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Validation of lung densitometry threshold at CT for the distinction between senile lung and emphysema in elderly subjects

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ABSTRACT: ***Validation of lung densitometry threshold at CT for the distinction between senile lung and emphysema in elderly subjects. M. Bellia, A. Benfante, M. Menozzi, G. Augugliaro, N. Scichilone, F. Cannizzaro, M. Midiri, V. Bellia.***

Background and Aims. **An ageing lung is characterised by distal airspace enlargement without alveolar wall destruction: therefore the anatomical distinction between senile lung and emphysema is clear-cut. In clinical settings the definition of precise boundaries between normalcy and pathology is more difficult with the risk of overdiagnosis. CT is an important diagnostic advancement in the field of COPD. Most methods for the evaluation of emphysema are based on the detection and measurement of areas characterised by a density level below a threshold assumed to characterize parenchymal destruction.**

Methods. **Our retrospective study included 47 healthy subjects (65-91 years), 36 never smokers and 11 former smokers. As a reference sample we recruited 9 patients with emphysema (69-81 years). Thoracic scan was performed by single slice spiral CT and acquired without contrast enhancement. For each scan and on both lungs we sampled eighteen regions of interest in the upper, middle and lower field. Mean lung density (MLD) and lower limit of normal (LLN) of density distribution were calculated.**

Results. **MLD for the whole study sample was -846±41 HU. -901 HU was the LLN of density distribution in the study sample. No significant correlation was noted between age and MLD. In the emphysematous sample the average lung density was -946±18 HU. The mean coefficient of variation was 3% in the healthy sample and 2% in the emphysematous one. The difference between groups was significant (p<0.0001). In one healthy subject only we measured a value slightly below the threshold reported in literature for conventional CT; no emphysematous value fell above the LLN.**

Conclusions. **This study highlights the fact that in the elderly the threshold level of lung density commonly adopted in diagnostic algorithms of emphysema is fully applicable. When applying this method to older subjects the risk of misinterpreting areas of physiologic non-destructive reduction of density as emphysema is low.**
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Keywords: Ageing, Emphysema, CT, Densitometry, Senile lung.

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Introduction

The reduction in birthrate and increase in life expectancy characterising recent decades are leading to the progressive aging of human population particularly in affluent countries [1]. Aging involves all organs and systems to a various extent. Respiratory system is particularly susceptible to time-related deterioration in structure [2-4] and function [5-7], since beside the genetically regulated physiological decline, it is exposed on a long term basis to environmental noxious factors including tobacco smoke, pollution and infections. Therefore there is a growing awareness of the fact that in the elderly population it may be difficult to distinguish between a "normal" and diseased lung [8-10]: for this reason there is an increased risk of overdiagnosing chronic obstructive pulmonary disease (COPD) among these subjects [11, 12].

In fact in spite of clear evidence of lack of destructive lesions, often senile lung (i.e. the pulmonary condition in healthy elderly persons) is still addressed as "senile emphysema", a misnomer to be reserved only to the late structural consequences of COPD [13].

The extensive use of computerised tomography (CT) has probably represented the most important diagnostic advancement recorded in recent years in the field of COPD [14-16]. Various methods for the evaluation of emphysema have been proposed on the basis of the quantitative assessment of attenuation dependent density of lung parenchyma [17-19].

In most cases these methods are grounded on the detection and measurement of areas characterised by a mean level of density below a definite threshold assumed to characterise areas of parenchymal destruction [20].

Senescence is accompanied by increased alveolar and ductal area implying a reduced attenuation of X rays and decreasing lung density at CT [8]. Investigations leading to the definition of density thresholds for diagnostic purposes have recruited adult individuals with minor participation of elderly subjects, if any. In this setting the present study aimed at answering the following questions: i) is the threshold level commonly adopted in diagnostic algorithms of emphysema applicable to the geriatric population? ii) how high is the risk of misinterpreting areas of physiologic non-destructive reduction of density as emphysema?

