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Sleep apnea and the impact on cardiovascular risk in patients with Marfan syndrome

Laura Muiño-Mosquera[1,2] | **Fré Bauters**[3] | **Karlien Dhondt**[3,4] | **Hans De Wilde**[2,5] | **Luc Jordaens**[5] | **Katya De Groote**[2] | **Daniel De Wolf**[2] | **Katrien Hertegonne**[3] | **Julie De Backer**[1,5]

[1]Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium

[2]Department of Pediatrics, Division of Pediatric Cardiology, Ghent University Hospital, Ghent, Belgium

[3]Department of Pneumology, Ghent University Hospital, Ghent, Belgium

[4]Department of Psychiatry, Division of Child and Adolescent Psychiatry, Pediatric Sleep Centre, Ghent University Hospital, Ghent, Belgium

[5]Department of Cardiology, Ghent University Hospital, Ghent, Belgium

Correspondence
Laura Muiño Mosquera, Centre for Medical Genetics, Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium.
Email: laura.muinomosquera@uzgent.be

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Abstract

Background: Marfan syndrome (MFS) is an inherited connective tissue disorder characterized by ectopia lentis, aortic root dilation and dissection and specific skeletal features. Obstructive sleep apnea (OSA) in MFS has been described earlier but the prevalence and its relation with the cardiovascular risk is still controversial. This study aimed to further investigate these aspects.

Methods: In this prospective longitudinal study, we performed an attended polysomnography in 40 MFS patients (60% women, 37 ± 12.8 years) and evaluated several cardiovascular parameters through echocardiography, resting electrocardiogram, 24 hr-Holter monitoring and serum NT-ProBNP measurements.

Results: We found that OSA was present in 42.5% of the patients and that higher body mass index was the most important factor associated with the presence of OSA. We observed that overweight was present in 27.5% of the patients in the whole cohort and in 55.6% if >40 years. Furthermore, when evaluating the impact of OSA on the cardiovascular system, we observed that patients with OSA tended to have higher systolic blood pressure, larger distal aortic diameters and a higher prevalence of ventricular arrhythmia. These differences were, however, not significant after adjusting for confounders.

Conclusions: Our study shows a high prevalence of OSA and a high prevalence of overweight in MFS patients. We found some trends between OSA and cardiovascular features but we could not establish a solid association. Our study, however might be underpowered, and a multicenter collaborative study could be very useful to answer some important open questions.

KEYWORDS
aortic aneurysm, aortic dissection, arrhythmia, cardiovascular risk, Marfan syndrome, sleep apnea

1 | INTRODUCTION

Marfan syndrome (MFS) (OMIM #154700) is a pleiotropic inherited connective tissue disorder caused by pathogenic variants in the fibrillin-1 (*FBN1*) gene (OMIM #134797). Ectopia lentis and aortic dilation or dissection in combination with typical skeletal traits are the most characteristic features (Judge & Dietz, 2005; Loeys et al., 2010; Pyeritz, 2018; Verstraeten, Alaerts, Van Laer, & Loeys, 2016). Other common findings include myopia, mitral valve prolapse, pneumothorax and dural ectasia (Loeys et al., 2010). Since aortic dissection is the leading cause of mortality in these patients, up until now, research in MFS has focused mainly on treatment of aortic dilation and prevention of dissection. However, with optimized management leading to increased survival, other cardiovascular and noncardiovascular features have gained relevance and deserve further study. Within the nonaortic cardiovascular manifestations, myocardial disease and ventricular arrhythmia have been described by several independent groups (Alpendurada et al., 2010; Aydin et al., 2013; De Backer et al., 2006; Hoffmann et al., 2013; Meijboom et al., 2005; Yetman, Bornemeier, & McCrindle, 2003). A few risk factors for ventricular arrhythmia, like an enlarged left ventricle and increased levels of N-terminal pro b-type Natriuretic peptide (NT-ProBNP) (Aydin et al., 2013; Hoffmann et al., 2013; Mah et al., 2018), a marker for ventricular dysfunction, have been identified in some patients, but additional makers still need to be detected. Within the noncardiovascular features, obstructive sleep apnea (OSA) seems to be highly prevalent in MFS although the prevalence varies significantly depending on the cohort and the method used for screening (30.8% home monitoring—64% in-hospital attended polysomnography [PSG]) (Cistulli & Sullivan, 1993; Kohler et al., 2009; Rybczynski et al., 2010). The underlying cause of OSA is not well elucidated but might be related to specific craniofacial features and higher upper airway collapsibility in MFS patients (Cistulli, Gotsopoulos, & Sullivan, 2001; Cistulli & Sullivan, 1995; da Palma et al., 2015). Whether patients carrying specific variants are more likely to develop OSA is unknown and the role of other frequently associated factors like age, sex, and higher body mass index (BMI) has not been studied in depth.

