

Pneumothorax and Bullae in Marfan Syndrome

Craig Karpman^a Gregory L. Aughenbaugh^b Jay H. Ryu^c

^aMayo Graduate School of Medicine, ^bDepartment of Radiology, and ^cDivision of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, Minn., USA

Key Words

Pneumothorax • Marfan syndrome • Bullous diseases

Abstract

Background: Increased risk of spontaneous pneumothorax has been described in patients with Marfan syndrome and has been attributed, in part, to the presence of apical blebs and bullae. **Objectives:** We assess the risk of pneumothorax and its relationship to the presence of apical blebs and bullae in patients with Marfan syndrome in the era of CT imaging. **Methods:** A retrospective cohort study was performed of all patients 13 years or older with Marfan syndrome evaluated at the Mayo Clinic, Rochester, Minn., USA, from 1998 through 2008. One hundred and sixty-six patients met the current diagnostic criteria for Marfan syndrome and had chest imaging studies available for review. **Results:** The median age was 40 years (range 14–71); 37% had a smoking history. Eight of 166 patients (4.8%) had experienced 1 or more episodes of spontaneous pneumothorax, and 2 of these 8 patients had 2 or more episodes. Apical blebs or bullae were identified on radiologic imaging in 16 patients (9.6%). Four of 16 (25%) patients with apical blebs or bullae had a history of spontaneous pneumothorax compared to 4 of 150 patients (2.7%) without blebs or bullae ($p = 0.003$). **Conclusions:** The frequency of blebs is relatively low in patients with Marfan syn-

drome but the risk of pneumothorax is significantly higher in those with radiologically detectable blebs or bullae. Chest CT scanning to identify blebs and bullae may allow risk stratification for pneumothorax in patients with Marfan syndrome.

Copyright © 2011 S. Karger AG, Basel

Introduction

Marfan syndrome is one of the most common inherited disorders of connective tissue and occurs worldwide. It is an autosomal dominant condition with a reported incidence of 1 in 3,000–5,000 individuals [1]. There is no predilection for either sex. Most patients with Marfan syndrome harbor mutations involving the *FBN1* gene which is located at chromosome 15q-21.1 [2]. The *FBN1* gene encodes the matrix protein fibrillin-1, an important component of both elastic and nonelastic connective tissues. It is the main protein of a group of connective tissue microfibrils that are essential to normal elastic fibrillogenesis. More than 25% of Marfan syndrome cases probably represent new mutations. In a minority of cases, a mutation in *FBN1* is not identified.

There is a wide range of clinical severity seen in patients with Marfan syndrome but, to date, no correlation

between the specific type of *FBNI* mutation and clinical phenotype has been recognized. Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation and dissection, is the main cause of morbidity and mortality in Marfan syndrome. However, patients with Marfan syndrome display manifestations in other organs including ocular, musculoskeletal and central nervous systems as well as the lung.

Several pulmonary manifestations of Marfan syndrome have been described [1, 3]. These include restrictive lung disease from pectus excavatum or scoliosis, emphysema, bullae, apical blebs and increased risk of spontaneous pneumothorax [3–7]. This increased risk of pneumothorax has been attributed to the presence of apical blebs, bullae, abnormal connective tissue constituents in the lung parenchyma, or increased mechanical stresses in the lung apices due to the tall body habitus [3, 5, 7]. These studies addressing the issue of spontaneous pneumothorax in Marfan syndrome were performed before the widespread use of CT in chest imaging. Herein, we reassessed the frequency of spontaneous pneumothorax, apical blebs and bullae in patients with Marfan syndrome seen in the current era of CT imaging. We also explored the relationship between these manifestations.

Patients and Methods

The study was undertaken at the Mayo Clinic in Rochester, Minn., USA. A computer-assisted search was performed to identify all cases of Marfan syndrome undergoing a first-time evaluation during an 11-year period from 1 January 1998 to 31 December 2008. The patients' confidentiality was maintained and approval was obtained from the Mayo Foundation Institutional Review Board prior to beginning the study. The diagnosis of Marfan syndrome was assigned using the revised diagnostic criteria published in 1996 [8]. This diagnostic scheme is still based largely on clinical findings in various organ systems but the requirements for criteria are more stringent compared to previous guidelines.

Since pneumothorax in Marfan syndrome has been reported in individuals beyond childhood, we limited this study to those 13 years or older, similar to a previous study on this topic [5]. Of 202 subjects identified who met these criteria, 27 did not have chest imaging studies (chest radiography or chest CT scan) available for current review and 9 other subjects did not have the lung apex included in CT imaging. The remaining 166 patients formed the study cohort with 110 chest CT scans and 56 chest radiographs (for those without a CT scan) reviewed. One of the 56 chest radiographs was performed in the setting of pneumothorax while others were taken with lungs fully expanded.