Material and Methods

The present retrospective study was carried out on two samples of subjects aged 65 years and over. The study sample included 47 healthy subjects aged 65-91 years (mean±SD = 75±7 years); among them 18 were males, 36 were lifelong non smokers while 11 were former smokers. None of them reported any personal history of respiratory diseases or symptoms. They were selected among subjects who had undergone a CT scan study as part of a follow up program of neoplasms affecting organs other than the lungs, or in the diagnostic work up of isolated peripheral lesions. For the purpose of the study we also adopted radiological exclusion criteria reported in table 1. We also excluded patients reporting the consumption of respiratory drugs or of drugs known or suspected to be toxic for the lungs. As a reference sample we recruited 9 patients who fulfilled the diagnostic criteria of COPD, according to GOLD guidelines, and showed imaging alterations of the lung compatible with emphysema. All of them were males; age ranged between 69 and 81 years (73±4.6 yrs). A thoracic scan was always performed by a single slice spiral CT equipment (multidetector 64 channels, Philips Medical System, Cleveland, Ohio, USA) according to the following protocol: axial scans from lung apices to bases were acquired with the patient in the supine position during an maximal lung inspiration, which corresponds to total lung capacity (TLC). Acquisitions were made with the following parameters: 8 mm slice thickness, 8 mm reconstruction index, 1,5 pitch, 120 Kv, 200 mAs. The regions of interest (ROI) [21] were selected from scans without contrast enhancement, viewed with a window level of -600 HU and width of 1600 HU. The analysis was carried out on scans obtained at three established levels: namely origin of great vessels, carina and origin of right lower pulmonary vein. All images were rendered anonymous. For each scan and on both lungs we manually selected ROI (Region of Interest), which are rounded regions of 5 mm diameter: this corresponds to the lowest areas that can be manually defined. Three ROI per lung field were selected in the upper, middle and lower part of the field [22, 23], at a minimum distance of 10 mm from mediastinal and parietal-costal pleura and avoiding great vessels and possible nodules. Lung density was then measured on 18 ROI per patient and mean values were calculated. The CT scans were analysed by one radiologist and two pulmonologists independently, and at different times. Statistical analysis was performed by Statview for Macintosh software package. Data was expressed as means and standard deviations. Student t test for unpaired samples was used for evaluating density difference between groups. Intra-subject variability was calculated as coefficient of variation, i.e. the ratio of the standard deviation to the mean. Analysis of variance (ANOVA) was applied to evaluate density differences between lung fields in the study group. Correlation between density and age was evaluated by simple regression analysis. A p value of (or below) 0.05 was considered as statistically significant. Lower limit of normal (LLN) was calculated as the lower fifth percentile of distribution.

Table 1. - Exclusion criteria for the study sample

Presence of any of the following:
- parenchymal masses
- pulmonary oedema
- pulmonary embolism
- ground glass areas
- bullae
- areas of centrilobular emphysema
- pleural diseases including mild to severe degree of pleural effusion, with or without evidence of compression atelectasis of adjacent parenchyma
- heart failure or cardiomegaly

Results

Density data, averaged for both lungs as well as for upper, middle and lower lung fields, are presented in figure 1. The inter-observer variability between the three observers was lower than 5%. Intra-subject variability of density distribution over lung fields, as assessed by the mean coefficient of variation, was 3% in the healthy sample and 2% in the emphysematous one. As a result of preliminary analysis in the study group (figure 2), density values measured in the subsamples of former and never smokers were not statistically different ($p=0.36$). Mean lung density (MLD) value over the whole study sample was -846±41 HU, with a range between -751 and -912 HU. In one case only we measured a value slightly below the threshold reported in literature for conventional CT (-910 HU) [24-27]. -901 HU was the LLN of density distribution in the study sample. No significant correlation was noticed between age and mean lung density. In the emphysematous sample the average lung density was -946±18 HU with values ranging between -916 and -979 HU (figure 3). The difference between the groups was statistically significant ($p<0.0001$), with no emphysematous value falling above the LLN.

Discussion

The results of the present study highlighted the fact that the threshold level commonly adopted in

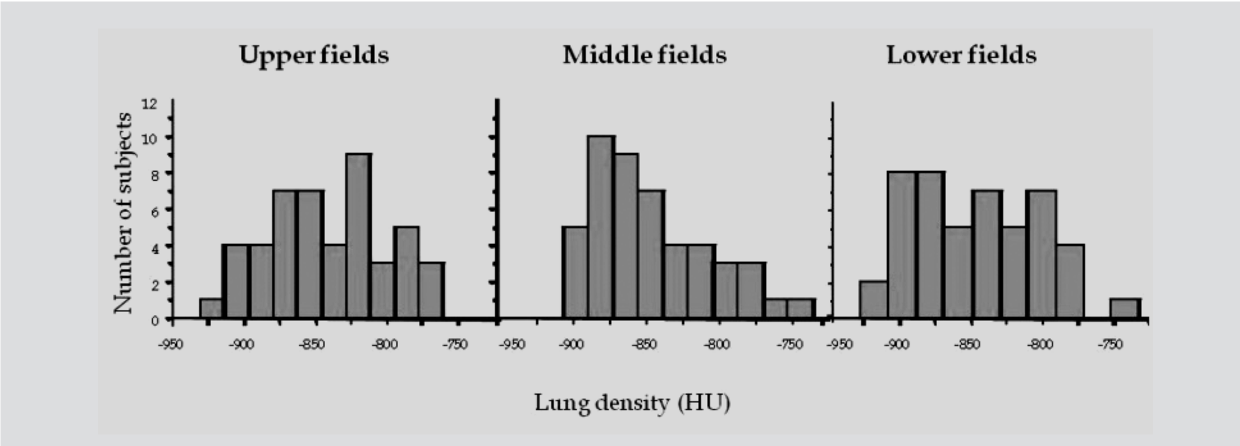

Fig. 1. - Distribution of lung density values in upper, middle and lower respiratory fields, in senile non emphysematous subjects.

