Sleep Apnea in Marfan’s Syndrome*
Increased Upper Airway Collapsibility During Sleep

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Marfan’s syndrome is a hereditary disorder characterized by a defect in connective tissue, resulting in tissue laxity. It is associated with a high prevalence of obstructive sleep apnea (OSA). The aim of this study was to determine whether excessive upper airway collapsibility during sleep is an important pathophysiologic factor predisposing these individuals to OSA. We measured upper airway closing pressures (UACP) during sleep in 12 patients with Marfan’s syndrome and 6 age-, and height-, and weight-matched control subjects. Ten of the patients had OSA, defined as an apnea/hypopnea index $\geq 5$. All patients with Marfan’s syndrome, including the two patients without OSA, demonstrated increased upper airway collapsibility during sleep, with a mean UACP of $-2.5\pm0.5$ cm H$_2$O during slow-wave sleep (SWS). In contrast, only two control subjects demonstrated upper airway closure. However, this was at significantly higher suction pressures, with a mean UACP of $-5.6\pm0.4$ cm H$_2$O during SWS ($p<0.005$). These data suggest that patients with Marfan’s syndrome have abnormally increased upper airway collapsibility during sleep. It is possible that this is related to the characteristic connective tissue defect of this disorder. (CHEST 1995; 108:631-35)

Key words: Marfan’s syndrome; obstructive sleep apnea; upper airway collapsibility

Marfan’s syndrome, which is inherited as an autosomal dominant trait, is defined on the basis of characteristic changes in three major connective tissue systems: the musculoskeletal, the eyes, and the cardiovascular system.\(^1\)\(^-\)\(^3\) More recently, the skin, central nervous system, and respiratory system have been shown to have characteristic involvement.\(^5\) It is thought to affect approximately 1 in 10,000 of the general population. The life expectancy of patients with Marfan’s syndrome is markedly reduced, primarily because disease of the aorta leads to aortic dissection and rupture.\(^5\)\(^,\)\(^6\)

We have previously reported a high prevalence of obstructive sleep apnea (OSA) among patients with Marfan’s syndrome.\(^6\)\(^,\)\(^7\) OSA is a common disorder that is characterized by repetitive closure of the pharynx during sleep. The typical patient with OSA is a middle-aged, centrally obese man.\(^8\) In marked contrast, patients with Marfan’s syndrome are tall, thin, and generally young. The reason for the high prevalence of OSA in patients with Marfan’s syndrome is unknown. One possibility is that the upper airway is abnormally collapsible. Clinically, patients with Marfan’s syndrome have lax tissues—hypermobile joints, increased skin elasticity, lens dislocations, and mitral valve prolapse, resulting from an abnormality of fibrillin.\(^9\)\(^,\)\(^10\) It is possible that the pharynx is similarly affected, leading to a lax upper airway.

Abnormal upper airway collapsibility is thought to be an important factor in the pathophysiology of OSA.\(^11\)\(^-\)\(^13\) However, there remains considerable uncertainty as to whether the loss of muscle tone represents a normal loss of tone with sleep in an abnormally narrow airway or whether there is an excessive, abnormal loss of tone. The floppy tissues in Marfan’s syndrome and the high prevalence of apnea in these subjects suggests that excessive airway collapsibility during sleep may be a possible mechanism in this syndrome. The major aim of this study was to measure an index of upper airway collapsibility during sleep and to compare the results with those in a matched control group, providing further insight into this possibility.

METHODS

We studied 12 patients with Marfan’s syndrome (8 men, 4 women) who had previously undergone standard nocturnal polysomnography as part of a prevalence study.\(^7\) All of these patients had been randomly recruited from the Marfan clinic at our institution. Ten of the patients in this study were randomly recruited from the original cohort; the remaining two patients were specifically selected because they were the only nonsnoring, nonapneic patients. We compared them with six age-, height-, and weight-matched control subjects (5 men, 1 woman). All subjects gave in-
formed consent and the study was approved by the Ethics Review Committee of our institution.

