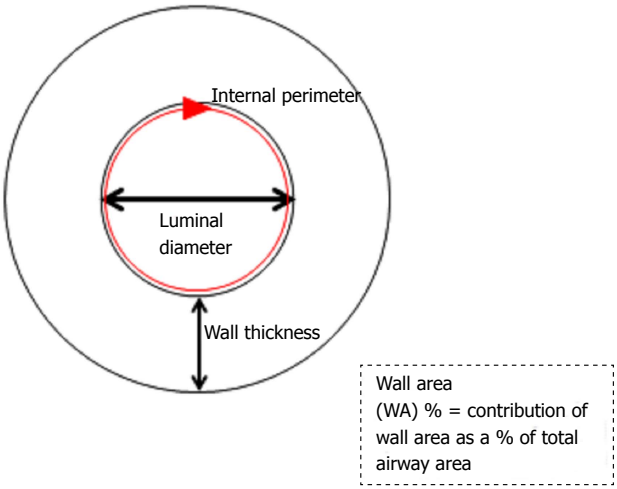

Figure 3 Airways disease measurements. Diagram to demonstrate various values calculated in assessing either the luminal or wall contribution to airway thickening.

of exacerbations and ultimately mortality[19,41,46-48]. In the NELSON trial (Dutch and Belgium Lung Cancer Screening Trial), Mohamed Hoesein *et al*[35,36] have shown smokers who normal lung function demonstrated evidence of emphysema on CT concluding that CT is a more sensitive in detecting emphysema than PFTs. However, the R^2 value between CT density and FEV1 even when adjusted for other variables remains 0.3-0.68 indicating that the parenchymal disease detected by CT density only contributes for 30% to 68% of the total variation[18,49-51]. Therefore other factors including small airways disease must additionally contribute to the altered lung function seen.

Airways disease

Quantification: Luminal area (LA) and the wall area (WA) (expressed as a percentage (%WA = WA/LA + WA*100)[52] can be derived from CT measurements, as well as bronchial wall thickness (BWT) as the square root of WA adjusted for the internal perimeter[53,54] (Figure 3). Airway measurements are often based on the full width at half maximum principle[55,56]. However, this method is known to overestimate the value of wall thickness and various algorithms for quantification are modifications are of this[57,58].

Validation: Nakano *et al*[52,55] demonstrated on histology slices that those airways with an internal diameter of greater than 0.75 cm could accurately predict the dimensions of small airways with an internal diameter of 1.27 mm (r = 0.57, P < 0.01) and in particular measurements from the right S1 segmental bronchus. Airway wall thickening as measured by CT is related to obstructive spirometry[59-62], and chronic sputum production is associated with increased likelihood of an exacerbation leading to a hospital admission[63], and death from a pulmonary infection[64]. Chronic bronchitis (cough and sputum production for at least > 3 mo in 2 consecutive years)[5] has a greater mean %WA and internal perimeter, and is associated with higher exacerbation and mortality rates[53,65,66].

CT quantification variability: The potential pitfall of CT analysis is that the various components must all be equal in order to compare like for like. These factors include using the same software programme[67], the same reconstruction algorithm[68-70], appropriately calibrating the scanner[26,29] and adjusting for volume[27,32,71]. If CT density logistics are standardised, then scans may be compared longitudinally to measure treatment effect, and combined from different centres. A detailed review of CT noise reduction by Dirksen *et al*[27] 2008 recommended using a soft reconstruction algorithm, with a slice thickness of 3-5 mm, at a low radiation dose using a phantom. As for volume adjustments, there is no general consensus as to which method is preferable, though physiologically adjustment using the patient's own volume measurements seems more intuitive.

Trials: CT has been used as an alternative outcome measure in therapeutic trials for patients with emphysema. When performing power calculations in the EXACTLE study using CT density as a measure of response to alpha one augmentation therapy, the author's calculated 494 patients would need to be recruited in each treatment arm for 3 years using FEV1 as the primary outcome measure[72]. In the RAPID trial however, they calculated 180 patients distributed over the two treatment arms would provide a power of at least 80% using two sided P value of 0.05[73].