The relation between cardiovascular risk and OSA has been widely studied in the general population. In non-MFS subjects, individuals with OSA seem to have a higher cardiovascular risk, showing higher prevalence of hypertension, stroke, and arrhythmia, although these findings are not always consistent (Bauters, Rietzschel, Hertegonne, & Chirinos, 2016; Cano-Pumarega et al., 2017; Lee, Nagubadi, Kryger, & Mokhlesi, 2008; O'Connor et al., 2009; Peppard, Young, Palta, & Skatrud, 2000). The relationship between OSA and aortic diameters has been studied in smaller samples but the results are inconclusive (Baguet et al., 2011; Cicek, Lakadamyali, Yağbasan, Sapmaz, & Müderrisoğlu, 2011; Gaisl, Bratton, & Kohler, 2015; Meuleman et al., 2008; Serizawa et al., 2008). Because of the intrinsic cardiovascular risk of MFS patients and the seemingly high prevalence of OSA in this population, a few studies investigating the relation of OSA and cardiovascular complications in patients with MFS have been done. Kohler and colleagues showed a linear correlation between proximal aortic growth and the apnea–hypopnea index (AHI), the most common parameter to evaluate OSA (Kohler et al., 2009). Furthermore, a reduction in aortic growth after treatment with CPAP has been described in several case reports (Cistulli, Wilcox, Sullivan, & Jeremy, 1997; Verbraecken, Paelinck, Willemen, Van de Heyning, & De Backer, 2003). Rybczynski et al. (2010) did not find, however, a significant relation between aortic dilation and the AHI but they found a relation between the AHI and left ventricular function, mitral valve surgery and atrial fibrillation (Afib). These results have not yet been confirmed by other groups.

The aim of our study was to investigate the prevalence of sleep apnea in our MFS population through an overnight attended PSG, and to identify additional factors which could be associated with sleep apnea in this concrete population. Furthermore, we wanted to study the association between sleep apnea and cardiovascular features.

2 | MATERIALS AND METHODS

2.1 | Subjects

Patients were recruited from an ongoing longitudinal study on cardiovascular risk factors in patients with MFS. All patients older than 12 years and known with a (likely) pathogenic variant in the *FBN1* gene, causing MFS, were invited to participate in the study. Of the 108 Marfan patients evaluated in our institution between January 2015 and June 2016, 89 agreed to participate. Six patients were excluded due to psychosocial problems ($N = 5$) or residency outside Belgium ($N = 1$), nine declined participation and four were excluded because of (desired) pregnancy. Of the 89 recruited patients, two were lost to follow-up and three were already treated for a known sleep-related breathing disorder (one patient was treated with CPAP for severe OSA, one patient was treated with BiPAP for hypoventilation syndrome and one patient had an uvulopalatopharyngoplasty for heavy snoring). Forty of the 84 eligible patients agreed to undergo an in-hospital attended PSG. One of these was excluded from the cardiovascular risk analysis because he had heart transplantation and aortic surgery at different levels. Figure 1 shows the inclusion procedure.

Since only half of the patients in the original cohort accepted to undergo a PSG and to exclude selection bias, clinical data of all patients ($n = 84$) including medical and family

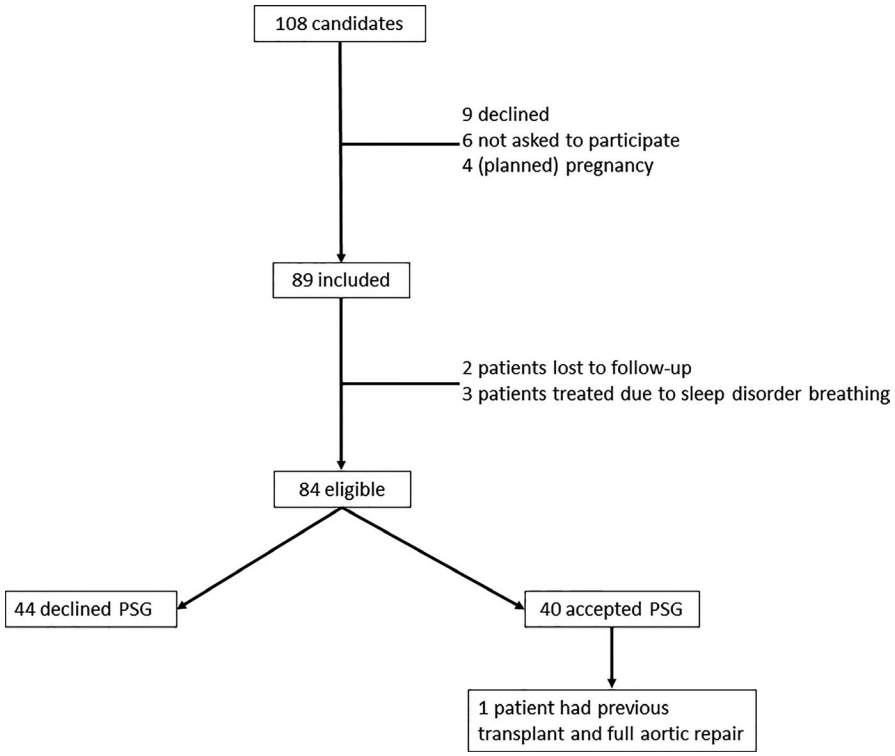

FIGURE 1 Flowchart of the inclusion and exclusion procedure. Patients were recruited from our outpatient clinic in the period between January 2015 and June 2016. Eighty-nine patients were included in a prospective longitudinal study of cardiovascular risk in Marfan syndrome. Of the eligible patients 40 agreed to undergo an in-hospital attended polysomnography. PSG, polysomnography