Standard nocturnal polysomnography was performed, with electroencephalograph (EEG), electro-oculograph (EOG), and submentum electromyograph (EMGgg) electrodes applied in the standard fashion for sleep stage determination.14 Respiratory variables included chest wall and abdominal motion (Respirate; Ambulatory Monitoring Inc; Airdsley, NY), diaphragm EMG (measured by surface electrodes), nasal airflow and pressure with a calibrated pressure transducer (Grass Volumetric; Grass Instruments; Quincy, Mass), and arterial oxyhemoglobin saturation (Ohmeda Biao 3700e; Louisville, Colo). An electrocardiogram was recorded continuously. All variables were recorded continuously on a 16-channel electroencephalograph (Grass Instruments; Quincy, Mass). Calculated respiratory variables were apnea/hypopnea index (AHI—the number of apneas and hypopneas per hour of sleep), apnea duration, and minimal oxygen saturation during apneas. Apneas were defined as cessation of airflow for at least 10 s. Hypopnea was defined as a reduction in amplitude of airflow or thoracoabdominal wall movement of greater than 50% of baseline for more than 10 s, associated with oxygen desaturation or arousal. These events were defined as obstructive if they occurred in association with continued diaphragm EMG activity and thoracoabdominal wall movement. Central events were defined as those accompanied by absence of diaphragm EMG activity and thoracoabdominal wall movement.

Upper airway closing pressures were measured using the technique previously described by Isaa and Sullivan.11,15,16 Briefly, a specially designed nasal continuous positive airway pressure (N-CPAP) mask, which allows for the provision of CPAP and complete external occlusion of the airway at the nose, was used. Complete nasal occlusion was produced by inflation of a rubber balloon catheter (Foley catheter). When the patient was asleep breathing quietly, with a patent upper airway maintained by CPAP, external nasal occlusion was performed at end-expiration. It has been shown previously that during nasal occlusion, each inspiratory effort produces a smooth progressive increase of suction pressure (measured in the nasal mask) to a maximum value, followed by a rapid return to baseline.13 With each subsequent occluded inspiratory effort, there is a more rapid increase in suction pressure with greater peak values, reflecting the breath-by-breath increase in respiratory drive during progressive asphyxia. However, as each occluded inspiratory effort becomes stronger, at some critical level, nasal pressure abruptly ceases to change during the inspiratory phase despite a further progressive increase in inspiratory effort, as indicated by the presence of incremental activity of the diaphragm EMG and Respirate (Ambulatory Monitoring, Inc). This indicates that the upper airway has closed between the nose and thorax. The validity of this technique has been verified by concurrent measurement of esophageal or tracheal pressure.11,16 To ensure that closure did not occur at the nares, rubber nasal prongs (which formed part of the N-CPAP mask) were used. Mouth leaks were prevented by the application of adhesive tape, and this was confirmed by use of thermocouples. The more negative the upper airway closing pressure (UACP), the less collapsible the airway. The values presented herein are means from numerous pressure determinations. All determinations were made during slow-wave sleep (SWS) in the supine position.

**Statistics**

All values are given as mean±SEM. Mean closing pressures were calculated for each subject, and these were subsequently used for statistical comparisons. Statistical comparisons were carried out by one-way analysis of variance (ANOVA), followed (where the omnibus F test was significant) by multiple planned linear comparisons. SEM values were derived from pooled error variances. A p value of less than 0.05 was considered significant.

**RESULTS**

Anthropomorphic data are presented in Table 1. Patients had mean age of 34±3 years, mean height of 183±3 cm, and mean weight of 73±4 kg. Control subjects were well matched for age, height, and weight. The control group consisted of five men and one woman, while the patient group consisted of eight men and four women. Ten of the 12 patients were previously shown to have mild to moderate OSA on standard polysomnography, with a mean AHI of 25±4/h (range, 6 to 48), and mean minimum oxygen desaturation of 84±2% (range, 93 to 70). None of the control subjects had OSA (ie, AHI <5). A total of 178 nasal occlusion tests were performed in the 18 subjects.

