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Automatic quantification of emphysema and airways disease on computed tomography

Landmark papers in respiratory medicine

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Computed tomography (CT) of the lungs is able to visualise the lungs with submillimetre resolution and has become the reference standard for emphysema assessment *in vivo*. CT, a simple densitometer, can aid automatic localisation and quantification of the extent of both emphysema and airway disease, nowadays with a radiation dose of below 1 millisievert for an average 70 kg adult. In this article we will give a brief overview of the three landmark studies describing the quantification of emphysema and small and large airways disease on CT.

Obstructive pulmonary diseases are characterised by the presence of airflow limitation caused by a combination of parenchymal destruction (*i.e.* emphysema) and airways disease (both small and large airways) in most cases due to tobacco smoking [1, 2]. Although spirometry is used to diagnose obstruction it is unable to differentiate between the underlying pathophysiological causes, and it is especially insensitive for diagnosis of emphysema and small airways disease. In addition, the extent to which both entities are present may differ between individuals with a "single disease" and it is conceivable that airways disease and emphysema need different treatment. A more accurate understanding of the degree of emphysema and airways disease in an individual patient may allow for better phenotyping and assist in finding specific therapeutic possibilities. As it is generally not feasible to obtain pathology samples of the lungs, CT offers a noninvasive method to assess the extent of emphysema and airway disease. Visual scoring of airways disease shows substantial inter- and intra-observer variability, and detailed assessment of the amount of emphysema is challenging and time-consuming. Automatic quantification may offer a solution to both localise and quantify the disease and has significantly evolved over the past decades.

Emphysema

Emphysema is the result of destruction of the alveolar walls leading to an abnormal permanent enlargement of air spaces distal to the terminal bronchioles [1]. CT is based on the differences

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in attenuation of X-rays between tissues (bone equals high attenuation, air equals low attenuation). Water, by definition, has a radiodensity in Hounsfield units (HU) of 0 and air has a radiodensity of –1000 HU. On CT, emphysema is depicted by the presence of abnormal low attenuation areas in the lungs. Visually areas of low-attenuation can be seen as abnormally dark areas (holes) in the lungs.

In 1984, Hayhurst *et al.* [3] showed that the frequency distribution of low attenuation voxels differed between individuals with and without a pathology of established emphysema. Their study included 11 patients in total, undergoing lung resection because of a lung tumour. The six patients with established emphysema had significantly more voxels in the –900 to –1000 HU range compared with the five patients without emphysema. It was concluded that the extent of low attenuation areas on CT could be used to measure the extent of emphysema. Four years later in a landmark study, Müller *et al.* [4] were the first to automatically quantify the extent of emphysema on chest CT. 28 patients who underwent lung resection because of a lung tumour were included in this study [4]. Quantification of emphysema on CT was carried out using the so-called "density mask" method, which automatically highlighted all low attenuation voxels below a predefined HU value. Three different HU values were examined, –900, –910 and –920 HU. The highlighted low attenuation values were automatically quantified and divided by the total lung volume to give a density mask score and density mask percentage. They compared these values with visual scores of emphysema and validated it with pathological grading of emphysema.

The automatic quantifications showed an excellent correlation with pathological emphysema (r=0.94). However, visual scoring of emphysema also showed excellent correlation with pathological grading of emphysema (r=0.90). The advantage of automatic quantification is that it is free of inter- and intra-observer variability and that is provides an exact percentage of the extent of low-attenuation areas. However, the value chosen to define areas of low-attenuation may differ among different scanners and CT (dose) protocols, and these values are sensitive to noise and inspiration level.

Large airways disease

The airways can be divided into the large (>2 mm) and small (<2 mm) airways. Because of the spatial limits of the CT scan the small airways cannot be directly visualised and only airway wall thickening of the large airways can be measured automatically. Small airways disease can be indirectly measured by quantifying air trapping on an expiration CT.

In the first study on quantification of the large airways manual outlining of the airway walls was carried out [5]. A disadvantage is that this is very time consuming and has high observer variability. The landmark publication by Nakano *et al.* [6] showed that automatic quantification of the large airways was feasible and associated with pulmonary function. Their study included 114 smokers, of which 94 had chronic obstructive pulmonary disease (COPD), and automatically measured the airway wall thickness of the apical bronchus to the right upper lobe because this bronchus was most reproducible between measurements and was visualised as a cross-section on axial CT images. The airway was measured using the so-called "full width at half maximum" (FWHM) method, which is based on attenuation increases and decreases as an X-ray travels through an airway. Accuracy of the automatic airway wall thickness measurements was validated in an airway phantom showing reasonable accuracy. Increased airway wall thickness was associated with lower forced expiratory volume in 1 s (FEV_1) and forced vital capacity. A drawback of their study method was using only a single specific airway to measure airway wall thickness, because airway wall thickness may differ by anatomic location. Also the use of FWHM leads to substantial overestimation of the real wall thickness. Correct methods can automatically segment the trachea and all large airways and solutions other than FWHM have been proposed.

Small airways disease

In contrast to emphysema and large airway walls, automatic quantification of air trapping has received little attention in the past two decades. Mets *et al.* [7] compared three techniques in COPD patients, but it remained difficult to separate air trapping from emphysematous regions, which both have a low attenuation on expiratory CT. Recently, Galbán *et al.* [8] published a paper that may become a landmark publication, in which they described a method to separate air trapping from emphysematous lung regions called parametric response mapping (PRM). PRM is a voxel-based method allowing quantification of air trapping by a pairwise analysis of the inspiration and expiration CT. Galbán *et al.* [8] showed that PRM was capable of automatically quantifying air trapping in 194 subjects participating in the COPDgene study. The included subjects spanned all four Global Initiative for Chronic Obstructive Lung Disease stages and control subjects with normal pulmonary function were also included. They showed that subjects with identical FEV_1 could show different degrees of air trapping and emphysema. Although the study by Galbán *et al.* [8] is very recent it could be regarded as a landmark study on the automatic quantification of air trapping. Recent studies also showed that PRM is

associated with FEV1 decline and improves diagnosis of COPD on CT [9, 10].

Summary

To sum up, automatic quantification of emphysema and large airways disease was introduced a few decades ago, but the automatic quantification of small airways disease (*i.e.* air trapping) is more recent. Nonetheless, the papers discussed have substantially increased our knowledge of automatic quantification of the different pathophysiological factors in obstructive pulmonary diseases. Despite many challenges, given the intrinsic limitations of CT, variations in patient instructions and novel CT reconstruction techniques, quantitative CT of the lungs will play a growing role in phenotyping of individual patients and the assessment of therapeutic interventions.

Conflict of interest

None declared.

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