A biomechanical hypothesis for the pathophysiology of apical lung disease

Aaron R. Casha [a,b,*], Alexander Manché [a], Liberato Camilleri [c], Ruben Gatt [d], Krzysztof Dudek [e], Michael Pace-Bardon [f], Marilyn Gauci [g], Joseph N. Grima [d]

[a] Department of Cardiothoracic Surgery, Mater Dei Hospital, Malta
[b] Department of Anatomy, Faculty of Medicine, University of Malta, Malta
[c] Department of Operational Research and Statistics, Faculty of Science, University of Malta, Malta
[d] Metamaterials Unit, Faculty of Science, University of Malta, Malta
[e] Department of Physics and Astronomy, Uniwersytet Zielonogórski, Zielona Góra, Poland
[f] Department of Medicine, Mater Dei Hospital, Malta
[g] Department of Anaesthesia, Mater Dei Hospital, Malta

ARTICLE INFO

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.

© 2016 Elsevier Ltd. All rights reserved.

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

* Corresponding author at: Department of Cardiac Services, Mater Dei Hospital, Msida MSD 2090, Malta.
E-mail address: aaron.casha@um.edu.mt (A.R. Casha).

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 anteroposteriorly 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
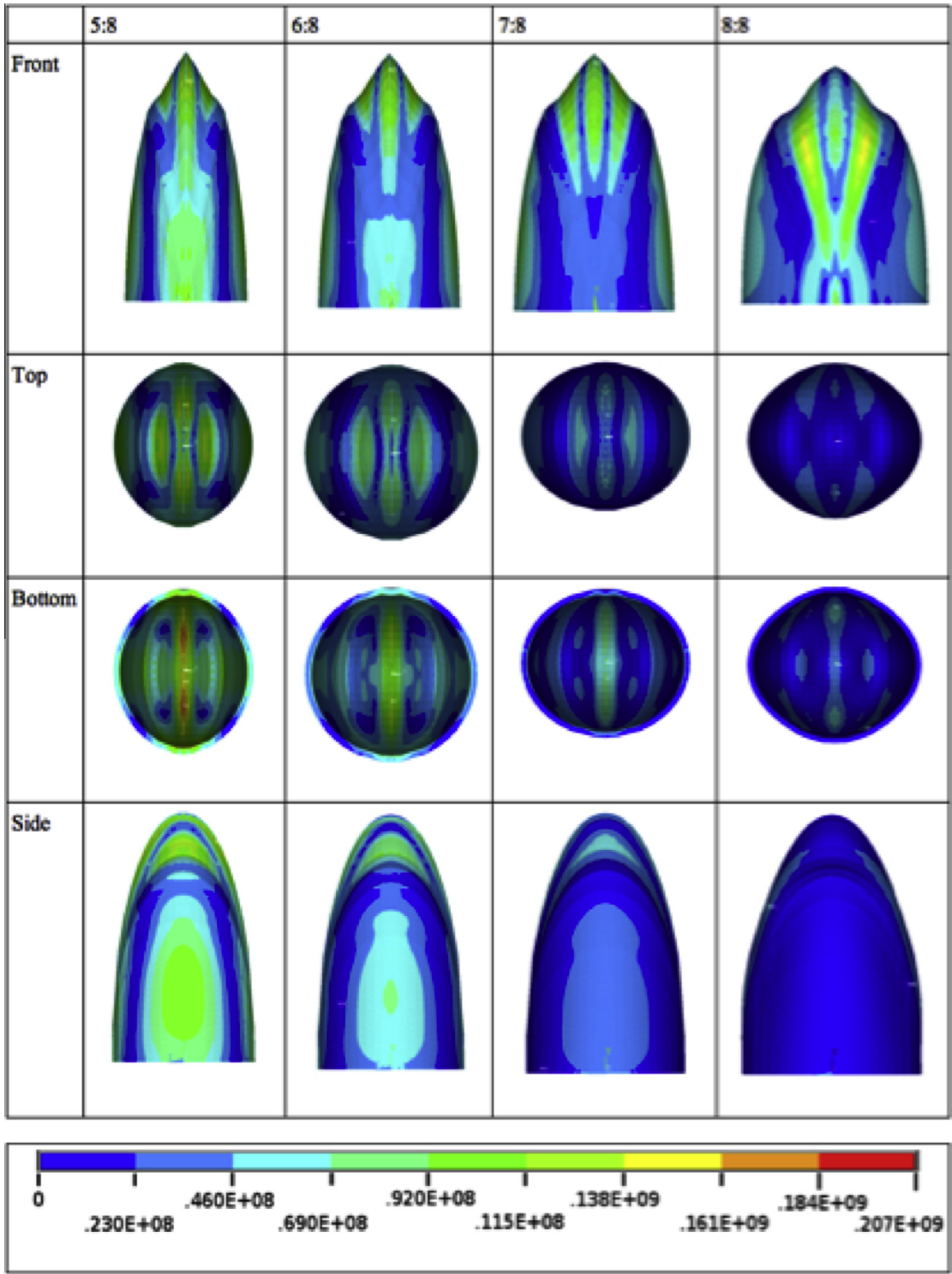
Fig. 1. Stresses within the pleura on maximal inflation with differing chest wall antero-posterior to lateral diameter ratios. Pleural stress is maximal at the apex and at the site of the first rib furrows in antero-posteriorly flattened chests. Modified after Casha [5].