CT has been used to measure response in both usual COPD and in Alpha 1 anti-trypsin deficiency and the summary detailing CT measure used, outcomes and the strengths and weaknesses of each study are presented in Table 4. Notably, in AATD the recent RAPID trial was the first RCT to demonstrate a significant improvement in lung density with alpha one augmentation therapy. Stockley *et al*[74] pooled the data from the two RCTs by Dirksen et al in 1999 and 2009 (EXACTLE), and with the increase in statistical power , augmentation therapy increased the lung density as measured by 2.997 g/L in comparison to the placebo arm (95%CI: 0.669 to 3.926, P = 0.006).

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) measures the behaviour of protons once a strong magnetic force is applied. The lungs have therefore been notoriously difficult to image due to the abundance of air and low proton density. However, technology has advanced so that MRI may capture changes in a much shorter time window and use inhaled gases (oxygen and hyperpolarised helium/xenon) that alter the proton behaviour in different ways, so that disease and heterogeneity in the lung may be detected. The benefits of MRI over CT and PFTs are the ability to acquire functional information with regards to ventilation, perfusion and alveolar diffusion,

Table 4 Summary of interventional drug trials using computed tomography measures as an outcome measure

Ref.	Study design	Pt N°	Duration	CT measure	Drug	Result
Usual COPD						
Shaker *et al*[75]	RCT	254	2-4 yr	Perc15 and -910HU	Budesonide or placebo	Annual fall in Perc15 ↑in the placebo arm *vs* budesonide (P = 0.09) Annual increase in -910HU↓in the budesonide arm (P = 0.02)
Hoshino *et al*[76]	RCT	54	16 wk	%WA, LA, BWT	Tiotropium, Indacaterol or both	Combination therapy resulted in a ↓in %WA and wall thickness (P < 0.01)
Nordenmark *et al*[77]	RCT	36	12 wk	BWT, air trapping index and %WA	Reversible neutrophil elastase inhibitor 60 mg BD	No difference
Shimizu *et al*[78]	Inter-ventional trial	23	1 wk	Airway inner luminal area	SFC	Ct detected the significant change in airway inner luminal area r = 0.65, P < 0.001
Alpha 1 Antitrypsin deficiency						
Stolk *et al*[79]	RCT	262	1 yr	Perc15	Parlovarotene	No benefit on lung density
Mao *et al*[80]	RCT-pilot study	20	9 mo	-910HU	ATRA	No benefit
Roth *et al*[81]	RCT feasibility study	148	9 mo	-910HU	Patients received ATRA either LD, HD, 13-cRA or placebo	No definitive clinical benefits
Dirksen *et al*[82]	RCT	32	3 yr	Perc15	Alpha1-antitrysin	CT analysis showed a non-significant trend towards a favourable effect. CT lung density twice as sensitive as PFTs
Dirksen *et al*[72] (EXACTLE)	RCT	77	2-2.5 yr	Perc15	Prolastin	CT densitometry more sensitive measure for the detection of emphysema progression than PFTs or health status indices
Chapman *et al*[73]	RCT	180	2 yr	Perc15	Alpha 1 proteinase inhibitor	Annual rate of density decline at TLC ↓in treatment group (P = 0.03)

CT: Computed tomography; WA: Wall area; LA: Luminal area; BWT: Bronchial wall thickening; SFC: Salmeterol/fluticasone; LD: Low dose; HD: High dose; 13-cRA: 13-cis retinoic acid; ATRA: All trans retinoic acid; RCT: Randomised controlled trial; TLC: Total lung capacity.

and any regional differences. MRI therefore could offer an attractive solution to evaluating underlying pathology and targeting treatment.