Table 1. Common manifestations related to Marfan syndrome (n = 166)

Characteristic	Patients
Aortic root dilation, dissection or prior aortic root replacement	111 (67)
Aortic valve regurgitation	69 (41)
Optic lens abnormality	53 (33)
Scoliosis	50 (30)
Pectus excavatum	45 (27)

Figures in parentheses are percentages.

Data Collection and Analysis

Medical records were reviewed to extract demographic data, smoking history, clinical features including a history of pneumothorax and comorbidities. Only 17 patients had pulmonary function data available, and thus, pulmonary function data were not analyzed. Radiologic studies were reviewed by 2 of the authors (J.H.R. and G.L.A.) independently, and differences in interpretation were settled by consensus. In those subjects with more than 1 chest imaging study, the most recent study was evaluated. Parenchymal abnormalities were noted, particularly apical blebs and bullae, along with pneumothorax. A bleb was defined as a gas-containing space in the subpleural lung, measuring ≤ 1 cm in diameter [9]. A bulla was defined as an airspace measuring >1 cm in diameter demarcated by a thin wall that is ≤ 1 mm in thickness [9].

All data were analyzed using the JMP 7.0 statistical software (SAS Institute, Cary, N.C., USA). The χ^2 test was used for the analysis of categorical data when values were >5 . Fisher's exact test was used for the analysis of categorical data when values were <5 .

Results

In this cohort of 166 patients, there were 97 (58%) males and 69 (42%) females. The median age of the cohort was 40 years (range 14–71). Sixty-two patients (37%) had a smoking history. The most common Marfan-related manifestation (table 1) was aortic root pathology (68%), followed by aortic valve regurgitation, optic lens abnormality, scoliosis and pectus excavatum. Eighteen (11%) described dyspnea on exertion or chronic dyspnea. Eleven (7%) patients had been diagnosed to have lung disease that included restrictive lung disease secondary to pectus or spine deformity (6 patients), asthma (3 patients) and chronic obstructive pulmonary disease (2 patients).

Eight patients (4.8%), 17–36 years of age, had experienced 1 or more episodes of spontaneous pneumothorax. Characteristics of these 8 patients and their management

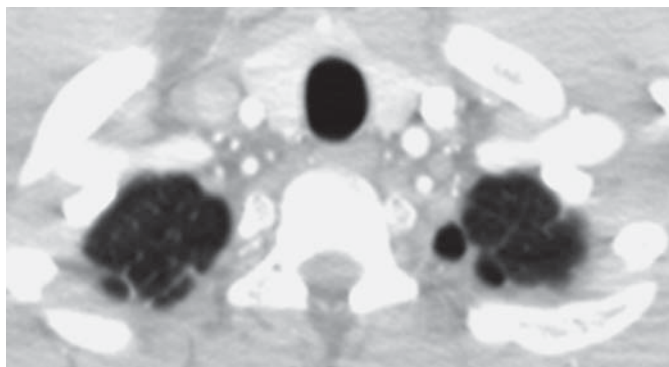


Fig. 1. CT scan of the chest of a 26-year-old woman with Marfan syndrome who had previously had 1 episode of left-sided spontaneous pneumothorax (at 17 years of age) managed with chest tube drainage alone. Small apical blebs are seen in the apex of the left lung. No other lesions were present in the lungs.

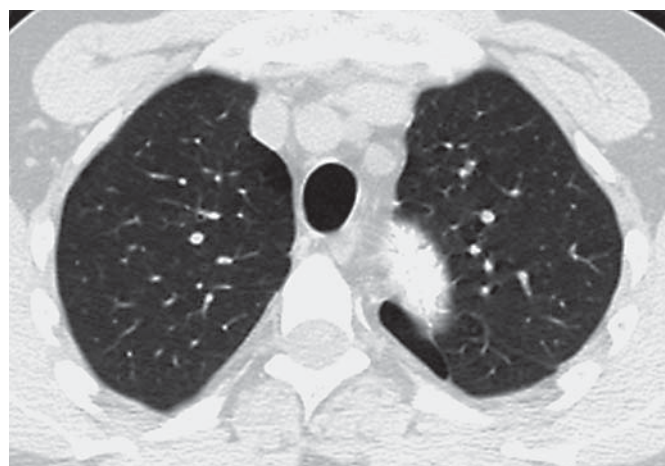


Fig. 2. CT scan of the chest of a 31-year-old woman with Marfan syndrome with no previous history of pneumothorax. A subpleural bulla is seen in the left lower lobe posteriorly. This patient also had biapical blebs and 2 other bullae.