chest [9]. There is a diminution of apical lung stress in rounded chests resulting from increasing age [5], with the flattest chests (and therefore higher apical stress) occurring in adolescents [29].

conventional theory, but can be explained by the low stress in the lung apex in the elderly and high apical stress in the young.

5.3. Gender

5.2.2. TB

Pulmonary TB in the elderly results in lower lobe pneumonia, similar to other bacterial infections [19], which does not fit in with

5.3.1. PSP

The incidence of spontaneous pneumothoraxes is much higher in males compared to females – 18-28/100,000 cases per annum
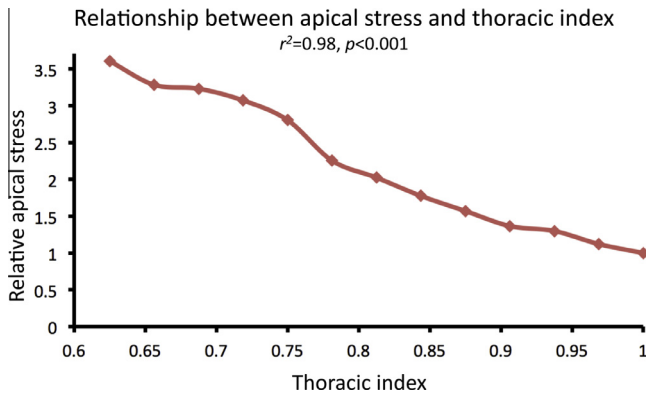
Fig. 2. Correlation between stress in the lung apex relative to lung base and thoracic index (ratio of antero-posterior to lateral chest wall diameters), $r^2 = 0.9748$ $p < 0.001$. Redrawn after Casha [6].

Fig. 4. Graph showing the association between BMI and TB incidence. Redrawn after Lonnroth [17].

for men and 1.2-6/100,000 for women [12]. Males have a statistically significant lower thoracic index, or antero-posteriorly flattened chest, than females starting from adolescence [9], and therefore suffer higher apical lung stress [5].

5.3.2. TB

The prevalence of TB is identically low in both sexes until adolescence, after which it is higher in males [28], with the increase occurring in puberty, and marked by the "sudden emergence" of cavitating lung disease typical of adults [17], see Fig. 3.

5.4. Low BMI

5.4.1. PSP

Low BMI is associated with a low thoracic index, or an antero-posteriorly flattened chest [30]. Such a flattened chest results in a tenfold increase in pleural stress in a lung finite element analysis, i.e. computer simulation model, compared with a rounder chest [6]. Patients with primary spontaneous pneumothorax are predominantly young tall thin males [10], with a diminished antero-posterior diameter and low thoracic index [31].

