The correlation between spinal and chest wall deformities and pulmonary function in Marfan syndrome

Hila Otremski¹
Roger F. Widmann²
Mary F. Di Maio³
Dror Ovadia¹

Abstract

Purpose Scoliosis, chest wall deformities and pulmonary involvement are common features of Marfan syndrome (MFS). We aimed to assess the impact of spinal and chest wall deformities on pulmonary function in paediatric MFS patients with a surgically managed spinal deformity.

Methods In this multicentre retrospective study, spirometry, lung volumes and radiographic imaging were performed on 26 MFS patients between the ages of seven and 18 years who were undergoing planned spinal fusion surgery for spinal deformity. A correlation analysis assessed the relationship between radiographic measurements of spinal and chest wall deformities and predicted total lung capacity (TLC), forced vital capacity (FVC) and the ratio between forced expiratory volume in one second and FVC (FEV1/FVC).

Results In total, 18 patients (70%) had impaired pulmonary function. Thoracic kyphosis (mean 19.3°; -32° to 54°) had a strong positive correlation with FEV1/FVC (r = 0.65; p < 0.001). Significant decrease in FEV1/FVC below 80% occurred at kyphosis under 15° (p = 0.004). Kyphosis had a moderate negative correlation with FVC (r = -0.43; p = 0.03). Chest wall deformity had a strong negative correlation with FEV1/FVC (r = -0.61; p = 0.001). The magnitude of the thoracic curve (mean 55.2°; 28° to 92°) had a significant moderate negative correlation with TLC (r = -0.45; p = 0.04).

Conclusion In MFS, three factors correlate with decreased pulmonary function measures: hypokyphosis, increasing chest wall deformity and increasing coronal curve magnitude. Hypokyphosis and increased chest wall deformity correlated with diminished FEV1/FVC; increasing thoracic spinal curvature with diminished TLC. Further analysis with a larger cohort will help better define the relationship between these deformities and pulmonary function in this unique population.

Level of Evidence: IV

Keywords: Marfan syndrome; scoliosis; chest wall deformity; pulmonary function; spinal deformity

Introduction

Marfan syndrome (MFS) is a connective tissue disorder with an estimated incidence of two to six persons per 100 000.¹ It is caused by mutations in the gene Fibrillin-1 (FBN1) on chromosome 15 that encodes the FBN1 protein, which is an essential part of the connective tissue of the cardiovascular and musculoskeletal systems. MFS is usually an autosomal dominant disorder, however, sporadic mutation is evident in up to 25% of cases.

Though a typical phenotype does exist for MFS, the clinical expression is broad and may differ even among members of the same family. The syndrome involves several body systems, most importantly the cardiovascular, ocular and skeletal systems.²,³ MFS’ effect on the skeletal system includes arachnodactyly, dolichostenomelia, generalized ligamentous laxity and chest, spine, pelvic and foot deformities.

A deformity of the thoracic cage (pectus carinatum or excavatum) and scoliosis are among the most common features of MFS and exist to some degree in approximately 60% of the patients.⁴-⁶ Pulmonary involvement in MFS can be found in approximately 63% of the patients. It may consist of restrictive or obstructive disease and occurs due to skeletal deformities or possible an abnormal lung parenchyma.⁷-¹¹
Previous studies have identified the relationship between the magnitude and shape of a scoliotic curve and pulmonary function in patients with adolescent idiopathic scoliosis.\textsuperscript{12-17} Additionally, the effect of chest wall deformities on pulmonary function has been described.\textsuperscript{18-20} There are few studies regarding pulmonary function in MFS, and the relationship between spinal or thoracic chest deformity and pulmonary function has not been well studied. The aim of this study was to determine the effect of scoliosis, kyphosis and chest wall deformity on the pulmonary function of pediatric patients with MFS.

Materials and methods

Patients

This study is a multicentre collaboration between two high volume paediatric orthopaedic departments. Institutional review board approval from both centres was obtained and a retrospective database search was performed identifying all patients with a diagnosis of MFS who had undergone spinal surgical intervention between the years 2000 and 2018. The diagnosis of MFS was made according to the revised Ghent nosology.\textsuperscript{21} Patients were excluded if they were > 21 years old at the time of surgery or if either radiographs or pulmonary function tests (PFT) prior to surgery were not available.