Table 2. Characteristics of 8 Marfan patients with spontaneous pneumothorax

Characteristic	Patients
Age at first pneumothorax, years	
Median	21
Range	17–36
Male sex	6 (75%)
Smoking history	
Current	1
Previous	2
Never	5
Number of pneumothorax episodes	
Median	1
Range	1–3
Management of pneumothorax	
Observation only	1
Chest tube drainage only	3
Pleurodesis	2
Surgical resection and pleurodesis	2

are outlined in table 2. Six of these patients had 1 episode of pneumothorax, 1 patient had 2 episodes of ipsilateral pneumothoraces, and the remaining patient had 3 episodes of unilateral pneumothoraces affecting both sides. The patient with 2 episodes of ipsilateral pneumothoraces underwent a pleurodesis, and the patient with 3 episodes

of pneumothoraces underwent a resection of apical blebs with pleurodesis on the side of the recurrent pneumothorax. A 36-year-old woman, the oldest of the 8 patients, experienced a spontaneous pneumothorax requiring chest tube placement during pregnancy. Two additional patients had a history of pneumothorax that was not spontaneous and was identified during the postoperative period after aortic root surgery.

Apical blebs or bullae were present in 16 (9.6%) patients as identified on chest CT or chest radiography (fig. 1, 2). These lesions were identified by CT in 11 patients (10.0% of those evaluated by CT) and by chest radiography in 5 patients (8.9% of those evaluated by chest radiography). Four of the 16 (25%) patients with apical blebs or bullae had a history of spontaneous pneumothorax compared to 4 of the 150 (2.7%) patients without bullae or blebs identified radiologically ($p = 0.003$). Thus, 4 of the 8 (50%) patients with a history of spontaneous pneumothorax had evidence of apical blebs or bullae. In all 4 patients, blebs or bullae were identified on the side where the pneumothorax occurred.

Of 62 patients with a history of smoking, 19 were active and 43 past smokers at the time of evaluation. The incidence of pneumothorax was similar between the patients with a smoking history (3 of 62, 4.8%) and the non-smokers (5 of 104, 4.8%; $p = 1.0$). We did not find a significant difference between the incidence of apical blebs or bullae in smokers (7 of 62, 11.3%) versus non-smokers

(9 of 104, 8.6%; $p = 0.777$). In patients with pectus excavatum, 1 out of 45 (2%) had a history of spontaneous pneumothorax and 4 (9%) had evidence of blebs or bullae. Both values were not significantly different ($p = 0.684$ and 1.0, respectively) when compared to patients without pectus excavatum.

The presence of blebs, bullae and spontaneous pneumothorax was also assessed in relation to the presence or absence of aortic root pathology. Five of 111 patients (4.5%) with aortic root disease had a history of pneumothorax, compared to 3 out of 55 patients (5.4%) without aortic root disease ($p = 0.529$). The patients with aortic root disease tended toward a lower prevalence of blebs and bullae compared to those without aortic root disease, i.e. 8 of 111 patients (7.2%) versus 8 of 55 (14.5%), respectively ($p = 0.111$).

Discussion

Marfan syndrome is a common inherited connective tissue disorder with several respiratory manifestations, with spontaneous pneumothorax being the most frequently reported [3]. In the current study, the frequency of spontaneous pneumothorax was found to be 4.8% in a cohort of patients with a median age of 40 years. Our patients with a history of pneumothorax were young adults with a mean age of 21 years at the time of their initial pneumothorax and more likely to be male (6 of 8 subjects). A positive correlation was found between the presence of apical blebs or bullae and the occurrence of spontaneous pneumothorax with more than a 9-fold increased risk of pneumothorax in those subjects with identifiable apical blebs or bullae. Current or past smoking history did not appear to increase the likelihood of spontaneous pneumothorax.

Two prior studies published in the 1980s reported the prevalence of pneumothorax in Marfan patients to be 4 and 11%, respectively [5, 7]. These 2 studies described patients experiencing spontaneous pneumothorax to be young adults and more often men than women, similar to our findings [5, 7]. Wood et al. [7] noted that spontaneous pneumothorax patients had a high prevalence of skeletal abnormality (8 of 11) such as pectus deformity, but we did not note a significant effect of pectus excavatum on the incidence of pneumothorax. Furthermore, we noted no significant correlation between pulmonary findings and the presence or absence of aortic root disease. Use of medications to reduce the incidence of aortic root dilatation may have confounded this analysis.