history, medication use and smoking status was recorded. All medical treatment was continued. In adults (>18 years) the Epworth Sleepiness Scale (ESS) (Johns, 1991) and the STOP-Bang (Chung, Abdullah, & Liao, 2016) questionnaire were used to assess a priori risk of OSA. Anthropometric data recording, blood pressure measurement after 10 min of rest and clinical investigation was performed in all patients. To evaluate conduction and rhythm abnormalities a standard 12-lead electrocardiogram (ECG) and a 24-hr ambulatory ECG (AECG) (Philips DigiTrack XT®, Philips and Trillium Platinum TM®, Medical Forest) were performed. The minimum, average and maximum heart rate, number of atrial extrasystoles, and number of ventricular extrasystoles were recorded. Complex ventricular ectopy was defined when couplets, triplets, or (nonsustained) ventricular tachycardia (VT) occurred. Heart rate variability was evaluated with the standard deviation of the NN interval (SDNN) and the square root of the mean squared difference of successive NN intervals (RMSSD). A standard echocardiography (Vivid S60N®, GE Healthcare, equipped with a 5S probe) to evaluate aortic diameters, valvular function and cardiac chamber dimensions and function was performed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines (Evangelista et al., 2010; Hiratzka et al., 2010; Lang et al., 2006). Patients with previous aortic root replacement (AoRR) were excluded for the analysis of the aortic sinus and ascending aorta. Additionally, 4.5 ml EDTA blood was drawn to measure the levels of NT-ProBNP.

All patients were prospectively followed up for a mean period of 30 ± 7 months. During follow-up, they underwent yearly physical examination, ECG and AECG, echocardiography and NT-proBNP measurement.

2.2 | Polysomnography

A full-night type 1 attended PSG was performed in our sleep center using a digital system (Brainnet for Windows, Medatec, Braine-le-Chateau, Belgium). Recordings included: electroencephalography, chin and left and right tibial electromyography, electrooculography, respiratory airflow through a nasal pressure transducer, pulsoximetry, and thoracic and abdominal respiratory inductance plethysmography. All electroencephalographic and cardiorespiratory signals were manually scored by an experienced sleep technician according to the 2012 guidelines of the American Association of Sleep Medicine (AASM Scoring Manual 2.0) (Berry et al., 2012).

An apnea was defined as a drop in airflow of at least 90% lasting at least 10s. A hypopnea was defined as an airflow reduction of at least 30% from baseline associated with a ≥3% oxygen desaturation or an arousal. Events were classified as obstructive, central or mixed, as defined by the AASM scoring guidelines. The AHI is the total number of apneas and hypopneas per hr of sleep time. The usual AHI cut-offs were used to classify the results as normal (AHI < 5/hr) or mild (5 ≥ AHI < 15/hr), moderate (15 ≥ AHI < 30/hr), and severe (≥30/hr) sleep apnea. Sleep apnea was defined as obstructive

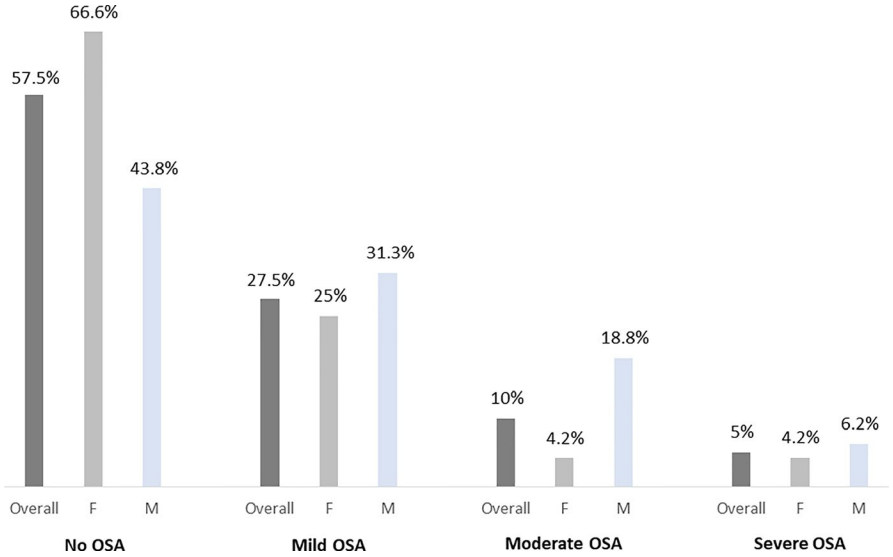

FIGURE 2 Prevalence of OSA in patients with Marfan syndrome. The dark grey bars represent the overall percentage of patients in each of the OSA categories. The light grey and blue bars represent the percentage of patients within each sex in each of the OSA categories. Overall the prevalence of OSA in MFS was 42.5% (33.3% in females and 56.2% in males, p-value = 0.151). F, female; M, Male; OSA, obstructive sleep apnea

if >50% of the events were obstructive (American Academy of Sleep Medicine Task Force, 1999).

2.3 | Genetic data

To study possible genotype–phenotype correlations, variants in the *FBN1* gene were classified according to their effect on the DNA structure as missense, in-frame, frameshift, nonsense, and splice-site variants. Variants were also classified according to the expected effect at the protein level (Franken et al., 2015). Frameshift and nonsense variants not affecting exon 65 or the last 50 nucleotides of exon 64 were considered to have a haploinsufficient (HI) effect, leading to the production of a reduced amount of normal fibrillin-1 (derived from the nonmutated allele). The other frameshift and nonsense variants and all missense variants were considered to have a dominant negative (DN) effect, leading to a shorter or a structurally abnormal but stable protein. These predictions were confirmed by the Mutation Taster software (Schwarz, Cooper, Schuelke, & Seelow, 2014). To classify the effect of the splice-site variants we used the Human Splicing Finder Software (Desmet et al., 2009), splice-site variants causing a change in the reading frame were considered as HI, while variants affecting splicing but not causing a change in the reading frame were considered as DN.