Spinal radiographic parameters

Preoperative radiographs were evaluated for scoliosis, thoracic kyphosis and chest wall deformity. Thoracic scoliosis and kyphosis were measured by a single trained observer (HO) who was not involved in the care of the patients using validated software for spinal measurements (Surgimap, Nemaris Inc., New York, New York).\textsuperscript{22} If two curves were present, the larger thoracic curve was used for the purpose of the study. Thoracic kyphosis was measured from the superior endplate of T5 to the inferior endplate of T12. Chest wall deformity was assessed using the sterno-vertebral (SV) ratio; this describes the ratio of the lateral width of the vertebral body at the level of the maximum SV distance in the midthoracic region, multiplied by 100. This number is divided by the distance between the posterior cortex of the sternum and the anterior cortex of the vertebral body at the same level.

PFTs

All patients underwent PFTs prior to surgery according to American Thoracic Society and European Respiratory Society guidelines.\textsuperscript{24} Spirometry and lung volumes were used to measure vital capacity (VC), total lung capacity (TLC), forced VC (FVC) and forced expiratory volume in one second (FEV1). A TLC and FVC ≥ 80% of the predicted value and a FEV1/FVC of ≥ 80% of the predicted value were considered normal.\textsuperscript{24,25} Interpretation of the PFT was based on established reference values available during the years of this study but in some instances varied from site to site.

Statistical analysis

The SPSS software (IBM, Chicago, Illinois) was used to analyze the correlation between the PFT results and the preoperative radiographic measurements (Cobb magnitude of the coronal plane thoracic curve, the sagittal plane Cobb angle between T5 and T12 and the SV ratio). Due to our limited sample size (26 patients) we used nonparametric statistical tests. Relationships between the variables were analyzed using Spearman’s rank correlation with a two-tailed test of significance. Quantitative variables were compared using the Mann-Whitney U test. Multiple regression analysis was not performed because of the small sample size. Statistical significance was defined as a p-value of < 0.05.

Results

In all, 35 MFS patients treated with spinal fusion between the years 2000 and 2018 were identified in a database search of both centres. Nine patients were excluded due to unavailable radiographs or PFTs. For the remaining 26
patients (13 female), the mean age at surgery was 13.8 years (7 to 18) and preoperative radiographs and PFT were reviewed (Table 1 and 2, respectively). One patient was missing a lateral radiograph and several patients had incomplete PFT data; in most of these cases lung volumes were not performed. Additionally, the spirometry data for patient 9 and the lung volume data for patient 20 were excluded from the statistical analysis because of the inability to perform these tests in a reproducible manner.

### Thoracic kyphosis

The mean thoracic kyphosis measured as the Cobb angle between T5 and T12 was 19.3° (-32° to 54°). The