Phenotyping with MRI

Airways disease: MRI is already used to visualise airway changes in more detail in cystic fibrosis, *e.g.*, inflammation, mucus plugging and bronchiectasis[83]. In this capacity, MRI is superior over CT with its ability to more accurately differentiate soft tissue, *e.g.*, remodelling/inflammation[84,85]. The increased airway resistance seen in small airways disease in asthma has also been evaluated by MRI. Where bronchoconstriction has resolved clinically MRI assessment of ventilation demonstrated focal, fixed obstructive defects that may be reversible with targeted therapies, *e.g.*, broncho-thermoplasty[86]. The ability of MRI to accurately measure the resultant degree of hyperinflation and air trapping has obvious potential clinical applications in COPD, *e.g.*, endobronchial coils/LVRS.

Emphysema: The apparent diffusion co-efficient (ADC) measured in MRI is a reflection of the amount of measured molecular movement, with more movement in emphysema where there are larger air sacs and destroyed alveolar walls[87]. Therefore a high ADC indicates more severe emphysema and could be used either diagnostically or for assessment longitudinally. As there is increased interest in using CT density as a direct measure of parenchymal response to augmentation therapy in AATD, ADC would be another potential option of measuring alveolar changes.

Vascular remodelling secondary to hypoxic vasoconstriction is likely part of a more systemic process associated with COPD. Perfusion studies, *i.e.*, dynamic contrast enhanced MRI may therefore act as another useful imaging biomarker to detect and prevent further disease[88]. For example, where there is a perfusion defect with preserved ventilation, then this maybe a target for bronchial dilators. Similarly where there is preserved perfusion, up to 20% have emphysematous regions which therefore may act as a map for targeted interventional therapies, *e.g.*, Bronchoscopic Lung Volume Reduction Surgery (BVRS)[89]. Jobst *et al*[90] showed the association between oxygen enhanced MRI and contrast enhanced MRI r value is 0.52 therefore there is a link but there are other factors in play such that one is not a surrogate for the other. A summary of how MRI can help phenotype COPD is given in Table 5.

Clinical validation: MRI findings from the various modalities have been correlated with lung function and CT density in numerous studies (Table 6), *R* values for FEV1 ranging from 0.61-0.72 and 0.45-0.9 for DLCO.

Pathological validation: One of the pathological hallmarks of emphysema is the destruction of alveolar walls and dilatation of respiratory bronchioles[103,104].

Table 5 Magnetic resonance imaging modalities to phenotype and treat chronic obstructive pulmonary disease

Phenotype	MRI modality	Findings	Suggested treatments
Airways disease	Hyperpolarised MRI	Detailed anatomical information of airway inflammation, oedema and mucus plugging[84,85] Regional information re. lung volumes, *e.g.*, focal bronchoconstriction	Nebulised antibiotics Chest clearance techniques[83] Broncho-thermoplasty[91] BVRS
Emphysema	Hyperpolarised MRI	Global high ADC[87] Low PaO_2[92]	Early disease detection Future alpha one augmentation therapy[1]
	Oxygen enhanced MRI	↑↓Relative enhancement signal[93,94]	Targets for resection Early emphysema detection
	Dynamic contrast MRI	Global microvascular reduction blood flow[95] Focal defects, small pulmonary emboli Increased pulmonary pressure	Lifestyle moderation Anticoagulation Treat as pulmonary hypertension

Potential treatments based on the phenotypes identified by the technique, but that have not yet been tested are noted by [1]in the table. MRI: Magnetic resonance imaging; BVRS: Bronchoscopic volume reduction surgery; ADC: Apparent diffusion co-efficient; KCO: Transfer co-efficient.