Since variants affecting exon 24–32 are considered to cause a more severe phenotype (Faivre et al., 2007) we specifically looked at genotype–phenotype correlations in this area.

2.4 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 package (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean and standard deviation, or median and interquartile range when appropriate. Categorical variables are presented as number and percentage.

We conducted descriptive statistics using the unpaired sample t test, the Mann–Whitney U test, and the Fisher exact test. Since AHI was not normally distributed, correlation analysis was performed using the Spearman correlation coefficient for continuous variables and the phi coefficient for categorical variables.

We performed logistic regression analyses to identify variables associated with an AHI $\geq$ 5. Those variables with a p-value $<$ 0.2 in univariate analysis were candidates to be used in a regression model. A p-value $<$ 0.05 was required for statistical significance in the final model. Cardiovascular outcome variables were selected from the univariate analysis if there was a significant difference between the groups with and without OSA and if these variables were correlated with the AHI. We conducted linear or logistic regression analyses to determine whether an AHI $\geq$ 5/hr was an independent factor associated with negative cardiovascular outcome. Candidate predictors for each outcome were identified from univariate analysis as previously described. AHI was adjusted for each of these predictors separately. We performed Kaplan–Meier survival analysis to compare the incidence of aortic and arrhythmic events between the groups with and without OSA during the time of follow-up.

2.5 | Ethical issues

The study was approved by the local Independent Ethics Committee and the Institutional Review Board of our hospital (Registration number: BE670201422783). All subjects participating in the study gave written informed consent.

3 | RESULTS

3.1 | Prevalence and risk factors associated with OSA

Of the 84 eligible patients, 40 (60% women, mean age 37 ± 12.8 years) agreed to have a PSG. The two adolescents, aged 14 years, were included in the analysis with the adult population. Baseline characteristics and a comparison between the patients accepting and declining PSG are presented in Table S1. There were no significant differences between these two groups except for a higher ESS score in the group agreeing to participate in the PSG study (median 7, IQR 4–11 vs. median 4, IQR 2–8, p-value = 0.029), however both scores fell within the normal range. Subjective sleepiness, defined as an ESS score higher than 10, was present in 29.3% of the patients in the participating group. The mean BMI of the PSG group was low, 21.9 ± 5.1 kg/m^2, however we observed that 27.5% of these patients had a BMI ≥ 25 kg/m^2. This percentage was even higher (55.6%) if patients ≥40 years were considered.

As shown in Figure 2 the majority of the patients (n = 23, 57.5%) had no OSA, 11 (27.5%) had mild, four (10%) moderate, and two (5%) severe OSA. Most events were of obstructive nature but 23 patients had sporadic episodes of central apnea during the investigation. Of these 23 patients, two stood out with 36 and 37 episodes of central apnea. Both patients had undergone AoRR, had mild to moderate residual aortic regurgitation but normal left ventricular function. SDNN and RMSSD was low in both patients (21 and 20 ms—reference value for age and sex: 34 ± 12 ms (Umetani, Singer, McCraty, & Atkinson, 1998) and 119 and 120ms—reference value for age and sex: 146 ± 30 (Umetani et al., 1998), respectively).

Although OSA was present in some young patients (the youngest at the age of 18 years), subjects with OSA were significantly older compared to the no-OSA group. Furthermore, patients with OSA had higher BMI and lower Marfan systemic score (Table 1). Next to age, BMI and Marfan systemic score, sex had a p-value < 0.2 and was also taken into consideration for the multivariate analysis. As shown in Table 2, the association between BMI and OSA remained significant after adjustment for age and sex (OR 1.4 per BMI unit, 95% IC 1.1–1.8, p = 0.009). Although age showed significant association with OSA in the univariate analysis (p = 0.010), this association was no longer significant in the adjusted model (p = 0.065). This model (BMI, sex and age) had a R^2 of 0.625 and area under de curve of 0.913, showing that this could be a good model to identify patients at risk. Other factors such as thorax deformity, scoliosis, smoking status or treatment with a beta-blocker were not significantly correlated with the presence of OSA. We could also not find a genotype–phenotype association (Table 1). The mean STOP-Bang score in the OSA group was significantly higher than in the no-OSA group (2.38 ± 1.31 vs. 1.14 ± 0.91, p = 0.002). As shown in the Table S2, however, the diagnostic performance of the STOP-Bang was weak, with a sensitivity of 47.1% and a positive predictive value of 80%. The ESS score was not different between patients with and without OSA (Table 1). The ESS performed even worse than the STOP-Bang questionnaire. Adding the STOP-Bang to the previous model increased the R^2 to 0.644 and the area under the curve to 0.922.

3.2 | Relation between OSA and cardiovascular features

Higher systolic blood pressure (p = 0.014), larger diameter of the descending aorta at the thoracic and abdominal levels (p = 0.002 and p = 0.002, respectively) and higher probability of complex ventricular events (p = 0.011) were found in Marfan patients with OSA (Table 1). This difference was however not significant anymore after adjusting for different confounding variables (Table S3), being age and/or BMI the most important (Figure 3).

Seven patients had undergone AoRR before enrolment (five in the group with OSA) and were not considered for the analysis of the proximal aortic diameters. Although the mean diameter of the aortic sinus and aorta ascendens was higher in patients with OSA, this difference was not significant (p = 0.341 and p = 0.051 respectively) (Table 1). Additionally, left ventricular diameter and function and NT-ProBNP levels did not differ significantly between both groups (Table 1).

