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PULMONARY FUNCTION, WORKING CAPACITY AND STRENGTH IN YOUNG ADULTS WITH MARFAN SYNDROME

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Objective: **To investigate pulmonary function, working capacity and isokinetic muscle strength in subjects with Marfan syndrome.**

Materials and methods: **Seventeen subjects, mean age 23 years, performed spirometry, maximal ergometer cycle tests and knee extension and flexion isokinetic torque tests.**

Results: **The subjects with Marfan syndrome had increased total and residual lung volume values compared with predicted values in healthy subjects and reduced peak oxygen uptake compared with healthy subjects of the same age. The isokinetic peak torque was reduced only at the highest velocity in the women.**

Conclusion: **Thirteen subjects were able to perform the bicycle test until exhaustion without cardiovascular complications or pulmonary restrictions. However, their aerobic capacity was considerably decreased, which we suggest is caused by deconditioning. Further investigations are needed to reveal how pulmonary and cardiovascular limitations change with ageing and to give guidelines for exercise.**

Key words: Marfan syndrome, pulmonary function, maximal oxygen uptake, isokinetic muscle strength.

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INTRODUCTION

The purpose of this study was to assess pulmonary function, aerobic capacity and isokinetic muscle strength in a group of 17 young adults with Marfan syndrome compared with predicted values in a normal population.

Marfan syndrome is an autosomal dominant connective tissue disorder. Reports of prevalence and incidence of the syndrome are variable. In Denmark, which has a similar ethnic and genetic population to that of Norway, the prevalence is reported to be 0.46 per 10,000 and the incidence 0.96 per 10,000 (1). Common to all patients with Marfan syndrome is a defect in the fibrillin proteins. Fibrillin is the major component of the microfibrils in all connective tissue, thus the syndrome causes a wide variety of clinical manifestations in different organs. According to the Gent criteria, diagnosis requires the presence of at least 2 major criteria in 2 different organ systems and the involvement of a third organ system (2). Presence of a family history or genetic markers can replace a major criterion. Some of the common manifestations of Marfan syndrome are skeletal abnormalities with a thorax deformation, height above the normal average, hypermobility and luxation of joints, ectopia lentis, dilatation or dissection of the aorta and mitral valve prolapse. The changes in the blood vessels and, particularly, in the aorta may be life threatening. The leading cause of premature death in patients with Marfan syndrome is dissection and incompetence of the ascending aorta and the aortic root. Hence, precautions have to be taken, and heavy physical activity is contraindicated with an aorta root dilatation above 5 cm (3). Since 1972 the life expectancy of people with Marfan syndrome has increased significantly due to medical and surgical treatment. However, many people with Marfan syndrome live with the possibility of early cardiac death. Due both to changes in different organ systems and restricted physical activity imposed either by health personnel, relatives or themselves, people with Marfan syndrome may experience limitations in their daily life and reduced participation in physical and social activities (4). Inactivity may follow, which in turn may influence oxygen uptake and muscle strength. The negative consequences of inactivity of the cardiorespiratory system are well known (5). Furthermore, low physical activity is associated with subjectively reported fatigue, low working capacity and endurance during everyday life (6). Maximal oxygen uptake is a reliable measurement of physical fitness (7), and muscle strength may be equally important for daily activities (8). Pulmonary function in subjects with Marfan syndrome has rarely been described in the literature, and may also be a limiting factor for physical performance. This study therefore addressed the question: Do subjects with Marfan syndrome have reduced pulmonary function, peak oxygen uptake and isokinetic muscle strength compared with healthy subjects?

MATERIALS AND METHODS

Materials

The study was approved by the Regional Ethics Committee for Medical Research. All patients gave their informed consent before participating.

Thirty-nine subjects in the age range 18–30 years with Marfan syndrome or Marfan-like symptoms were registered at the National Resource Centre for Seven Rare Disorders in Norway (TRS) in 1997.

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Table I. *Characteristics of 17 young adults with Marfan syndrome and reference values for the Norwegian population. Data are given as mean (SD)*

	Women		Men	
	Subjects with Marfan syndrome (n = 13)	Norwegian population	Subjects with Marfan syndrome (n = 4)	Norwegian population
Age (years)	24 (5)	24 (6)	27 (4)	24 (6)
Weight (kg)	67 (14)	66	95 (7)	73
Height (cm)	179 (6)	166	195 (6)	180
BMI (weight/height^2)	21 (4)	20–25	25 (3)	20–25

They were sent written information about the study and asked to participate on a voluntary basis. Twenty-two subjects volunteered. However, 5 of the 22 subjects did not fulfil the Gent classification criteria (9). Seventeen of the subjects (13 women and 4 men) were included in the study. Age and anthropometrics are given in Table I.