Table 6 Studies correlating magnetic resonance imaging with other clinical variables

MRI modality	FEV1	Gas transfer	CT density (LAA% 950HU)
Hyperpolarised gas	-0.632-0.76[38,86,92,96,97]	-0.45-0.82[38,92,98,99]	0.8-0.9[96,100]
O_2 enhanced	-0.74[93]	DLCO: 0.911[94] KCO: 0.66[93]	
DCE-MRI	[1]0.677[101]		
UTE-MRI[2]		0.6[102]	0.72[102]

[1]Dynamic contrast measured by the signal intensity perfusion defect (SIpd); [2]Ultra-short echo time-MRI. CT: Computed tomography; DLCO: Transfer factor for carbon monoxide; FEV1: Forced expiratory volume in 1 second; UTE-MRI: Ultra-short echo time-MRI; DCE-MRI: Dynamic contrast enhanced magnetic resonance imaging measured by the signal intensity perfusion defect (SIpd).

Histologically this may be measured by the surface area to volume ratio (SA/V) and this was compared with MRI findings in five patients who had undergone bilateral lung transplant for end-stage COPD. Using He-MRI and measuring the ADC, the correlation between histology and MRI findings was very strong (r = 0.96)[105]. Morino *et al*[106] in an animal model measured the correlation between dynamic contrast MRI and alveolar enlargement as defined by the mean linear intercept (Lm) and this demonstrated a slightly weaker correlation though still significant (r = -0.77, P < 0.001).

Quantification of emphysema using MRI

Oxygen enhanced MRI: Proton MRI measures the longitudinal and transverse relaxation times (T1 and T2 respectively) after the strong magnetic force has been applied[85]. Oxygen molecules shorten the T1 relaxation time, and mapping the degree of change can depict the heterogeneity of ventilation within the lungs[107]. The mean wash in time maps of oxygen created significantly correlates to FEV1 and FEV/FVC ratio (-0.74 for both) demonstrating its strong relationship to current measures of ventilation[93]. The degree of altered signal change as depicted by the mean relative enhancement signal has a stronger correlation with gas transfer (r = 0.83)[94] and therefore as well as acting as a map of ventilation, oxygen enhanced MRI may also reflect alveolar-capillary gas transfer 4214[93]. O_2 MRI has also been demonstrated to be able to separate emphysematous patients from asymptomatic smokers[92].

Benefits of offering oxygen enhanced MRI particularly over other inhaled gases acting as a contrast is that it may technically be implemented at most centres without the need for specialist equipment but would require specialist software[85]. There is no breath holding manoeuvres required which is preferable in COPD patients, the signal artefacts are relatively low as is the overall cost. However, the scanning time is considerably longer (30 min *vs* 5 min) and the repeatability has not yet been confirmed[108].

Hyperpolarised MRI

ADC: Using spin technology to hyperpolarise inhaled gases through polarised laser light, the signal enhancement is amplified and then measured[107]. The larger the range of movement of the gas particles, the higher the ADC. Therefore in emphysematous alveoli where there is destruction of attachments, there will be more movement, and a higher ADC[87]. For this reason ADC can give information about alveolar anatomy unlike HRCT. ADC correlates with lung function, and is sensitive at detecting differences between emphysematous and non-emphysematous patients[109].

Helium MRI of alveolar partial pressure

PaO_2: Based on the rate of polarised helium decay in relation to regional oxygen concentration, and the diffusion across alveolar membranes, the alveolar partial pressure of PaO_2 can be calculated[87,110]. This can detect changes in asymptomatic current smokers, as well as correlating with lung function, SGRQ and 6MWD[92].