During a mean follow-up time of 30 ± 7 months, seven patients had an arterial event: two women had a type A aortic dissection (one at the level of the sinus of Valsalva at a diameter of 47 mm and one at the level of the arch after previous AoRR); one woman underwent elective AoRR and subsequently presented a type B aortic dissection; two men underwent elective AoRR; one woman required aortic valve replacement due to severe aortic valve insufficiency after AoRR and one woman presented spontaneous coronary artery dissection. Of these seven patients, three had mild OSA and one moderate OSA. Aortic root growth over the study period was similar between the groups (0.3 mm/year IQR 0.30–1.5 for patients with OSA and 0.5 mm/year IQR 0–0.9 for patients without OSA, p = 0.894). Four patients had an Afib episode and one patient had a sustained VT episode. Three of the four patients with Afib had OSA. The patient with sustained VT did not have OSA. We did not find a significant higher rate of cardiovascular events in the group with OSA (HR 0.599, p = 0.439 for aortic events and HR 1.458, p = 0.227 for Afib). The two patients with severe OSA were treated with nasal CPAP (nCPAP) according to the standard

TABLE 1 Characteristics of Marfan patients with and without OSA

	AHI < 5 (n = 23)	AHI ≥ 5 (n = 17)	p-value[a]	Correlation coefficient [b]	p-value[c]
General features					
Age (yr)	32.1 ± 11.4	44.75 ± 14.3	0.004*	0.382	0.015*
Male (%)	7 (30.4)	9 (52.9)	0.151	−0.227	0.151
BMI (kg/m^2)	19.5 ± 3.6	25.6 ± 4.5	<0.001*	0.434	0.005*
Marfan systemic score[d]	8.9 ± 3	6.6 ± 3.8	0.039*	−0.330	0.037*
Pectus excavatum (%)	11 (47.8)	6 (37.5)	0.379	−0.102	0.522
Pectus carinatum (%)	4 (17.5)	4 (25)	0.425	0.093	0.563
Scoliosis (%)	20 (87)	10 (62.5)	0.082	−0.286	0.075
Smoking (%)	3 (13)	1 (6.3)	0.452	−0.110	0.492
Genetic data					
Type of variant (DNA effect)					
Missense (%)	12 (52.2)	17 (41.2)	0.491	−0.109	0.491
Frameshift (%)	4 (17.4)	6 (35.3)	0.196	0.204	0.196
Nonsense (%)	6 (26.1)	2 (11.8)	0.428	−0.177	0.263
Splice-site (%)	1 (4.3)	1 (5.9)	1	0.035	0.826
In-frame (%)	0 (0)	1 (5.9)	0.425	0.186	0.239
Type of variant (protein effect)					
Haploinsufficient	9 (39.1)	7 (41.2)	0.896	−0.021	0.896
Localization					
Within exons 24–32	4 (17.4)	3 (17.6)	1	0.003	0.983
Sleep questionnaires					
ESS score	6.1 ± 3.3	9.1 ± 5.6	0.052	0.252	0.132
STOP-bang score	1.1 ± 0.91	2.4 ± 1.31	0.002*	0.649	<0.001*
Cardiovascular features					
Use of BB (%)[e]	16 (69.6)	11 (68.8)	0.614	−0.009	0.957
AoRR at baseline (%)	2 (8.7)	5 (31.3)	0.071	0.289	0.071
SBP (mmHg)	122.9 ± 15.0	136.2 ± 16.3	0.014*	0.469	0.003*
DBP (mmHg)	69.5 ± 10.5	72 ± 9.1	0.444	0.330	0.043*
Ao sinus (mm)	40.6 ± 4.5	42.4 ± 4.6	0.341	0.129	0.489
Ao asc (mm)	29.8 ± 4.8	33.7 ± 3.1	0.051	0.363	0.089
Ao arch (mm)	21.9 ± 3.6	25.9 ± 4.9	0.009*	0.293	0.087
Ao des (mm)	17 (16–18.5)	21 (18–23.3)	0.002*	0.622	<0.001*
Ao abd (mm)	16.1 ± 2.8	19.7 ± 3.6	0.002*	0.474	0.004*
LVEDD index (mm/m^2)	25.7 ± 4.4	24.5 ± 5	0.441	−0.201	0.240
LVmass index (gr/m^2)	80.9 ± 27.4	108 ± 44.5	0.026*	0.286	0.081
LVEF (%)	67.4 ± 8.1	72.2 ± 10.6	0.130	0.225	0.187
RVEDD index (mm/m^2)	15.8 ± 2.6	15.3 ± 3	0.633	−0.286	0.113
TAPSE	21.1 ± 4.1	21.9 ± 4.1	0.569	0.197	0.243
E wave (cm/s)	74 ± 21.1	69 ± 18.1	0.451	−0.217	0.185
E/A ratio	1.7 ± 0.59	1.3 ± 0.4	0.047*	−0.309	0.056
Em (cm/s)	9.3 ± 2.8	8.8 ± 2.1	0.576	−0.159	0.368
LA vol index (ml/m^2)	23.4 ± 11.5	31.5 ± 18.4	0.111	0.174	0.302
NT-proBNP (pg/ml)	66.5 (24.3–112.5)	83 (55–294)	0.119	0.113	0.443

(Continues)

TABLE 1 (Continued)