Both women and men were above mean body height for the Norwegian population. The mean body weight was within normal limits for the women, but above for the men (10). Eight subjects (6 women and 2 men) out of 16 (data on the 17th subjects are missing) exercised regularly for more than 30 minutes at least once a week, and 8 subjects (5 women and 3 men) out of 17 were smokers. For comparison approximately 50% of the Norwegian population exercise regularly and 33% are smokers (10). All subjects, except 1 man with Charcot Marie Tooth Syndrome, were without coexisting diseases.

Before exercise testing the subjects underwent echocardiography and examinations for cardiovascular affection, including measurements of the aorta diameter. Exclusion criteria were aorta diameter above 5 cm or dissection of the aorta wall.

In all subjects the ejection fraction was normal. Four subjects (2 men and 2 women) had undergone cardiac surgery, and 5 subjects (2 men and 3 women) used β-blockers. In addition, 1 man had both undergone cardiac surgery and used β-blockers.

Nine out of 16 subjects (data on the 17th subject are missing) reported that they had been advised to restrict their physical activity. However, after the echocardiography examination, only 2 subjects with an aorta dilatation above 50%, but below 5 cm, were given restrictions to maximal exercise testing. In these 2 subjects it was advised that the systolic blood pressure should not increase above 160 mmHg and/or the heart rate should not increase more than 50% above resting values.

Test procedures and measurements

The tests were performed at Sunnaas Rehabilitation Hospital, University of Oslo, and monitored by a medical doctor. Testing took place only on days when an ambulance helicopter was available.

Spirometry. Spirometry was performed in a sitting position by water spirometry (SensorMedics 2400, SensorMedics Corporation, California, USA) and forced vital capacity (FVC), forced expiratory volume for 1 second (FEV1), maximal voluntary ventilation (MVV), total vital capacity (TVC), residual volume (RV) and lung diffusion capacity for CO (DLCO) were measured.

All 17 subjects with Marfan syndrome performed the spirometry test, and the results were compared with predicted values for sex, height and age in healthy persons (European updated predicted values, European Respiratory Society, 1993).

Bicycle ergometer test. Exercise testing was performed on a bicycle ergometer (Siemens Ergomed 840, Siemens, Erlangen, Germany) with a stepwise increment in workload every third minute until exhaustion. The pedalling frequency was 60 revolutions per minute, and the initial workload was 50 watt. The increment was 50 watt for the men and 2 of the women and 25 watt for the remaining women, determined by expected work capacity after previous tests. Oxygen uptake (VO_2), ventilation (VE) and respiratory exchange gradient (R) were measured breath by breath during exercise, and a mean was calculated every minute (Jaeger EOS Sprint, E Jaeger Gmbh, Germany or SensorMedics 229, SensorMedics Corporation, California, USA). Some of the subjects had difficulties in maintaining the proper pedal frequency, and in those cases the highest value of the oxygen uptake was chosen. Electrocardiogram (ECG) and heart rate were registered continuously by standard methods (Siemens Sicard 460, Siemens, Erlangen, Germany and Cardiac Monitor 573, KONE Corp. Espoo, Finland). The heart rate at the end of every minute was used as the representative value for the current minute. Blood pressure (BP) was measured the last minute of each workload, i.e. every third minute, using a microphone and a cuff around the right arm (Paramed Model 9300, Paramed Tech Inc. Palo Alto, California, USA). The perceived exertion was reported immediately after measuring the blood pressure using Borg's 15-grade scale (from 6 to 20) for ratings of perceived exertion (RPE scale) (11). Three minutes after exhaustion a blood sample was collected from the fingertip for measuring the lactate concentration in the blood (YSI 1500 Sport Lactate analyser, YSI Incorporated, Ohio, USA).

The tests were stopped if the ECG showed pathological changes according to regular criteria for stress ECG (12), and when the subjects who had been given restrictions reached predetermined values in blood pressure and heart rate (systolic blood pressure above 160 mmHg and/or heart rate increase above 50%).