5.4.2. TB

Secondary pulmonary TB is associated with low BMI at various levels of TB incidence, see Fig. 4, without an obvious biological
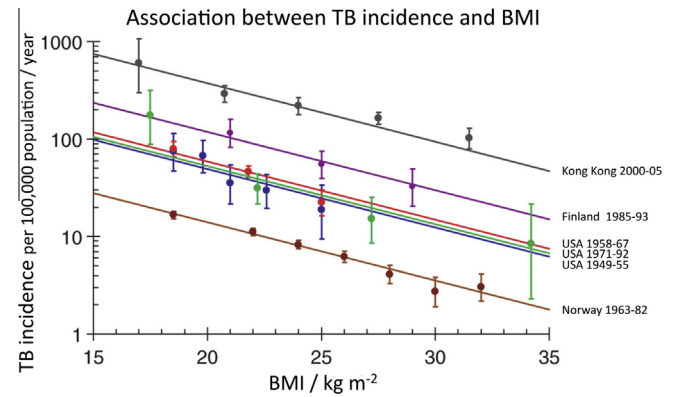
mechanism [32]. Lonnroth reviewed seven prospective studies that removed the confounding effect of weight loss caused by TB and showed that the incidence of new pulmonary TB was five times higher in a low BMI group (BMI < 21) as compared to a high BMI group (BMI > 31) [15], in spite of the fact that high BMI patients with diabetes have an increased susceptibility to TB. However this remarkable association between pulmonary TB and BMI was not observed for extra-pulmonary TB [33], suggesting that low BMI predisposes to an increased risk for pulmonary TB only, and not for non-pulmonary TB.

6. Predictions from hypothesis

A useful hypothesis, as defined by Stephen Hawkings, has to be a predictive hypothesis [34]. Since spontaneous pneumothorax and tuberculosis are hypothesized to have a similar biomechanical cause, these pathologies are predicted to occur concurrently fairly frequently even though both TB and spontaneous pneumothorax are rare. The incidence of TB is typically about 7:100,000 [35], and that of spontaneous pneumothorax 18:100,000 in Swedish males [36], suggesting that concurrent disease should be extremely rare. However 5.4% of spontaneous pneumothorax patients had TB and 2.1% of patients with TB had spontaneous pneumothorax [37], implying that the pathophysiology of these two different pathologies must be connected, as predicted by this hypothesis.
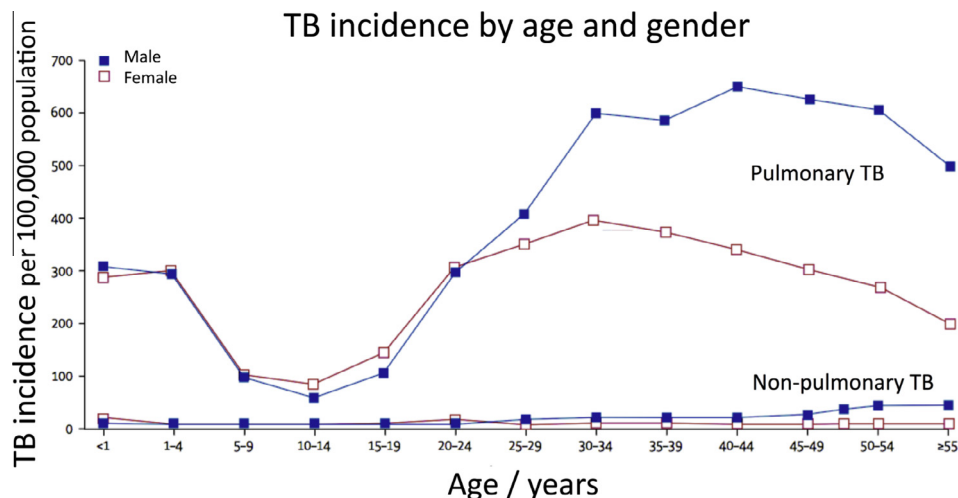

Fig. 3. Incidence of tuberculosis in males and females by age group. There is a sudden increase in disease in adolescent males due to a sudden increase in pulmonary TB, but not in non-pulmonary TB. Redrawn after Donald [17].

Apical pleural stress, secondary to the flattened chest wall shape, should specifically only affect pulmonary TB and not TB in other organs. The reactivation of TB increases in adolescence and young adults, in males more than females, only in the lung similar to lung apical stress, in contrast with reactivation of non-pulmonary TB, which remains constant and low [17], see Fig. 3.

The fact that lung bullae or blebs occur in 15% of the population [7] suggests that the pool of individuals at high risk of TB progression would be a similar percentage. This hypothesized proportion would fit in with the prediction by Esmail, based on the epidemiology of TB, that the at-risk population for TB reactivation is significantly smaller than the 2.33 billion immune-sensitized by *Mycobacterium tuberculosis* [38].