Helium ventilation MRI: Following a breath hold, the thoracic volume can be calculated together with He ventilated images in order to calculate the percentage ventilated volume and ventilation defect volume%

Table 7 Summary of studies comparing magnetic resonance imaging and computed tomography in chronic obstructive pulmonary disease

Ref.	Year	Pt No.	Variables	Results
Ley *et al*[96]	2004	13	ADC and EI *vs* FEV1	ADC *vs* FEV1, $R = 0.7$ EI *vs* FEV1, $R = 0.5$ MLD *vs* FEV1, $R = 0.4$
Ohno *et al*[93]	2008	71	O_2 enhanced MRI (mean wash in time and relative enhancement ratio), CT defined lung volumes *vs* lung function	Mean wash in time *vs* FEV1, $r = -0.74$ Relative Enhancement Ratio *vs* KCO, $r = 0.66$ CT lung volume *vs* FEV1, $r = 0.61$ CT lung volume *vs* KCO, $r = 0.56$
Van Beek *et al*[98]	2009	94	ADC and MLD *vs* FEV1/FVC and DLCO	ADC *vs* Fev1/fvc, $r = 0.5$ MLD *vs* Fev1/fvc, $r = 0.52$ ADC *vs* DLCO, $r = 0.59$ MLD *vs* DLCO, $r = 0.29$
Diaz *et al*[38]	2009	27	ADC and EI *vs* FEV1 and DLCO	ADC *vs* FEV1, $r = 0.67$ EI *vs* FEV1, $r = 0.55$ ADC *vs* DLCO, $r = -0.82$ Perc15 *vs* DLCO, $r = 0.6$
Quirk *et al*[114]	2011	30	Hyperpolarised He *vs* CT density in at risk smokers	Lung morphometry *vs* %LAA 950: Significant difference seen in those still smoke, not on CT
Xia *et al*[101]	2014	55	+ve rate of Perfusion defects *vs* CT changes	Early COPD: MRI detected 8/8, *vs* CT 3/8 $P = 0.003$ Mod. COPD: MRI detected 9/9, *vs* CT 7/9 $P = 0.47$
Hueper *et al*[95]	2015	144	DCE-MRI *vs* CT density	PMBF *vs* %LAA 950: Evidence of non-linearity, $P = 0.015$

ADC: Apparent diffusion co-efficient; EI: Emphysema index; FEV1: Forced expiratory volume in 1 second; MLD: Mean lung density; MRI: Magnetic resonance imaging; DLCO: Transfer factor for carbon monoxide; KCO: Transfer co-efficient; COPD: Chronic obstructive pulmonary disease; DCE-MRI: Dynamic contrast enhanced-magnetic resonance imaging.

(VDV%)[85,111]. This was able to discriminate between healthy smokers and those with COPD in a 2015 trial, but there was no significant correlation with spirometry[111].

The main drawbacks of hyperpolarised helium MRI are that hyperpolarised helium is in limited supply and expensive. The technique requires specialist centres with appropriately trained radiologists[85], and patients are required to breath hold for around 20 s, which is very challenging for patients with COPD. However, hyperpolarised MRI has no radiation dose and gives high spatial resolution. It provides detailed regional information about gas exchange and ventilation, and its repeatability has been established[108].

Perfusion: Detecting early changes in the vascularity of patients at risk of developing emphysema could potentially act as another early biomarker of disease. Dynamic Contrast Enhanced MRI involves injecting contrast and measuring the amount of time taken for the contrast to pass through the pulmonary circulation, *i.e.*, the longer the time taken, the more flow restriction there must be. Transit time of blood through the pulmonary circulation is notoriously rapid, though MRI with ultra-fast capabilities is able to capture this[112,113]. Not only is this technique feasible it also correlates to clinical parameters. Hueper *et al*[95] demonstrated this is possible on a microvascular scale, and demonstrated evidence of disease in patients with COPD in areas of lung not emphysematous on CT.

Trials: Multiple studies have demonstrated that MRI correlates more strongly with PFTs than CT does (Table 7). However at this early stage it still remains unclear if MRI is more sensitive, as the literature is not as advanced.

Nuclear imaging

Nuclear imaging techniques provide useful information regarding ventilation and perfusion which can be used for assessing emphysematous lungs and regional contributions. There is no significant scope for information regarding soft tissue and fine anatomical measurements, and therefore whilst can measure the severity of emphysema to a certain degree, it is not able to phenotype in the same way as CT/MRI.