With chest radiography alone, Wood et al. [7] identified 5 of 100 (5%) patients with Marfan syndrome to have apical bullae, while Hall et al. [5] noted bullous apical lesions in 9 of 249 subjects (3.6%). With the addition of CT scanning in the majority of subjects, we found a higher prevalence than expected, with 16 of 166 subjects (9.6%) having apical bullae or blebs. However, it should be noted that the presence of blebs and bullae has been described in normal subjects as well. Amjadi et al. [10] performed bilateral thoracoscopic evaluation in the course of thoracic sympathectomy for idiopathic hyperhidrosis and identified blebs in 6% of 250 otherwise healthy subjects (mean age 29 years) with no preexisting lung disease. Similarly, Lesur et al. [11] described the presence of bullae on CT scanning in 2 of 20 control subjects (10%) with no history of lung disease. Thus, it is unclear whether the frequency of blebs and bullae in Marfan patients is truly higher than in normal subjects. In addition, it remains controversial as to whether blebs and bullae are the actual sites of air leakage in patients with primary spontaneous pneumothorax [10–13]. Aside from the presence or absence of blebs, abnormal connective tissue constituents in the lung parenchyma of Marfan patients may predispose to pneumothorax.

The frequency of spontaneous pneumothorax is higher in patients with Marfan syndrome than in the general population [3, 5]. Due to this increased incidence, these individuals have been advised to avoid scuba diving, fast ascents in elevators and playing brass instruments, as those activities may lead to a pneumothorax [14, 15]. Our findings indicate that not all individuals with Marfan syndrome have the same increased risk of spontaneous pneumothorax, and by using available imaging studies, physicians may be able to stratify patients into higher- and lower-risk groups. If future studies confirm the ability to risk stratify using chest CT scanning, one may be able to de-escalate the concern for spontaneous pneumothorax in many patients with Marfan syndrome, i.e. those without apical blebs or bullae.

Although we find the presence of blebs and bullae to be associated with the risk of pneumothorax in patients with Marfan syndrome, it is possible that blebs and bullae may not be the actual sites of air leak in patients with these lesions. For example, some investigators have suggested that blebs and/or bullae have no predictive value for recurrence in patients with primary spontaneous pneumothorax (patients without underlying lung disease) and that peripheral airway obstruction with airtrapping may be the main mechanism for pneumothorax in these subjects [13, 16–18]. In addition, fluorescein-en-

hanced thoracoscopy has revealed areas of parenchymal abnormality that are not identified by white light thoracoscopy and may potentially be the sites of air leak ('pleural porosities') in patients with primary spontaneous pneumothorax [19]. These types of investigations have not been performed in patients with Marfan syndrome. However, previous reports have identified emphysematous changes of varying severity in histopathologic examination of lung biopsy and autopsy specimens from patients with Marfan syndrome [20–22]. Aberrant fibrillin-1 expression was recently implicated in the pathogenesis of early emphysema in humans [23]. It is plausible that defective connective tissue components may give rise to both blebs and bullae as well as to the increased risk of pneumothorax without blebs and bullae necessarily being the sites of air leak in patients with Marfan syndrome. Indeed, some of our patients who experienced spontaneous pneumothorax did not have radiologically identifiable parenchymal lesions.

There are limitations to our study results. Patient selection was based on individuals seeking treatment at a large referral medical institution. It is possible that evaluation of this cohort led to an overestimation of the prevalence of both cardiac and pulmonary comorbidities in the Marfan population, indicating that the true likelihood of spontaneous pneumothorax may be less frequent than described. Not all patients underwent chest CT scanning. Thus, we provided the data on the frequency of blebs and bullae separately for those evaluated by chest radiography

and CT. In addition, the retrospective study design did not allow for formal calculation of incidence, allowing only comparison to prior similarly designed studies. Although the size of the cohort was smaller when compared to the 249 patients evaluated by Hall et al. [5], we used a more stringent diagnostic criterion for Marfan syndrome and it is the first study to use CT scans to evaluate the presence of parenchymal abnormalities [8]. Longitudinal observational data would be more informative in providing lifetime incidence of pneumothorax in Marfan syndrome.

Conclusions

In conclusion, the incidence of spontaneous pneumothorax in patients with Marfan syndrome was relatively low and was even lower in patients without radiologically detectable blebs or bullae. Smoking did not appear to influence the risk of pneumothorax in individuals with Marfan syndrome. Chest CT scanning to identify blebs and bullae may allow risk stratification for pneumothorax in patients with Marfan syndrome and influence lifestyle recommendations and management decisions.