All 12 patients with Marfan’s syndrome, including

![Figure 1](http://journal.publications.chestnet.org/pdfsaccess.ashx?url=/data/journals/chest/21720/ on 06/26/2017)
the 2 without OSA, demonstrated increased upper airway collapsibility during sleep, with a mean UACP of -2.5±0.5 cm H₂O during SWS. The two nonsnoring, nonapneic patients had a mean UACP of -3.5±1.1 cm H₂O, which was not significantly different from the group with OSA. A typical recording is shown in Figure 1. In marked contrast, control subjects generated a mean peak inspiratory pressure of -7.1±0.5 cm H₂O, this being limited by upper airway closure in only two of the subjects. Furthermore, in these two control subjects, the closure occurred at significantly higher suction pressures than in patients, with a mean UACP of -5.6±0.4 cm H₂O (p<0.005). The remaining four control subjects generated peak inspiratory mask pressures of -7.8±0.4 cm H₂O, without evidence of closure, and often leading to arousal (Fig 2). The UACP and peak inspiratory pressure data are presented in Table 2.

Univariate regression analysis revealed that mean UACP during SWS correlated significantly with AHI (r=0.6, p<0.05) in the 14 subjects (12 patients and 2 controls) who demonstrated upper airway closure.

**DISCUSSION**

In a previous study, we showed that 64% of randomly recruited patients with Marfan’s syndrome (n=25) had OSA, with a mean AHI of 20±3.7 These patients are quite different from the typical sleep apnea population—they are tall, thin, and young. Therefore, it is possible that different mechanisms are important in the pathogenesis of OSA in this group. Our data herein demonstrate that patients with Marfan’s syndrome have significantly increased upper airway collapsibility during sleep compared with control subjects. In particular, even in the two nonsnoring, nonapneic patients, the airway closed when subjected to low levels of suction pressure. Therefore, it is possible that upper airway laxity is an important pathophysiologic mechanism accounting for the high prevalence of OSA in these patients.

Issa and Sullivan measured closing pressures during sleep in healthy subjects,15 nonapneic snorers,16 and patients with OSA.11 They found that normal subjects generated peak inspiratory pressures of -16.1±1.2 cm H₂O before arousal, without evidence of upper airway closure. In contrast, snorers and patients with OSA showed evidence of upper airway closure; in patients with OSA, this occurred at lower suction pressures than in nonapneic snorers. Mean UACP for patients with OSA was -4.2±0.2 cm H₂O during SWS; nonapneic snorers had a mean UACP of -5.8 cm H₂O during nonrapid eye movement sleep.16 The patients with Marfan’s syndrome in this study had a mean UACP of -2.4±0.1 cm H₂O during SWS. This suggests that these patients have more collapsible upper airways than the patients with OSA studied by Issa and Sullivan,11 all of whom were obese and had more severe OSA (mean AHI 55±4/h). Furthermore, other studies of upper airway collapsibility in OSA have all been carried out in obese patients.13,17,18 Moreover, weight loss is associated with improvements in upper airway function during wakefulness19 and sleep,20 emphasizing a link between obesity and upper airway collapsibility. It is important to stress that patients with Marfan’s syndrome are tall and thin, and yet this study found that their degree of upper airway collapsibility is

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21720/)

**Table 2—Peak Inspiratory Mask Pressures for Patients and Control Subjects**

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<th>Marfan—</th>
<th>Marfan—</th>
<th>Control</th>
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<td></td>
<td>With OSA</td>
<td>No OSA</td>
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<td>10</td>
<td>2</td>
<td>6</td>
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<tr>
<td>Peak mask pressure, cm H₂O</td>
<td>-2.3±0.5</td>
<td>-3.5±1.1</td>
<td>-7.1±0.6</td>
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*In all patients, both with and without OSA, the peak inspiratory mask pressure was limited by upper airway closure, and therefore the peak pressure is equivalent to the UACP. In contrast, closure occurred only in two control subjects, with a mean UACP of -5.6±0.4 cm H₂O. Marfan=Marfan’s syndrome. Number of occlusion tests given in parentheses.