Positron emission tomography

Positron emission tomography (PET) measures gamma rays emitted from molecules labelled with radioisotopes, and an image of where the molecules concentrated is created. Most commonly PET is used in oncology to look for the extent and spread of malignant disease by using labelled glucose, and determining metabolically active sites. There has been increased recognition of the role of increased neutrophil activity in COPD. 18-FDG has been used as a surrogate marker of neutrophilic inflammation in order to ascertain if it could be a useful biomarker[115]. The authors found uptake was significantly higher in the upper zones in those with COPD compared with healthy controls ($P = 0.009$) and correlated with lung function. They additionally tried to

Table 8 Practical considerations for positron emission tomography *vs* single photon emission computed tomography

Modality	Advantages	Disadvantages
PET	Increased resolution	Cyclotron and radiopharmaceutical preparation Rapid repeat testing not possible[87]
SPECT	Lower cost More widely available. Dynamic SPECT give time course of ventilation	Lower spatial and contrast resolution

PET: Positron emission tomography; SPECT: Single photon emission computed tomography.

Table 9 Studies correlating single photon emission computed tomography with other clinical variables

Modality	*R* value	Ref.
DCE-MRI	0.50-0.67	Molinari *et al*[127]
FEV1	-0.64	Bajc *et al*[121] Jögi *et al*[122]
FEV/FVC	-0.63, 0.67	Bajc *et al*[121] Jögi *et al*[122]
He-MRI	0.45	Stavngaard *et al*[128]
DLCO	0.57	Sandek *et al*[123]

DCE-MRI: Dynamic contrast enhanced magnetic resonance imaging; FEV1: Forced expiratory volume in 1 second; FEV1/FVC: Forced expiratory volume in 1 second/forced expiratory volume; He-MRI: Helium-magnetic resonance imaging; DLCO: Transfer co-efficient of carbon monoxide.

use PET-CT as an outcome measure for augmentation therapy in patients with AATD but found no significant difference in readings before and after treatment.

Vidal Melo *et al*[116] labelled and injected nitrogen (13-NN-labelled saline) in 15 patients with COPD. Nitrogen has very low solubility in blood and therefore in the lungs diffuses rapidly in to alveolar space[117]. PET scanning with this method exploits these features of nitrogen so that areas where there is high concentration of nitrogen in the lung initially must be well perfused. Furthermore, once the patient breathes, nitrogen is washed out and therefore areas with retained nitrogen are less well ventilated.

Single photon emission CT

Using this method, the labelled radioisotope emits one rather than two gamma rays during the decay process, and for this reason has less radiation but subsequently less resolution. Labelled agents are inhaled (*e.g.*, xenon) and injected (*e.g.*, technetium DTPA) and the contributions of ventilation/perfusion ascertained. The merits of both tests are summarised in Table 8. The clinical application of single photon emission CT in COPD are largely sub-divided into pre-operative assessment for those considered for lung volume reduction surgery (including bullectomy), and for the early detection of emphysema.

SURGICAL ASSESSMENT

Assessing V/Q mismatch can give functional information about regions of inadequate ventilation not visible on CT, and is cheaper and more convenient than MRI. Suga *et al*[118] demonstrated its usefulness particularly in the pre-operative assessment for bullectomy, and the valuable information gained regarding function of lung tissue within and surrounding the bullous before it is resected. A retrospective analysis was performed on patients who had undergone endobronchial valve placement (EBVs) and perfusion as measured by perfusion scintigraphy. They found that those with lower baseline local perfusion benefitted from EBV placement independent of the lobe, summarising that assessing a patients perfusion pre-operatively may be a method of calculating predicted benefit[119]. Finally, Sudoh *et al*[120] compared PET/CT to PPO segment counting in predicting post-operative outcomes but found no superiority.