This hypothesis may also cover the pathophysiology of chronic pulmonary histoplasmosis, massive fibrosis of the lung due to silicosis, coal-workers pneumoconiosis [21], ankylosing spondylitis, extrinsic allergic alveolitis and aspergillosis by abnormal clearance of inhaled material from apical bullae associated with a low BMI and low thoracic index chest wall shape [5]; such patients would be expected to present at a young age – between twenty to forty years age.

7. Screening

Although thoracic ultrasound can be used to diagnose apical bullae, experience is limited with few published reports and the procedure is both operator-dependent and limited with possible poor echographic windows [39,40], However since low dose computerized tomography (CT) has been proposed as a safe and effective yearly screening tool for lung cancer [41] with a 0.3 mSe radiation exposure, as compared with the conventional contrast CT radiation dose of 7 mSe; low-dose CT scanning could also be used to screen for apical blebs or bullae in young adult males with a low BMI. The emphasis here is on low radiation CT scanning, as higher dose CT scans are known to result in an increase in lung cancer [42,43]. It is hoped that low-dose thoracic CT may provide the enhanced screening required to eradicate TB by identifying the at-risk population with congenital bullae that are likely to be responsible for TB progression and dissemination.

It is hoped that this paper will stimulate further investigations in this field, in particular to assess the effectiveness of population screening for TB in low thoracic index, low BMI individuals with subclinical apical lung bullae. A clinical trial designed to compare the efficacy of low-dose CT screening in TB patients versus non-TB patients with low BMI and similar age would also permit computer modeling of apical stresses and may further help to support the hypothesis. It is hoped that this may deliver important public health consequences in terms of screening, since cavitating pulmonary TB is the major pathway for TB transmission.

8. Conclusion

This paper introduces the concept of a common pathophysiological pathway for apical lung disease through a biomechanical mechanism. It attempts to validate this hypothesis by showing this hypothesis to be simple and plausible following Occam's razor; that it offers a complete explanation for the four epidemiological factors of age, gender, apical location and low BMI; that it explains special cases like TB and PSP in the apex of the lower lobe; and is predictive about the incidence of concomitant TB and PSP. Further, this hypothesis clarifies why only pulmonary tuberculosis increases at adolescence due to changes in thoracic index; suggests that the at-risk population for TB reactivation would be limited to only the 15% of the population with congenital apical bullae; and

indicates a potential method of TB screening – thus addressing the requirements for a complete model [34].

References

[1] Gurney JW, Schroeder BA. Upper lobe lung disease: physiologic correlates. Rev Radiol 1988;167:359–66.
[2] Thomas RJ. Particle size and pathogenicity in the respiratory tract. Virulence 2013 Nov;4:847–58.
[3] Balasubramanian V, Wiegeshaus EH, Taylor BT, Smith DW. Pathogenesis of tuberculosis: pathway to apical localization. Tuber Lung Dis 1994;75:168–78.
[4] Nemec SF, Bankier AA, Eisenberg RL. Upper lobe – predominant diseases of the lung. AJR 2013;200:W222–37.
[5] Casha AR, Manché A, Gatt R, Wolak W, Dudek K, Gauci M, et al. Is there a biomechanical cause for spontaneous pneumothorax? Eur J Cardiothorac Surg 2014;45:1011–6.
[6] Casha AR, Camilleri L, Manché A, Gatt R, Attard D, Wolak W, et al. A hypothesis for reactivation of pulmonary tuberculosis: how thoracic wall shape affects the epidemiology of tuberculosis. Clin Anat 2015;28:614–20.
[7] Amjadi K, Alvarez GG, Vanderhelst E, Velkeniers B, Lam M, Noppen M. The prevalence of blebs and bullae among young healthy adults: a thoracoscopic evaluation. Chest 2007;132:1140–5.
[8] Stephenson SF. Spontaneous pneumothorax: the sharp rib syndrome. Thorax 1976;31:369–72.
[9] Takahashi E, Atsumi H. Age differences in thoracic form as indicated by thoracic index. Hum Biol 1955;27:65–74.
[10] Noppen M, de Keukeleire T. Pneumothorax Res 2008;76(2):121–7.
[11] MacDuff A, Arnold A, Harvey J, On behalf of the BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline. Thorax 2010;65(Suppl 2):ii18–31.
[12] Melton LJ, Hepper NGG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. Am Rev Respir Dis 1979;120:1379–82.
[13] Voge VM, Anthracite R. Spontaneous pneumothorax in the USAF aircrew population: a retrospective study. Aviat Space Environ Med 1986;57:939–49.
[14] Cegielski P, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004;8:286–98.
[15] Lonnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol 2010;39:149–55.
[16] Diwan VK, Thorson A. Sex, gender, and tuberculosis. Lancet 1999;353:1000–1.
[17] Donald PR, Marais BJ, Barry 3rd CE. Age and the epidemiology and pathogenesis of tuberculosis. Lancet 2010;375:1852–4.
[18] Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:392–402.
[19] Fitzgerald DW, Sterling TR, Haas DW. Mycobacterium tuberculosis. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier; 2014. p. 2787–818.
[20] MacGregor RR. Tuberculosis: from history to current management. Semin Roentgenol 1993;28:101–8.
[21] Goodwin RA, DesPrez RM. Apical localization of pulmonary tuberculosis, chronic pulmonary histoplasmosis, and progressive massive fibrosis of the lung. Chest 1983;83:801–5.
[22] Jeong YJ, Lee SK. Pulmonary tuberculosis: up-to-date imaging and management. Am J Roentgenol 2008;191:834–44.
[23] Rao NA, Sadiq MA. Recent trends in the radiological presentation of pulmonary tuberculosis in Pakistani adults. JPMA 2002;52:501–3.
[24] Mukhamedov K, Muzrabekov A, Massavirov S, Ismailova F, Djurayev N. Fibrous cavernous pulmonary tuberculosis complicated by spontaneous pneumothorax. Eur Respir J 2011;38(S44):457.
[25] Arya M, George J, Dixit R, Gupta RC, Gupta N. Bilateral spontaneous pneumothorax in miliary tuberculosis. Indian J Tuberc 2011;58:125–8.
[26] Margolis M, Gharagozloo F, Tempesta B, Trachiotis GD, Katz NM, Alexander EP. Video-assisted thoracic surgical treatment of initial spontaneous pneumothorax in young patients. Ann Thorac Surg 2003;76:1661–4.