Thirteen subjects completed the bicycle test and stopped due to general exhaustion, while 4 subjects (3 women and 1 man) interrupted the test. Two of these 4 subjects were stopped because of pathological changes in ECG, and 2 reached the above-mentioned predetermined medical limits.

The main criterion for obtained maximal oxygen uptake is a levelling off in oxygen uptake, where no increase in oxygen uptake is seen in spite of an increased workload. Levelling off is highly dependent on exercise protocol, and is seldom found in the present model (13, 14). None of the subjects in our study reached a plateau level. If the oxygen uptake does not reach a plateau level, a lactate concentration in the blood above 8 mM is used to indicate the limit for oxygen uptake (15). However, well-trained subjects are able to obtain higher levels of blood lactate than untrained subjects (15, 16) and in the present study we were examining patients with a lower expected fitness level than the healthy population. Thus, we considered the oxygen uptake to be close to maximal when the lactate concentration in the blood was above 6 mM instead of above 8 mM. We denoted the subjects reaching this level as "La $>$6 mM group". Those subjects who reported 19 or 20 in perceived exertion on the Borg scale, but did not reach lactate concentrations in the blood above 6 mM, were denoted as the "La $<$6 mM and Borg score $\geq$19 group". More unreliable criteria for maximal oxygen uptake are R-value above 1.15 and obtained maximal predicted heart rate, hence, these criteria were not chosen to indicate maximal oxygen uptake in the present study. In the following "peak oxygen uptake" is used for the uptake at exhaustion, since the denotation "maximal" uptake indicate either fulfilment of the levelling off criterion or a lactate concentration above 8 mM. The peak oxygen uptake was compared with healthy subjects at the same age and gender (15). The formula used to predict maximal heart rate was: 220 beats/min minus the subject's age (15). Values above 90% of predicted were considered maximal (17). Data for all subjects without β-blocking medication are given in Table IIIa. Three of the women and 1 of the men completing the bicycle test used β-blockers, and their results are listed separately in Table IIIb. The results for the man with Charcot Marie Tooth syndrome are included in Table IIIa, but are also listed separately in Table IIIb.

Cybex isokinetic muscle test. Peak torques (Nm) for knee flexion and extension were measured by Cybex 340 or Cybex Norm (Cybex

International Inc. Ronkonkoma, NY, USA). The protocol started with 5 minutes warm-up aerobic ergometer cycling. After the cycling the subjects were seated in the apparatus and the leg to be tested was stabilized with a thigh strap. The test procedure consisted of 3 trial repetitions with maximal effort at 60 degrees per second (°/s) immediately followed by 3 registered maximal repetitions. After 20 seconds rest the same procedure was repeated for 240 °/s. Both limbs were tested in randomized order. The repetitions with the highest registered peak torque for flexion and extension was chosen and compared with values for untrained healthy control subjects (Strøm, V., Sunnaas Hospital, Clinical Physiological Laboratory, reference values, unpublished). In the control group mean age and weight (SD) was 25 (2) years and 60 (6) kg for women (n = 13) and 29 (4) years and 77 (7) kg for men, respectively. Three women with Marfan syndrome did not perform the isokinetic muscle test, and the man with both Marfan and Charcot Marie Tooth Syndrome was excluded.

Statistics

All analysis was performed with the statistical package for social science (SPSS, version 11.0). Too few men were participating to justify a statistical comparison. Intra-subjective comparison of blood pressure data at rest and at exhaustion in the Marfan women were analysed by paired-samples *t*-test. Pulmonary function in smokers and non-smokers and knee flexion and extension peak torque measurements in the healthy reference group and the Marfan women were analysed by independent-samples *t*-test. The distribution of the results is given as mean, (SD) and minimum and maximum values. The subjective ratings on the Borg scale were considered ordinal data and given as median with minimum and maximum values.