---

**Table 1 Spinal curvatures and chest wall deformity characteristics**

| Case | Sex | Age, yrs | Scoliosis, ° | Thoracic kyphosis D5–12, ° | SV ratio |
|------|-----|----------|--------------|-----------------------------|---------|
| 1    | F   | 15       | Lt. T1-10 39 | 34                          | 21.07   |
| 2    | F   | 13       | Rt. T5-10 68 | 50                          | 26.7    |
| 3    | F   | 13       | Rt. T5-11 66 | 21                          | 22.7    |
| 4    | F   | 13       | Rt. T4-10 74 | 19                          | 27.9    |
| 5    | F   | 12       | Lt. T5-11 67 | n/a                         | 0.55    |
| 6    | F   | 15       | Lt. T5-11 48 | 29                          | 21.9    |
| 7    | F   | 10       | Rt. T5-12 86 | 48                          | 18.2    |
| 8    | F   | 12       | Rt. T6-12 57 | 26                          | 44.9    |
| 9    | M   | 14       | Rt. T6-10 34 | 23                          | 20.4    |
| 10   | M   | 15       | Rt. T6-12 61 | 29                          | 18      |
| 11   | F   | 10       | Rt. T5-10 50 | -1.8                        | 33.3    |
| 12   | F   | 7        | Lt. T6-11 38 | 29                          | 24.4    |
| 13   | M   | 15       | Rt. T6-11 88 | 22                          | 47.4    |
| 14   | M   | 17       | Rt. T4-L1 59 | 19                          | 29.4    |
| 15   | F   | 17       | Rt. T5-12 57 | 27                          | 43.1    |
| 16   | F   | 17       | Rt. T6-L1 74 | 54                          | 24.9    |
| 17   | M   | 16       | Rt. T7-L1 59 | 30                          | 19.4    |
| 18   | M   | 12       | Rt. T5-10 29 | -19°                        | 24.4    |
| 19   | M   | 13       | Rt. T7-L1 92 | 3                           | 28.9    |
| 20   | M   | 13       | Rt. T5-11 42 | 25                          | 34.07   |
| 21   | M   | 15       | Rt. T7-L1 55 | -9°                         | 40.8    |
| 22   | M   | 17       | Lt. T2-8 29  | -32°                        | 109     |
| 23   | F   | 10       | Rt. T5-10 35 | 1                           | 33.9    |
| 24   | M   | 18       | Rt. T6-10 28 | 14                          | 39.5    |
| 25   | M   | 17       | Lt. T3-8 50  | 17                          | 34.6    |
| 26   | M   | 15       | Rt. T6-11 51 | 26                          | 44.8    |

*minus sign depicts lordosis

**Table 2 Pulmonary functional test measurements**

| Case | VC, % | RV, % | TLC, % | FVC, % | FEV1, % | FEV1/FVC, % |
|------|-------|-------|--------|--------|---------|-------------|
| 1    | n/a   | n/a   | n/a    | 45     | 52      | 100         |
| 2    | n/a   | 131   | 86     | 59     | 62      | 85          |
| 3    | 75    | 116   | 87     | 91     | 99      | 93          |
| 4    | n/a   | n/a   | n/a    | 83     | 79      | 92          |
| 5    | 71    | 113   | 81     | 71     | 64      | 77          |
| 6    | 43    | 128   | 65     | 41     | 48      | 99          |
| 7    | n/a   | n/a   | n/a    | 30     | 32      | 89          |
| 8    | 65    | 120   | 79     | 66     | 58      | 74          |
| 9    | 88    | 121   | 95     | 81     | 90      | 91          |
| 10   | n/a   | n/a   | n/a    | 76     | 77      | 95          |
| 11   | n/a   | n/a   | n/a    | 73     | 64      | 85          |
| 12   | n/a   | 143   | 104    | 83     | 90      | 116         |
| 13   | 49    | 242   | 91     | 40     | 37      | 81          |
| 14   | 81    | 154   | 101    | 93     | 77      | 89          |
| 15   | n/a   | n/a   | n/a    | 65     | 65      | 88          |
| 16   | n/a   | n/a   | n/a    | 55     | 54      | 48          |
| 17   | n/a   | n/a   | n/a    | 77     | n/a     | 82          |
| 18   | n/a   | 91    | 98     | 112    | 82      | 63          |
| 19   | 54    | 47    | 46     | 60     | 52      | 73          |
| 20   | 67    | 989   | 255    | 71     | 54      | 70          |
| 21   | 57    | 61    | 59     | 55     | 45      | 74          |
| 22   | 58    | 128   | 72     | 49     | 46      | 78          |
| 23   | 103   | 53    | 90     | 99     | 93      | 80          |
| 24   | 123   | 98    | 117    | 116    | 102     | 82          |
| 25   | 87    | 102   | 94     | 87     | 92      | 90          |
| 26   | n/a   | 82    | 56     | 51     | 49      | 82          |

VC, vital capacity; RV, residual volume; TLC, total lung capacity; FVC, functional vital capacity; FEV1, forced expiratory volume in one second; n/a, not available.
negative values depict a reversal of the natural kyphotic thoracic spine into a lordotic angle. The thoracic kyphosis had a strong positive correlation (Table 3) with FEV1/FVC (n = 25; r = 0.65; p < 0.001). A significant decrease in FEV1/FVC below 80% occurred at kyphosis under 15° (p < 0.005) (Fig. 2). Additionally, the degree of kyphosis had a moderate negative correlation with FVC (n = 24; r = -0.43; p = 0.03) and moderate positive correlation with the residual volume (RV) (n = 16; r = 0.55; p = 0.02). No significant correlation was found between the thoracic kyphosis and FEV1 (n = 24; r = -0.18; p = 0.39).

