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A biomechanical hypothesis for the pathophysiology of apical lung disease

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ABSTRACT

Objective: A hypothesis is presented suggesting that the pathogenesis of apical lung disease is due to progression of subclinical congenital apical bullae in people with low Body Mass Index (BMI), a combination present in 15% of the population, due to high pleural stress levels present in the antero-posteriorly flattened chests of these individuals.
Design: The hypothesis was tested for validity in two apical lung pathologies with widespread epidemiological literature, namely tuberculosis (TB) and primary spontaneous pneumothorax (PSP), assessing whether the hypothesis could identify high-risk populations, explain exceptional cases like apical lower lobe disease and confirm predictions.
Results: The biomechanical hypothesis can explain the high-risk factors of apical location, age, gender and low-BMI build, as well as the occurrence of disease in the apex of the lower lobe, in both TB and PSP patients. A predicted common pathogenesis for apical lung disease was confirmed by the higher-than-expected incidence of concomitant TB and PSP.
Conclusion: Pleural stress levels depend on chest wall shape, but are highest in the apex of young males with low BMI, leading to growth of congenital bullae that can eventually limit clearance inhaled material, superinfect or burst. This hypothesis suggests that low-dose computerized tomography may be used to screen for TB eradication. This paper is the first to propose a biomechanical mechanism for all apical lung disease pathophysiology.

1. Introduction

Some lung pathologies are localized preferentially in the lung apex. The reason for this may due to the variation in ventilation, perfusion, ventilation-perfusion ratio and lymphatic flow present between different areas of the lung.

In the normal erect posture, the apex is relatively hyperventilated due to well-expanded alveoli resulting from the combination of a high negative apical pleural pressure but limited compliance resulting in a local respiratory alkalosis [1]. Gravity restricts perfusion to the apex, with lymphatic flow showing a similar pattern, driven by perfusion and respiratory motion.

Small-sized inhaled particles can bypass the mucociliary escalator and may require clearance from the alveoli [2]. This is said to explain the upper lobe occurrence of emphysema secondary to cigarette smoke inhalation, pneumoconiosis from inhaled particulates, and extrinsic allergic alveolitis and aspergillosis from inhaled antigens.

The apical location of the highly aerobic Mycobacteria and other granulomatous disease is explained by the high partial pressures of oxygen in the lung apex, the relative hyperventilation and decreased apical lymphatic clearance; with apical cavitation occurring after tuberculous reactivation [3]. Furthermore, local apical

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respiratory alkalosis may explain the upper lobe location of metastatic pulmonary calcification [1].

Distortion of the apex of the lung, dragged down by gravity, and restricted chest wall mobility may cause increased mechanical stress and may account for apical pulmonary disease like ankylosing spondylitis [4]. A possible biomechanical cause with increased mechanical stress has also been suggested for primary spontaneous pneumothorax (PSP) and reactivation of tuberculosis (TB) [5,6].

The hypothesis considered here is that pre-existing congenital lung bullae progress through a biomechanical mechanism, and predispose to most apical lung disease by bursting of the bulla, or abnormal clearance of a bacterial superinfection or inhaled material. In effect, the apical bulla causes apical lung disease. This hypothesis should not be discordant with existing theories, and yet deliver a more complete explanation.

2. Hypothesis

Lung blebs or bullae at the apex of the lung, with walls less than 1 mm in thickness, occur in about 15% of 'normal' subjects, with this cohort having a significantly lower BMI than controls [7]. Progression of these bullae in low BMI individuals occurs due to high mechanical stress levels resulting from a combination of the prolate ellipsoid shape of the lung apex (the shape of an American football) and the presence of lung furrows caused by prominent first ribs [8], with the stress magnified by coughing in an antero-posteriorly flattened low BMI chest [5], see Figs. 1 and 2.

The progress of such subclinical apical lung bullae may lead to rupture and PSP, but may also lead to super-infection that can occur in a pre-existing cavity that may limit clearance inhaled material in the case of TB, aided by apical scarring that may impair lymphatic drainage. Thus the cavity occurs before the onset of TB or other apical pathology, not afterwards.