	AHI < 5 (n = 23)	AHI ≥ 5 (n = 17)	p-value[a]	Correlation coefficient [b]	p-value[c]
ECG and 24 hr-Holter investigation					
PR-interval (ms)	153.2 ± 22.8	163.3 ± 25.1	0.210	0.144	0.388
QRS-duration (ms)	96.6 ± 12.5	86.9 ± 23.7	0.106	−0.018	0.913
QTc time (ms)	419.1 ± 25.4	419,8 ± 17.4	0.925	0.029	0.865
Average HR (bpm)	65.7 ± 7.3	62.6 ± 17.7	0.457	0.038	0.823
Min HR (bpm)	46.1 ± 5.1	46.3 ± 5.1	0.936	−0.179	0.283
Max HR (bpm)	129.6 ± 23.8	114.9 ± 20.6	0.059	0.114	0.497
RMSSD (ms)	65 (51.5–82)	63 (35–91)	0.427	−0.136	0.430
SDNN (ms)	185 (138.5–199.5)	161 (119–178)	0.028*	−0.366	0.026*
SVES/24 hr	5 (2–38)	14 (6–42)	0.442	0.100	0.549
VES/24 hr	6 (2–100)	42 (4–312)	0.137	0.266	0.094
VE (%)	8 (34.8)	7 (46.7)	0.346	0.119	0.464
Complex ventricular event (%)	3 (13)	8 (53.3)	0.011*	0.434	0.007*

Note: Data are mean ± standard deviation or median (interquartile range) when appropriate, except when otherwise indicated.
Abbreviations: Ao, aortic; AoRR, Aortic root replacement; ARB, Angiotensin Receptor Antagonist; BB, Beta-blocker; BMI, Body mass index; DBP, Diastolic blood pressure; ECG, electrocardiogram; ESS, Epworth sleepiness scale; HR, Heart rate; LA, left atrium; LVEDD, Left ventricular end diastolic diameter; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of Brain Natriuretic Peptide; RMSSD, square root of the mean squared difference of successive NN intervals; RVEDD, Right ventricular end diastolic diameter; SBP, Systolic blood pressure; SDNN, standard deviation of the NN interval; SVES, Supraventricular extrasystole; VE, ventricular ectopy; VES, Ventricular extrasystole.
[a]p-Value of univariate analysis.
[b]Spearman for continuous variables and Phi for categoric variables.
[c]p-Value of correlation analysis.
[d]Marfan systemic score: this is a scoring system which takes into consideration several characteristic features of MFS and assigns each of them a value between 1 and 3, 3 being the most specific for the disease. A score of ≥7 is considered abnormal and in combination with aortic disease and/or ectopia lentis is diagnostic of MFS.
[e]Use of BB alone or in combination with ARB. Three patients and 1 patient in the AHI < 5 and AHI ≥ 5 group respectively were taking Losartan in monotherapy.
*Statistic significant at the $p < 0.05$ level.

treatment procedure in our hospital. These patients experienced subjective improvement of fatigue and quality of life. Their aortic sinus diameter at baseline was 43 mm for the male and 38 mm for the female patient and remained stable during the study period. The male patient experienced Afib 2 years after initiation of treatment with nCPAP.

4 | DISCUSSION

In previous studies, a relative high prevalence of OSA has been reported in patients with MFS. Although patients with MFS have higher cardiovascular risk than the general population and additional risk factors could, in theory, further increase this risk, the relation between OSA and cardiovascular features is still a matter of debate. In our study, we confirm a high prevalence of OSA (42.5%) in MFS. Although the mean BMI of our cohort was low, BMI was the strongest risk factor for OSA. In fact, we found that the prevalence of overweight was relatively high (27.5% overall and 55.6% if ≥40 years). Although patients with OSA showed higher systolic blood pressure, larger distal aortic diameters, and higher prevalence of complex ventricular events, these differences were no longer significant after adjusting for confounding variables.

The prevalence of OSA in MFS patients found in our study is comparable with previous reports (Kohler et al., 2009; Rybczynski et al., 2010). In the general population, OSA prevalence varies strongly depending on the studied group, and mainly the applied diagnostic technique and hypopnea scoring definition. Overall, the prevalence of OSA in the general population defined as an AHI ≥ 5, ranges between 9% and 38% (Senaratna et al., 2017). Therefore the prevalence in our cohort is at least comparable to the general population. Two earlier reports on MFS patients showed that in comparison to age- and sex-matched controls, patients with MFS had a significantly higher prevalence of OSA (32.8% vs. 11.5% in the study of Kohler and colleagues [Kohler et al., 2009] and 64% vs. 8% in the study of Cistulli and Sullivan [Cistulli & Sullivan, 1993]). In our cohort those patients accepting and declining PSG were very similar (as shown in Table S1), but differ in the ESS score. Although the ESS score was not high in the patients accepting PSG, it is possible that there is a bias and that this cohort may not be representative for the whole MFS population.

TABLE 2 Regression models used to predict OSA

	Odds Ratio	95% CI	*p*-Value
BMI (per kg/m^2)	1.353	1.109–1.651	0.003*
Age (per yr)	1.084	1.019–1.153	0.010*
MFS systemic score[a]	0.820	0.671–1.003	0.053
Model 1 (BMI, Age, Sex[b])	1.401	1.089–1.802	0.009*
Model 2 (BMI, Age, Sex[b], Stop-BANG)	1.4	1–1.8	0.025*

Abbreviations: BMI, Body Mass Index; MFS, Marfan syndrome; yr, year.
[a]Marfan systemic score is a scoring system which takes into consideration several characteristic features of MFS and assigns each of them a value between 1–3, 3 being the most specific for the disease. A score of ≥7 is considered abnormal and in combination with aortic disease and/or ectopia lentis is diagnostic of MFS.
[b]Reference category: female.
*Statistic significant at the level of $p < 0.05$.