Thoracic coronal curve
The mean thoracic curve was 55.2° (28° to 92°). The magnitude of the thoracic curve had a significant moderate negative correlation (Table 3) with TLC (n = 19; r = -0.45; p = 0.04). A significant decrease in TLC below 80% occurred at 40° (p = 0.02) (Fig. 3). No other significant correlation was found between the coronal curve magnitude and the PFT.

Chest wall deformity
Examination of the SV ratio revealed a mean ratio of 33.3 (18 to 109). It had a strong negative correlation (Table 4) with FEV1/FVC (n = 24; r = -0.61; p = 0.001) (Fig. 4). No other significant correlations were found between the SV ratio and the other PFT measurements.

Discussion
A well-known association has been established between spinal deformity and pulmonary function. Numerous studies in the adolescent idiopathic scoliosis population have found a correlation between increasing thoracic scoliosis and hypokyphosis with pulmonary impairment.12-17 Similar associations have been found in more unique populations such as osteogenesis imperfecta and arthrogryposis multiplex congenital.23,26-28 Both a restrictive and an obstructive pulmonary pattern have been described in populations with spinal deformity. The restrictive findings can be attributed to decreased chest wall compliance, decreased rib excursion, possible decreased respiratory strength and the effect of placing the diaphragm at a mechanical disadvantage for inspiration and expiration. It has been suggested that obstructive lung disease could be secondary to increased airway smooth muscle tone, asthma variant, lower airway malacia or intrathoracic airway compression due to chest wall deformity. Recently, the 3D effect of scoliosis on the tracheobronchial tree has been demonstrated by using chest CT reconstruction of the spine and airway.29 In this study bronchial compression correlated with reduction in FEV1/FVC, and it was most strongly associated with the loss of kyphosis. This would explain why some patients have mixed ventilatory findings on their pulmonary function, i.e. restriction and obstruction.

Not infrequently, patients with spinal deformities may have concomitant pectus deformities. PFTs in children with pectus excavatum has shown normal lung function as well as restrictive and obstructive disease.30,31 Though the presence of scoliosis in these studies did not seem to have a statistically significant effect on lung function, patients with more severe pectus deformity seem to be more likely to have scoliosis.

Murine models of MFS have demonstrated impaired lung development characterized by enlarged alveolar air spaces, reduced alveolar septation and increased lung compliance.32-34 The most comprehensive study of the microscopic findings of the human lung with MFS has found a pattern of distal acinar emphysema.10 Clinical studies involving large numbers of individuals with MFS are few. In a retrospective analysis of PFTs in 69 patients, 30 had scoliosis, 15 had pectus excavatum and 21 had both skeletal deformities.7 This study used sitting height, a measure that more accurately reflects the length of the thorax, in order to avoid the inappropriate use of predicted values based on standing height. In other

### Table 4 Correlation of sterno-vertebral ratio and pulmonary function tests

| Cases, n | Spearman’s r | p-value |
|----------|--------------|---------|
| VC       | -0.13        | 0.68    |
| RV       | -0.006       | 0.98    |
| TLC      | -0.106       | 0.67    |
| FVC      | -0.04        | 0.85    |
| FEV1     | -0.18        | 0.38    |
| FEV1/FVC | -0.61        | 0.001   |

VC, vital capacity; RV, residual volume; TLC, total lung capacity; FVC, functional vital capacity; FEV1, forced expiratory volume in one second.
words, standing height in this population would underestimate the true value of the lung function data obtained by spirometry and lung volumes. This study revealed that only patients with moderate to severe pectus excavatum or scoliosis had reductions in the FVC and FEV1, diagnostic for restrictive lung disease; TLC was reduced in patients with pectus excavatum. Important to note is the fact that the severity of the chest wall deformity was judged only by inspection of the external appearance and not by examining patient’s imaging.