EARLY DISEASE

The pathobiological theory that COPD is a systemic disorder with ongoing inflammation and microvascular changes is exploited in assessment of V/Q mismatch. Changes in perfusion may well precede visible changes on CT and certainly lung function, and has therefore potential to diagnose and initiate treatment earlier if required[121,122].

Validation

A summary of correlations between SPECT and various other clinical measures is shown in Table 9. There is moderate-strong correlation with FEV1 but less so with gas transfer and MRI (0.45-0.67)[123]. With regards to sensitivity and specificity for emphysema diagnosis, MRI would seem superior to perfusion scintigraphy[124]. There is a very small amount of work regarding pathological validation and nuclear imaging, but so far these are animal models only[125,126].

OCT

OCT works through a bronchoscope and using near infra-red rays instead of soundwaves (used in ultra-sound), can give extremely precise image of the airway. Using two light beams with one shone onto a mirror to act as a standard measure, the other beam is directed into the tissue and the pattern and the amount that is reflected back is interpreted as an image[129]. It can visualise around 2-3 mm and gives almost a histological

Table 10 Demonstration of how optical coherence tomography could phenotype in chronic obstructive pulmonary disease

Condition	OCT method	Findings	Suggested treatments
Chronic bronchitis	Endoscopic	Increased volume of submucosal glands; central airway inflammation[133-135]	Investigations directed towards asthma overlap syndrome; targeted inhaled steroids
Emphysema	Anatomical OCT	Can visualise collapsibility dynamically[136]	Bronchodilators; smoking cessation

OCT: Optical coherence tomography.

view of the airway wall[130]. Unlike ultrasound which requires a water medium and direct contact to operate, the OCT probe doesn't need to be pressed against the airway wall. Better than CT or MRI, OCT can give a clear view of the airway wall components, *i.e.*, the submucosa, the smooth muscle, and cartilage[131]. In asthma and COPD where there is ongoing inflammation and subsequent airway remodelling, OCT would serve a purpose to view the causes of airway wall thickening and intra-luminal narrowing. The technology is already used in ophthalmology and cardiology, but in respiratory despite having promising capacity, it is still in its research phase.

PHENOTYPING

OCT can only image as far as the device carrying it (usually a bronchoscope) can go. Therefore this technology is limited to the airways and not the parenchyma. However, through creating a pleural window, and miniaturised devices within a 30 gauge needle, the probe can be inserted through the chest wall[132]. The potential for phenotyping patients in COPD could be assessing the amount of active inflammation, airway remodelling/fibrosis to assess why there are regional problems with sputum production or bronchiectasis. Those in favour of OCT have optimistic views that assessing airway pathology would make way for targeted therapeutic interventions (Table 10). OCT is in its infancy however, and more trials are needed.

CLINICAL VALIDATION

There have been two studies that have compared OCT to FEV1, both from the same group in 2008 and then 2014[137]. They find the correlation in these two studies between FEV1 and OCT to be strong (-0.75 and -0.78 respectively) though the 2014 study only found a significant correlation in the male subjects. The slope of the line plotted between OCT and FEV *vs* CT and FEV1 was steeper, and therefore the authors concluded OCT's potential superiority over CT for assessing small airways disease.

PATHOLOGICAL VALIDATION

Tsuboi took 7 human lungs immediately resected for lung cancer, and placed the OCT camera down. They showed that the images of the airway and of the alveolus taken from OCT matched though seen on histology, *i.e.*, definition between submucosa, smooth muscle and cartilage, and then the structure of the alveoli and its adjacent bronchial wall. In a small number of subjects, no statistical analyses were performed but the results are visually convincing[131,138].

CONCLUSION

Quantitative imaging techniques provide sensitive, repeatable and accurate information in COPD patients, and are likely to be used increasingly for both diagnosis and measuring the response to treatment. There are differences in the application of each modality and common pitfalls to be recognised, and standardising each of them is necessary before they can become a bigger player in clinical practice.

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P- Reviewer: Andell P, Meteran H, Pavasini R **S- Editor**: Song XX
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