The majority of the episodes of sleep apnea were obstructive; however some patients presented sporadic episodes of central apnea. Two patients presented a higher amount of central apnea with a total of 36 and 37 episodes respectively during the study. Central apnea has been associated with heart failure and Afib in non-MFS patients (Naughton, 2016; Rowley & Badr, 2017). In the study of Rybczynski and colleagues a surprisingly high amount of central sleep apnea in their cohort was observed (almost half of the events were of the central type). OSA was also independently associated with Afib, lower left ventricular ejection fraction and higher levels of NT-ProBNP in this study. The two patients with central sleep apnea in our study had AoRR in the past and had moderate aortic valve regurgitation. However their left ventricular ejection fraction was in the lower range of normal (58%) and their NT-proBNP level was not elevated. We therefore think that central apnea as a consequence of heart failure was not an issue in our patients. The only observation we could make, is that these two patients had low values of RMSSD and SDNN, two indexes of heart rate variability, indicating a possible degree of autonomic dysfunction. Autonomic dysfunction has already been associated with chemoreceptor and baroreceptor alterations (Hakim, Gozal, & Gozal, 2012) and could possibly explain central sleep apnea in these patients. The study of autonomic dysfunction was beyond the scope of this study but may need further attention.

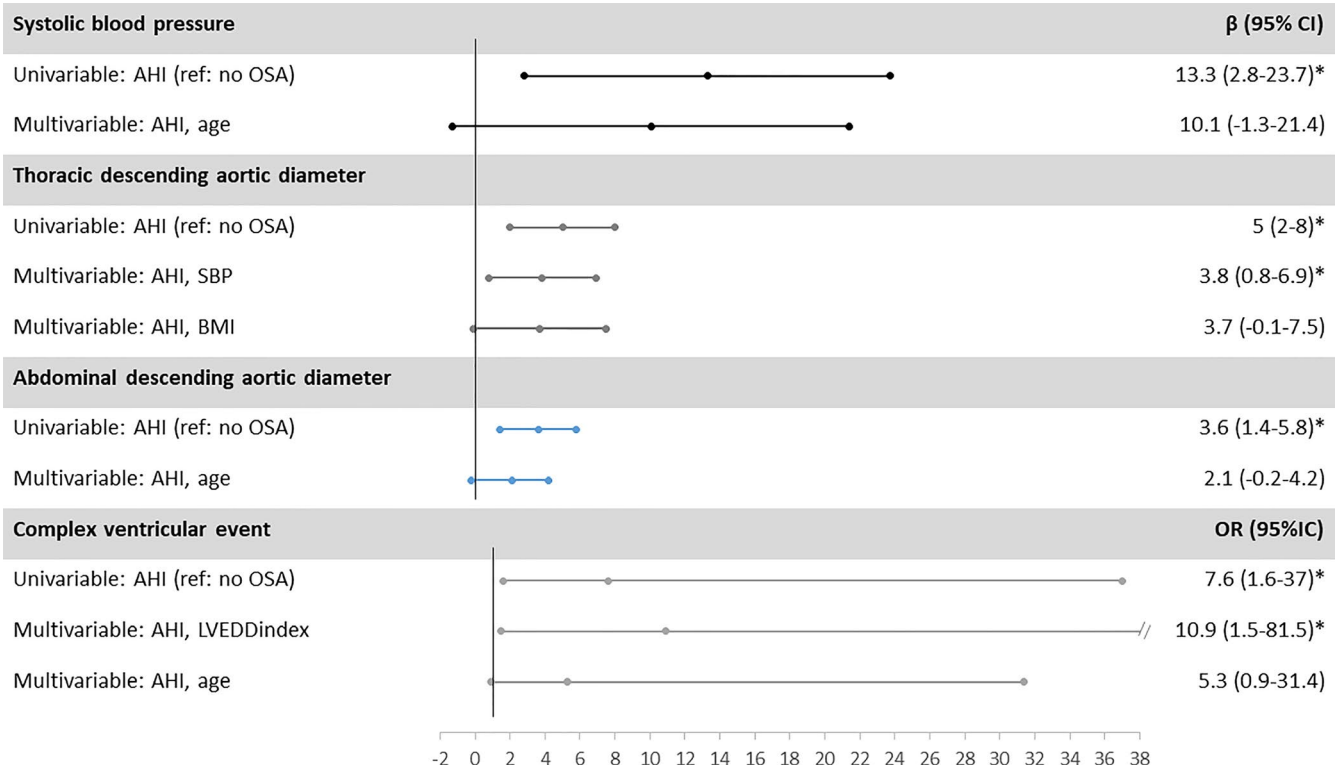

FIGURE 3 Adjusted regression models to study the independent association between OSA and different cardiovascular features. Continuous outcome variables (systolic blood pressure and distal aortic diameters) were analyzed using linear regression and therefore the regression coefficient (β) is given. Categoric outcome variables (complex ventricular arrythmia) were analyzed using logistic regression and therefore the odds ratio (OR) is given. *Statistic significant at a value of $p < 0.005$. For linear regression confidence interval (CI) could not include the 0, for logistic regression the CI could not contain the 1. AHI, apnea–hypopnea index; BMI, body mass index; LVEDD, left ventricular end diastolic diameter; OSA, obstructive sleep apnea; SBP, systolic blood pressure