&agr;<0.05 compared with control subjects. No significant difference between Marfan—with OSA and Marfan—no OSA groups. Statistical comparisons were carried out by one-way ANOVA, using mean pressure data for each subject, rather than individual occlusion tests.
in fact more severe than that of previously studied obese patients with OSA. Although this does not prove that the intrinsic connective tissue defect of Marfan's syndrome is the causative factor, it does provide support for this hypothesis. Moreover, it supports the general hypothesis about OSA in which abnormally high airway compliance could be a factor.

Only two control subjects in our study demonstrated upper airway closure, with UACPs in the range previously seen in nonapneic snorers.\textsuperscript{16} Although neither subject had OSA, they both admitted to occasional snoring when provoked by nasal obstruction or alcohol consumption. The remaining four control subjects generated a mean peak mask pressure of \(7.8\) cm H\(_2\)O prior to arousal, which is less than that observed in the study by Issa and Sullivan.\textsuperscript{15} However, they observed a wide range of mask pressures, both within and between control subjects, indicating variable degrees of arousability. The pressures observed in the control subjects in this study fall within that range.

A significant correlation was observed between UACP and AHI. However, this correlation was not strong, which suggests that other factors are also important determinants of apnea frequency. Likely factors include the resistance upstream to the collapsible segment and arousability. Notably, two nonsnorers, nonapneic patients in this study also had evidence of increased upper airway collapsibility during sleep, with a mean UACP of \(-3.5\pm1.1\) cm H\(_2\)O during SWS. This was not significantly different from the OSA group. The finding of a readily collapsible upper airway in these two nonapneic, nonsnoring patients with Marfan’s syndrome is of particular interest. A possible explanation is that upper airway laxity is the underlying mechanism predisposing patients with Marfan’s syndrome to sleep-disordered breathing, with other variables subsequently determining the age of onset and severity. One possible important variable is nasal resistance; a subject is more likely to have apnea if high nasal resistance is associated with a lax upper airway. However, there were no obvious reasons why these two patients differed from the others. Clearly it is not possible to draw definitive conclusions based on these two patients, and it will be important to study more nonsnorers, nonapneic patients with Marfan’s syndrome to verify these findings.

Patients with the Marfan’s syndrome have an inherited connective tissue defect. Hollister et al\textsuperscript{21} reported that fibrillin, a component of the microfibrillar system associated with elastin, was lacking in cultured dermal fibroblasts from patients with Marfan’s syndrome. The gene defect has recently been localized on chromosome 15,\textsuperscript{22} and this chromosome has also proved to be the location of the gene for fibrillin.\textsuperscript{23} It appears that most affected families carry their own distinct mutation. Clinically, these patients have lax tissues, eg, skin laxity, hypermobile joints, lens dislocations, mitral valve prolapse, and aortic root dilatation. This study demonstrates that the upper airway is also lax, at least during sleep, suggesting that the connective tissue defect also affects the pharynx.

In conclusion, we have demonstrated that patients with Marfan’s syndrome have abnormally increased upper airway collapsibility during sleep, compared with normal control subjects. In particular, two nonsnorers, nonapneic patients also demonstrated marked collapsibility. In addition, the degree of collapsibility observed in these tall, thin patients is greater than that previously observed in typically obese patients with more severe forms of OSA. Although these findings do not prove that the observed increased upper airway collapsibility in these patients is due to the intrinsic connective tissue abnormality of this disease, they do point to a possible specific abnormality of upper airway function in patients with Marfan’s syndrome compared with the general OSA population. We speculate that this possible specific abnormality of upper airway function relates to tissue laxity, resulting from the connective tissue defect that occurs in these patients. However, it will be important to study more patients with Marfan’s syndrome who do not snore or have OSA to resolve this question.

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REFERENCES