[27] Lesur O, Delorme N, Frogamet JM, Bernadac P, Polu JM. Computed tomography in the aetiological assessment of idiopathic spontaneous pneumothorax. Chest 1990;98:341–7.

[28] Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of TB. Int J Tuberc Lung Dis 1998;2:96–104.

[29] Openshaw P, Edwards S, Helms P. Changes in rib cage geometry during childhood. Thorax 1984;39:624–7.

[30] Bellemare JF, Cordeau MP, Bellemare F. Thoracic dimensions at maximum lung inflation in normal subjects and in patients with obstructive and restrictive lung diseases. Chest 2001;119:376–86.

[31] Peters RM, Peters BA, Benirschke SK, Friedman PJ. Chest dimensions in young adults with spontaneous pneumothorax. Ann Thorac Surg 1978;25:193–6.

[32] Cegielski JP, Arab L, Cornoni-Huntley J. Nutritional risk factors for tuberculosis among adults in the United States, 1971–1992. Am J Epidemiol 2012 Sep 1;176 (5):409–22.

[33] Tverdal A. Body mass index and incidence of tuberculosis. Eur J Respir Dis 1986 Nov;69(5):355–62.

[34] Stephen Hawking Larsen K. A Biography. Greenwood Publishing Group; 2005.

[35] World Bank. 2015. Incidence of Tuberculosis. Available at: URL: http://data.worldbank.org/indicator/SH.TBS.INCD/countries. Accessed on 13 January 2015.

[36] Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. Eur Respir Rev 2010;19:217–9.

[37] Freixinet JL, Caminero JA, Marchena J, Rodríguez PM, Casimiro JA, Hussein M. Spontaneous pneumothorax and tuberculosis: long-term follow-up. Eur Respir J 2011;38:126–31.

[38] Esmail H, Barry 3rd CE, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Phil Trans R Soc B 2014;369 20130437.

[39] Campione A, Luzzi L, Gorla A, Terzi A. About ultrasound diagnosis of pulmonary bullae vs. pneumothorax. J Emerg Med 2010;38:384–5.

[40] Sandionigi F, Cortellaro F, Forni E, Coen D. Lung ultrasound: a valid help in the differential diagnosis between pneumothorax and pulmonary blebs. Emergency Care J 2013;9:3.

[41] National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. NEJM 2011;365:395–409.

[42] Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 2009;180:445–53.

[43] Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial (DLCST): status after five annual screening rounds with low-dose CT. Thorax 2012;67:296–301.