The biomechanical hypothesis thus links low BMI body builds with an antero-posteriorly flattened chest wall shape and increased apical pleural stress, with the stress resulting in progression of apical cavities and causes development of apical lung pathology. An antero-posteriorly flattened thorax is commonly found in young males [9].

3. Problems with conventional pathogenesis of apical lung disease

3.1. Primary spontaneous pneumothorax

Noppen stated that the pathogenesis of PSP is unknown, and is therefore defined as a disease with no apparent cause, in the absence of underlying lung disease [10]. PSP is a significant global health issue [11], with an incidence of 18-28/100,000 cases per annum for men and 1.2-6/100,000 for women [12], and until recently these patients were thought to have a "heritable defect" in their structure [13].

3.2. TB

TB infection occurs in two stages: initial primary infection with *Mycobacterium tuberculosis* and reactivation or progression to active secondary disease [14]. Conventionally, the reason why TB selects the apex of low BMI males after adolescence for reactivation has remained elusive [15]. The reason why males have a higher incidence of TB is also unknown [16]. The increase in male infection rate in adolescence is said to be marked by an enigmatic "sudden emergence" of cavitating lung disease typical of adults [17,18].

Conventional theory suggests that the apical and posterior segments of the upper lobes are sites of high pO_2 levels [19], and impaired lymphatic drainage [20,21]. As pulmonary TB has a predilection to the apical region of the lower lobe [22,23], this suggests that oxygen levels and gravity may not be such important factors after all; however our model fits as the 'bullet' shape of the lower lobe apex would result in increased pleural stress.

Besides not explaining disease in the apex of the lower lobe, conventional theory does not explain the reason why tuberculous disease emerges in male adolescents, see Fig. 3, or the connection with a low BMI, or why the increase in adolescence occurs in the lungs and not in other organs. Furthermore, conventional theory does not explain why tuberculous pneumothorax rarely develops in miliary pulmonary TB as compared to secondary TB [24,25].

4. Methods

The epidemiology of apical lung disease was investigated to distinguish high-risk populations. TB and PSP were selected due to their more extensive epidemiological literature. In both pathologies, disease occurred in (a) the lung apices of (b) young (c) males with a (d) low BMI build. The biomechanical hypothesis was then tested in three ways to evaluate its validity. Firstly to assess whether the hypothesis offered complete explanations for the four patterns of risk described above; secondly whether it could explain exceptional cases like disease in the apices of the lower lobes; and thirdly whether it was predictive.

Since this hypothesis suggests a common pathogenesis for apical lung disease, the incidence of concomitant TB and PSP was predicted to be significantly raised. Another prediction was that high apical pleural stress, secondary to the flattened chest wall shape, would specifically only affect pulmonary TB and not TB in other organs; and that the at-risk population for TB reactivation would be limited to the 15% of the population with congenital apical bullae rather than the general population. Ethical approval was not required for this retrospective study.

5. Results

5.1. Apex of the lung

5.1.1. PSP

Video-assisted thoracic surgery (VATS) has shown blebs in almost all (76–100%) PSP patients, with blebs commonly present in patients reaching surgery [26], and often seen on CT scanning [27]. The bullet shape of the apex of the upper lobe results in a tenfold increase in stress compared to the base [6], explaining the location of apical lung bullae.

5.1.2. TB

The apical location of secondary TB in the lungs is well described. The biomechanical hypothesis explains the development of bullae in the upper lobe apex, but also apical lower lobe pneumothoraces and tuberculosis [22], due to the stress-inducing bullet shape of the apex of the lower lobe. However, the conventional explanations of high oxygen levels and gravity do not explain occurrence of TB disease in the apex of the lower lobes.

5.2. Age

5.2.1. PSP

Primary spontaneous pneumothorax typically occurs in males between the ages of ten and thirty years [28]. Mean thoracic index (ratio of antero-posterior to lateral chest wall diameters) is significantly lower in males and changes with age leading to rounder