Risk factors for OSA in non-MFS subjects are male sex, age, and higher BMI (Senaratna et al., 2017; Tufik, Santos-Silva, Taddei, & Bittencourt, 2010). Although in our cohort the proportion of males with OSA was higher and those patients with OSA were significantly older, only BMI was independently associated with OSA (OR 1.4 per kg/m^2, 95% IC 1.1–1.8, $p = 0.009$). In our clinical practice, we observed that a subgroup of MFS patients present visceral obesity at a young age while others develop this with age. Finding such a high percentage of overweight in our cohort (27.5% of the patients in the whole cohort and in 55.6% if >40 years) was slightly surprising, but not unexpected. In fact a previous report of Yetman and McCrindle (2010) in MFS patients aged 38 ± 13 years, found similar rates of overweight (36%). Although obese patients have the highest risk of OSA, the risk for patients with overweight (BMI 25–30 kg/m^2) is still increased (OR 2.6, 95% IC 1.9–3.7) (Tufik et al., 2010) and therefore the realization that MFS patients also have overweight, especially in older ages is important. When considering a prediction model to identify patients at risk of OSA, the strongest model seems to include age, sex, and the STOP-Bang score next to the BMI. Although the STOP-Bang score did not have a high sensitivity (47.1%), it had a high specificity (90.5%), meaning that if positive, the probability for having OSA is high. The sensitivity and specificity of the ESS score were lower (35.5% and 85.7% respectively) and therefore we think that using the STOP-Bang as screening tool could be more useful. We did not include measurements of facial features or airway collapsibility, as done in previous studies (Cistulli et al., 2001; Cistulli & Sullivan, 1995). We can therefore not exclude that these parameters need to be taken into consideration in a predictive model of OSA for MFS.

Controversy still exists regarding the association between OSA and cardiovascular risk in MFS. Although Kholer et al. showed a correlation between aortic root diameter and the AHI (Kohler et al., 2009) and higher incidence of aortic events (aortic surgery or dissection) in those MFS patients with OSA (Kohler et al., 2013), neither we nor Rybczynski and colleagues (Rybczynski et al., 2010), could confirm this association. Similar to our study, Rybczynski et al. found enlarged diameters of the descending aorta associated with the AHI but this association was not significant after adjusting for age and BMI. Systolic blood pressure and proximal aortic diameters did not correlate with the AHI in their study (Rybczynski et al., 2010).

In contrast to the general population, was the relationship between OSA and myocardial dysfunction and arrhythmia has been evaluated in several studies (Gottlieb et al., 2010; Holmqvist et al., 2015; Mehra et al., 2006; Sun, Shi, Li, & Chen, 2013), scarce data are available in MFS patients. Lower left ventricular function, higher levels of NT-proBNP and higher frequency of Afib were associated with a higher AHI in the study of Rybczynski et al. (Rybczynski et al., 2010). We did not find any association between OSA and myocardial dysfunction or Afib but saw a tendency in the incidence of Afib (three of the four patients with Afib had OSA).

Our study had some limitations and therefore some questions remain unanswered. (a) Although we were not able to show a higher cardiovascular risk in those MFS patients with OSA, our cohort might be too small and patients with AHI ≥ 15 might need to be considered separately in a multicenter study. (b) We did not consider subjective measures of "disease burden" such as quality of life or frame of mind. There is still controversy in the literature regarding the effect of OSA and its treatment on these matters (Batool-Anwar et al., 2016; Coman, Borzan, Vesa, & Todea, 2016; Gaisl et al., 2017; Jehan et al., 2017). We are not aware of specific trials, studying the effect of CPAP and improvement of OSA in quality of life in patients with MFS. One study has been performed in patients with Ehlers Danlos syndrome (EDS), another connective tissue disorder, showing a beneficial effect (Guilleminault et al., 2013). Further study of quality of life and frame of mind in MFS patients needs more attention and might guide the decision on whether treatment is necessary or not. (c) At this point we have no longitudinal data on how OSA evolves in MFS. To study this, it would be, useful to repeat the PSG after a few years to test whether the number of events increases over time and to allow for a concrete recommendation on how to manage OSA in MFS patients. (d) Although the mean BMI was low, we observed a high prevalence of overweight in our cohort, especially in the older patients. Given the strong association between overweight and OSA, we hypothesize that maybe treating overweight could have, at least, similar effect on cardiovascular health as treating OSA. A randomized controlled trial in obese patients with moderate to severe apnea showed similar reductions in blood pressure between the groups treated with CPAP, weight loss and combination therapy (Chirinos et al., 2014). Studying the effect of overweight reduction in MFS on cardiovascular health in general and on OSA in particular, could be useful.

In conclusion, as in the general population, OSA has a high occurrence in MFS patients and is strongly associated with BMI. Until now no significant association between OSA and cardiovascular outcome in MFS can be stablished. However, ours and previous studies may be underpowered and collaborative efforts are still necessary to answer some important questions. Another relevant aspect is that with increasing survival and aging, the classical view of MFS patients as long and slender seems to shift and new risk factors among which sleep apnea and overweight may need to be targeted.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Laura Muiño-Mosquera https://orcid.org/0000-0002-3094-7807

Julie De Backer https://orcid.org/0000-0001-8878-1507

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