Financial Disclosure and Conflicts of Interest

None.

References

- 1 Judge DP, Dietz HC: Marfan's syndrome. *Lancet* 2005;366:1965–1976.
- 2 Ramirez F, Dietz HC: Marfan syndrome: from molecular pathogenesis to clinical treatment. *Curr Opin Genet Dev* 2007;17:252–258.
- 3 Tanoue LT: Pulmonary involvement in collagen vascular disease: a review of the pulmonary manifestations of the Marfan syndrome, ankylosing spondylitis, Sjogren's syndrome, and relapsing polychondritis. *J Thorac Imaging* 1992;7:62–77.
- 4 Dwyer EM, Troncale F: Spontaneous pneumothorax and pulmonary disease in the Marfan syndrome. Report of two cases and review of the literature. *Ann Intern Med* 1965;62:1285–1292.
- 5 Hall JR, Pyeritz RE, Dudgeon DL, Haller JA: Pneumothorax in the Marfan syndrome: prevalence and therapy. *Ann Thorac Surg* 1984;37:500–504.
- 6 Streeten EA, Murphy EA, Pyeritz RE: Pulmonary function in the Marfan syndrome. *Chest* 1987;91:408–412.
- 7 Wood JR, Bellamy D, Child AH, Citron KM: Pulmonary disease in patients with Marfan syndrome. *Thorax* 1984;39:780–784.
- 8 DePaepe A, Devereux RB, Deitz HC, Heinnekam RCM, Pyeritz RE: Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417–426.
- 9 Hansell DM, Bankier AA, MacMahon TC, McLoud TC, Muller NL, et al: Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697–722.
- 10 Amjadi K, Alvarez GG, Vanderhelst E, Velkeniers B, Lam M, et al: The prevalence of blebs or bullae among young healthy adults: a thoracoscopic investigation. *Chest* 2007;132:1140–1145.
- 11 Lesur O, Delorme N, Formaget JM, Bernadac P, Polu JM: Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. *Chest* 1990;98:341–347.
- 12 Bense L, Lewander R, Eklund G, Hedenstierna G, Wiman LG: Nonsmoking, non-alpha1-antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of the lungs. *Chest* 1993;103:433–438.
- 13 Noppen M, De Keukeleire T: Pneumothorax. *Respiration* 2008;76:121–127.
- 14 Dean JCS: Marfan syndrome: clinical diagnosis and management. *Eur J Hum Genet* 2007;15:724–733.
- 15 Dietz HC: Marfan syndrome. National Center for Biotechnology Information, 2009. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=marfan>.

- 16 Schramel FM, Postmus PE, Vanderschueren RG: Current aspects of spontaneous pneumothorax. *Eur Respir J* 1997; 10:1372–1379.
- 17 Schramel FM, Zanen P: Blebs and/or bullae are of no importance and have no predictive value for recurrences in patients with primary spontaneous pneumothorax. *Chest* 2001; 119:1976–1977.
- 18 Smit HJ, Golding RP, Schramel FM, Deville WL, Manoliu RA, Postmus PE: Lung density measurements in spontaneous pneumothorax demonstrate airtrapping. *Chest*, 2004; 125:2083–2090.
- 19 Noppen M, Dekeukeleire T, Hanon S, Stratakis G, Amjadi K, et al: Fluorescein-enhanced autofluorescence thoracoscopy in patients with primary spontaneous pneumothorax and normal subjects. *Am J Respir Crit Care Med* 2006; 174:26–30.
- 20 Dwyer EM Jr, Troncale F: Spontaneous pneumothorax and pulmonary disease in the Marfan syndrome. Report of two cases and review of the literature. *Ann Intern Med* 1965; 62:1285–1292.
- 21 Sayers CP, Goltz RW, Mottiaz J: Pulmonary elastic tissue in generalized elastolysis (cutis laxa) and Marfan's syndrome: a light and electron microscopic study. *J Invest Dermatol* 1975; 65:451–457.
- 22 Dominguez R, Weisgrau RA, Santamaria M: Pulmonary hyperinflation and emphysema in infants with the Marfan syndrome. *Pediatr Radiol* 1987; 17:365–369.
- 23 Robbesom AA, Koenders MM, Smits NC, Hafmans T, Versteeg EM, et al: Aberrant fibrillin-1 expression in early emphysematous human lung: a proposed predisposition for emphysema. *Mod Pathol* 2008; 21:297–307.