diagnostic algorithms of emphysema based on lung density measurement is entirely applicable to the geriatric population. Secondly, by applying this method to older subjects the risk of misinterpreting areas of physiologic non-destructive reduction of density as emphysema is minor.

It is recognised that aging of lungs is characterised by distal airspace enlargement without alveolar wall destruction [8, 9]: therefore on anatomical basis the distinction between senile lung and emphysema is clear. However in the clinical setting, where CT scan is the best approximation of anatomical study, the definition of precise boundaries between normalcy and pathology may be more difficult since the physiological increase in the size of airspace could influence CT densitometry [28, 29].

In fact it has been generally accepted that for the sake of quantification of emphysema [30, 31] acceptable density threshold values are -900 -910 HU for conventional CT and -950 HU for HRCT [12, 32]. However this assumption has not taken the effect of aging into account and has never been validated in an elderly population.

In fact the relationship between aging and lung densitometry is controversial. An early paper investigating the CT density patterns in the normal lung, at various respiratory manoeuvres, reported the lack of correlation between density and age [33]: however, the requisite part of the study carried out relating to inspiratory breath holding concerned a limited number of subjects (nineteen), whereas the elderly component included only 5 subjects aged 60-70 years. A similar limitation affects a more recent study performed by High Resolution CT (HRCT) in a sample of 42 healthy subjects aged 23-72 years, including only 10 subjects aged 60 years and over [34]. Unsurprisingly, no correlation was found between mean lung density and age: however a significant correlation was reported between age and the extension of pulmonary area with attenuation values below the threshold of -950 HU [34]. More recently a different sort of evidence on age-related increase in peripheral airspace content has been reported by Lee *et al* who assessed air trapping by performing HRCT at end inspiration and at end expiration [35]. The study group consisted of 82 asymptomatic subjects whose age ranged 20 to 80 years (including 17 individuals aged 61 years or older). The extent of air trapping increased with age and the correlation was statistically significant.

A limitation of these studies was their cross-sectional design. Soejima *et al* [21] within the context of a study on smoking-induced lung density changes in subjects aged 59±12 yrs, submitted a subgroup of 36 asymptomatic non smoker subjects to annual monitoring over 5 years. During this period MLD did not significantly change, unlike what observed in smoke-exposed subjects, although in the middle or lower lung field the %LAA (relative area of low attenuation with CT values less than -912 HU) was significantly higher also in never-smokers after five years. Qualitative evidence on longitudinal changes has been produced by a Swedish group: in a previous study, Tylen *et al* performed HRCT in 57 smoking and 32 never-smoking healthy men 60 years of age [36]. The presence of emphysematous lesions was visually detected in 25 of 57 smokers, and in only one never smoker. At a 6-year interval no emphysematous lesions were detected in never smokers: however, septal lines, subpleural nodules and focal ground glass opacities were observed in both smokers and never smokers, although with increasing frequency in the former category [37].

These results demonstrate that aging of the lung is associated not only to an enlargement of airspaces mimicking emphysema. This is con-

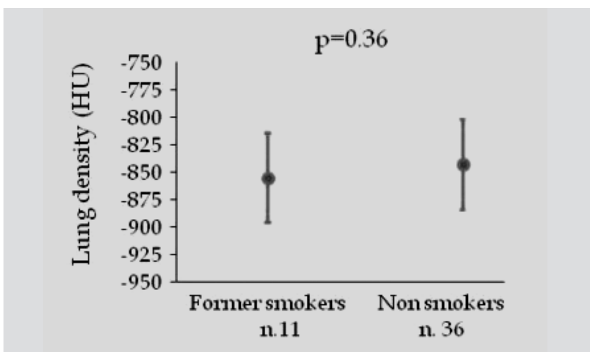

Fig. 2. - Comparison of mean values of lung density in subsample of non-emphysematous subjects: former smokers *vs* non smokers.