In our study of 26 MFS patients we identified 70% of the patients having some form of pulmonary impairment similar to the 63% found in the literature.11

An increased thoracic lordosis and SV ratio correlated with diminished FEV1/FVC suggestive of obstructive disease (r = 0.65; p < 0.001; and r = -0.61; p = 0.001, accordingly). Both parameters represent the thoracic anteroposterior space, a decrease in which has been demonstrated in the past as limiting the expansion of the thoracic cavity and impairing pulmonary function.20,31 Furthermore, we found a significant decrease in FEV1/FVC below 80% occurring at kyphosis under 15° (p < 0.005) (Fig. 2).

In addition, in our study, there was a positive correlation between increasing RV and increasing degrees of kyphosis. Residual volume is a sensitive measure of air trapping and the data suggest that MFS patients with more severe kyphosis are at an increased risk. Other factors frequently associated with thoracic spine deformities such as costovertebral joint stiffness, sternal deformity, decreased muscular strength or malposition of diaphragmatic insertion into ribs and thoracic vertebral bodies, can adversely affect the movement of the diaphragm and respiratory mechanics contributing to air trapping. This warrants further investigation.

In accordance with previous studies, increased thoracic coronal curve magnitude correlated with diminished TLC (r = -0.45; p = 0.04), suggestive of restrictive disease, with a significant decrease in TLC below 80% occurring at 40° (p = 0.02) (Fig. 3). We did not find any other significant correlation between the curve magnitude and PFT.

To the best of our knowledge this is the first study of MFS correlating the magnitude of the spinal and chest wall deformity with PFT. Consistent with previous studies (not in MFS individuals), we found a significant correlation between increased thoracic lordosis and coronal curve magnitude and diminished pulmonary function. Additionally, we found a significant correlation between increased chest wall deformity (as manifested in the SV ratio) and pulmonary function impairment (Fig. 4).

Several limitations should be noted; the data was retrospective and collected over a period of ten years. Additionally, not all the patients had lung volumes or diffusing capacity for carbon monoxide (DLCO) performed; 40% of the patients had incomplete PFT data, which highlights the challenges in assembling large volume data in these complex patients. Standing height or arm span measurements, rather than sitting height, were used. This will underestimate the true lung function in this population due to the abnormal length of the arms and legs. In addition, the lung function predicted values used for normal reference values could have varied between institutions, and over time, thus introducing another variable in data collection and results. Further analysis with a larger cohort of patients will help better define the true relationship between these deformities and their influence on pulmonary function in MFS.
3. Dietz H. Marfan Syndrome. 2001 Apr 18 [Updated 2017 Oct 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1555/.

4. De Maio, F, Fichera A, De Luna V, et al. Orthopaedic aspects of Marfan syndrome: the experience of a referral center for diagnosis of rare diseases. Adv Orthop 2016;2016:827591.

5. Sponseller PD, Hobbs W, Riley LH III, Pyeritz RE. The thoracolumbar spine in Marfan syndrome. J Bone Joint Surg (Am) 1995;77-A:867-876.

6. Demetraopoulos CA, Sponseller PD. Spinal deformities in Marfan syndrome. Orthop Clin North Am 2007;38:563-572, vii.

7. Streeter EA, Murphy EA, Pyeritz RE. Pulmonary function in the Marfan syndrome. Chest 1987;91:408-412.

8. Wood JR, Bellamy D, Child AH, Citron KM. Pulmonary disease in patients with Marfan Syndrome. Thorax 1984;39:780-784.

9. Giske L, Stanghelle JK, Rand-Hendrikssen S, et al. Pulmonary function, working capacity and strength in young adults with Marfan syndrome. J Rehabil Med 2003;35:221-228.

10. Dybdal K, Farver C. Pulmonary histologic changes in Marfan syndrome: a case series and literature review. Am J Clin Pathol 2011;136:857-863.