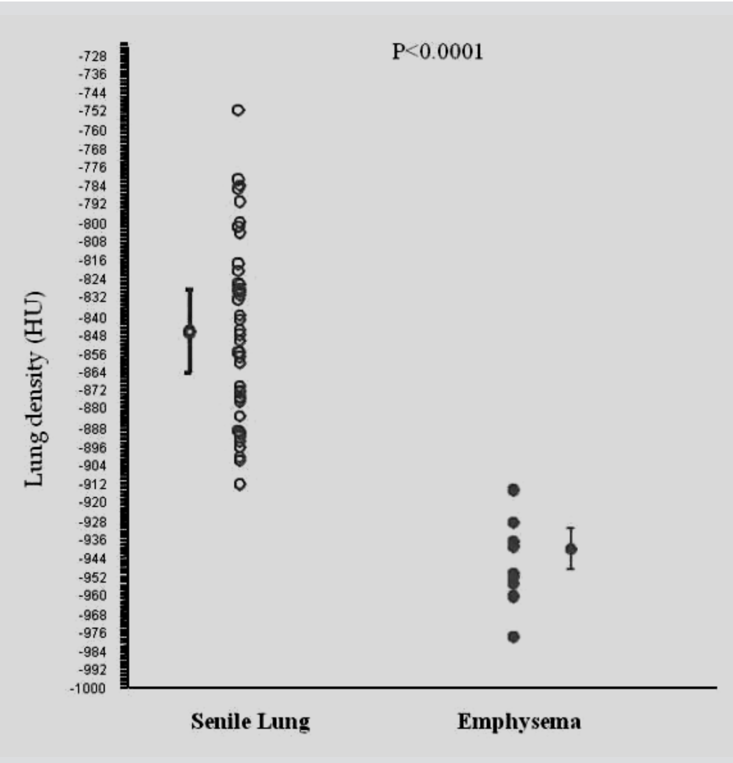

Fig. 3 - Difference in lung density values between senile lungs and emphysematous lungs. Level of statistical significance is indicated.

firmed by a recent study focused on asymptomatic elderly subjects comparing 40 volunteers aged over 75 years with a smaller group under 55 (mean age: 39.4 years) [38]. A limited predominantly subpleural reticular pattern was identified in 60% of older subjects; conversely, 25% showed thin walled cystic airspaces. Such lesions were never observed in in the younger group. Bronchial dilation and bronchial wall thickening were also common in the older group.

These results may explain why, although lung densitometry effectively distinguished senile lungs from the emphysematous ones, our results, as well as those coming from previous studies in the literature failed to find a correlation with age: in fact the increase in size of distal portions of the lung is a cardinal feature of aging process in the lungs but it is not the only one. It is reasonable to expect that at least in some cases age-related interstitial alterations, as those reported by Copley *et al* [38], increase x-ray attenuation and density thus obscuring to some extent the effect of peripheral structure dilatation and increase in air content. Densitometric studies suggest a decrease of approximately 50 HU between 20 and 70 years of age. The pathophysiology of structural and functional age-related changes has not been fully addressed, although pathologic studies have shown that, in healthy individuals, a progressive increase in alveolar diameter with ageing occurs [9, 39].

A potential limitation of this study may be the inclusion of both lifelong non-smokers and former smokers in the study sample. However a preliminary analysis excluded significant differences in lung density between subgroups: in addition, lung density measurements clearly discriminated between non emphysematous subjects as to exclude any confounding role of smoking past history in our study. A technical limitation concerns the use of conventional CT, i.e. of 8 mm sections, whereas the reference technique for the assessment of emphysema is HRCT, which is based on the evaluation of 1 mm sections. However, in our institution a prospective study submitting healthy elderly subjects to radiation exposure could have not been considered ethically warranted. Therefore we decided to avail ourselves of scans mostly obtained from patients with suspect or ascertained extrapulmonary oncologic diagnosis where the usual technique was traditionally based on 10 mm sections with the use of contrast medium. The threshold was chosen based on the literature specifically available for conventional CT. The resulting discrimination between clinically ineffective consequences of physiologic aging and emphysema is so straightforward as to make us confident that diagnostic procedures in HRCT based on the relevant density threshold would yield even better performance.

In conclusion our study highlights the diagnostic power of CT based methods for detection and quantification of emphysema even in the oldest old, avoiding unnecessary or harmful interventions.

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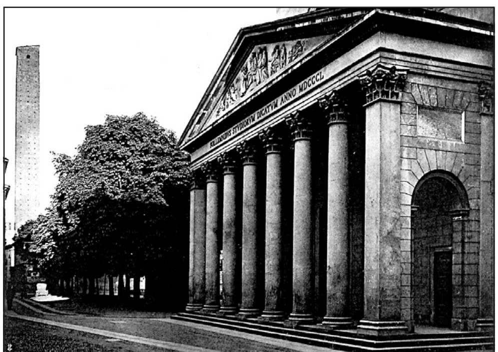

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