11. Corsico AG, Grosso A, Tripon B, et al. Pulmonary involvement in patients with Marfan Syndrome. Paedinerva Med 2014;56:177-182.

12. Johnston CE, Richards BS, Sucato DJ, et al. Correlation of preoperative deformity magnitude and pulmonary function tests in adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2005;30:1096-1102.

13. Weinstein SL, Zavala DC, Ponseti IV. Idiopathic scoliosis: long-term follow-up and prognosis in untreated patients. J Bone Joint Surg (Am) 1981;63-A:702-712.

14. Newton PO, Faro FD, Gollogly S, et al. Results of preoperative pulmonary function testing of adolescents with idiopathic scoliosis. A study of six hundred and thirty-one patients. J Bone Joint Surg (Am) 2005;87-A:1937-1946.

15. Upadhyay SS, Mullaji AB, Luk KD, Leong JC. Relation of spinal and thoracic cage deformities and their flexibilities with altered pulmonary functions in adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 1995;20:2415-2420.

16. Yaszay B, Bastaorn TP, Bartley CE, Parent S, Newton PO. The effects of the three-dimensional deformity of adolescent idiopathic scoliosis on pulmonary function. Eur Spine J 2017;26:1658-1664.

17. McPhail GL, Ehsan Z, Howells SA, et al. Obstructive lung disease in children with idiopathic scoliosis. J Pediatr 2015;166:1018-1021.

18. Kelly RE Jr, Mellins RB, Shamberger RC, et al. Multicenter study of pectus excavatum, final report: complications, static/exercise pulmonary function, and anatomic outcomes. J Am Coll Surg 2013;217:1080-1089.

19. Kelly RE Jr, Obermeyer RJ, Nuss D. Diminished pulmonary function in pectus excavatum: from denying the problem to finding the mechanism. Ann Cardiothorac Surg 2016;5:466-475.

20. Koumbourlis AC. Pectus deformities and their impact on pulmonary physiology. Paediatr Respir Rev 2015;16:18-24.

21. Loeyes BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-485.

22. Lafage R, Ferrero E, Henry JK, et al. Validation of a new computer-assisted tool to measure spino-pelvic parameters. Spine J 2015;15:2493-2502.

23. Widmann RF, Bitan FD, Laplaza FJ, et al. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. Spine (Phila Pa 1976) 1999;24:1673-1678.

24. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis 1991;144:1202-1218.

25. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-968.

26. Li Y, Sheng F, Xia C, et al. Risk factors of impaired pulmonary function in arthrogryposis multiplex congenital patients with concomitant scoliosis: a comparison with adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2018;43:E456-E460.

27. McPhail GL, Howells SA, Boesch RP, et al. Obstructive lung disease is common in children with syndromic and congenital scoliosis: a preliminary study. J Pediatr Orthop 2013;33:781-785.

28. Redding GJ, Hurn H, White KK, et al. Persistence and progression of airway obstruction in children with early onset scoliosis. J Pediatr Orthop 2018 Oct 8. (Epub ahead of print)

29. Farrell J, Garrido E. Effect of idiopathic thoracic scoliosis on the tracheobronchial tree. BMJ Open Respir Res 2018;5:e000264.

30. Koumbourlis AC, Stolar CJ. Lung growth and function in children and adolescents with idiopathic pectus excavatum. Pediatr Pulmonol 2004;38:339-343.

31. Lawson ML, Mellins RB, Paulson JF, et al. Increasing severity of pectus excavatum is associated with reduced pulmonary function. J Pediatr 2011;159: 236-242.

32. Lee JJ, Galatiioto J, Rao S, Ramirez F, Costa KD. Losartan attenuates degradation of aorta and lung tissue micromechanics in a mouse model of severe Marfan syndrome. Ann Biomed Eng 2016;44:2994-3006.

33. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006;312: 177-181.

34. Uriarte JJ, Meireles T, Del Blanco DG, et al. Early impairment of lung mechanics in a murine model of Marfan Syndrome. PLoS One 2016;11:e0152124.