RESULTS

Pulmonary function

The TVC and RV were generally larger in the subjects with Marfan syndrome than in the normal population (Table II). Thirteen subjects obtained a TVC above normal range, and the mean was approximately 30% above mean average values. The mean RV was twice as high as predicted, and all subjects except 1 obtained a RV outside normal range. The ratio RV/TVC was approximately 40% compared with 25% in the normal population. The mean FVC and the ratio FEV_1/FVC were within normal limits. The ratio FEV_1/FVC was above 75% in 12 subjects, while 5 subjects obtained values between 68% and 75%, indicating a slight obstructive component of respiration. Three of these 5 subjects were men; 1 was cardiac operated and 1 was both cardiac operated and a smoker. The MVV in the subjects with Marfan syndrome were generally within normal limits, except for a reduction of 30% in 2 women. Neither of these 2 women were smokers, but 1 was cardiac operated. The mean ratio MVV/FEV_1 was lower than expected in the Marfan women. Most of the subjects with Marfan syndrome obtained DLCO values in the lower range of predicted. However, 4 women and 1 man obtained values below 75% of predicted, which is characterized as outside normal range. One of the 4 women smoked, and 1 both smoked and was cardiac operated (Table II). Statistical comparisons of FVC, FEV1, FEV1/FVC, MVV, MVV/FEV_1, TVC, RV and DLCO between smokers and non-smokers showed comparable mean values ($p > 0.21$).

Peak oxygen uptake

Ten women and 3 men with Marfan syndrome completed the bicycle test. Four of these 13 subjects used β-blockers. For the subjects without β-blocking medication, the mean peak VO_2 was 1.8 (0.3) l/min for the women (n = 7) and 2.4 (0.2) l/min for the men (n = 2) (Table IIIa) compared with approximately 2.3 l/min and 3.2 l/min in healthy moderately trained women and men of the same age (15). Thus, the peak oxygen uptake in the subjects with Marfan syndrome was reduced by 20–30%. If the results are given in ml/kg/min, which is the common denomination to represent aerobic fitness, the reduction was approximately 30% in the women and 50% in the men compared with predicted values from an untrained normal population (14). Two women in the group were smokers. The peak VO_2 for 1 of

Table II. *Spirometric measurements in 17 patients with Marfan syndrome. Data are given as mean (SD) min–max*

	Women (n = 13)		Men (n = 4)	
	Subjects with Marfan syndrome	Predicted values	Subjects with Marfan syndrome	Predicted values
FVC (l)	4.7 (0.3) 4.3–5.3	4.4 (0.2) 4–4.6	5.6 (0.8) 4.6–6.4	6.2 (0.5) 5.7–6.7
FEV1 (l)	3.9 (0.3) 3.2–4.4	3.8 (0.2) 3.5–4.0	4.1 (0.3) 3.8–4.4	5.1 (0.4) 4.75–5.5
FEV1/FVC (%)	83 (6.3) 71–91	83.8 (0.4) 83–84	74.5 (6.2) 68–83	82.5 (0.6) 82–83
MVV (l/min)	115.2 (20.6) 72–157	133.2 (6.3) 122.5–140.5	161.5 (24.6) 136–185	178.3 (12.9) 166–193
MVV/FEV1 (%)	29.7 (4.1) 22.5–38.1	35 (0.3) 34–35	39.5 (8.1) 31.7–46.9	35 (0.04) 35
TLC (l)	7.8 (0.9) 6.2–10.1	6 (0.3) 5.4–6.5	9.2 (1.6) 7.0–10.9	8.5 (0.6) 7.9–9.2
RV (l)	3.3 (0.5)[#] 2.7–4.6	1.7 (0.1) 1.5–1.8	3.6 (1.1) 2.4–5.0	1.9 (0.05) 1.9–2
RV/TLC (%)	41.4 (3.1) 37–46	27.5 (0.8) 27–29	39 (6) 34–46	24.8 (1) 24–26
DLCO (ml/min/mmHg)	25.1 (4.2)[#] 18.6–33.5	31.8 (1.2) 29.7–33	35.7 (3) 31.7–38.1	41.3 (2.8) 38.7–44.5

[#]n = data on 1 subject missing. For abbreviations see Materials and Methods.

Table IIIA. *Working capacity, peak values, in a bicycle ergometer exercise test in 9 patients with Marfan syndrome without β-blocking medication. Data are given as mean (SD) min–max. The 2 men had undergone cardiac surgery*

		Women (n = 7)	Men (n = 2)
Age		23 (5) 18–32	26 (5) 22–29
$VO_{2\ peak}$ (l/min)		1.75 (0.27) 1.31–2.01	2.44 (0.17) 2.32–2.56
$VO_{2\ peak}$ (ml/kg*min)		25.3 (2.9) 20.2–28.8	24.4 (0.4) 24.1–24.7
VE_{max}/MVV (%)		60 (10) 47–77	48[#] –
R value		1.13 (0.16) 0.95–1.34	1.02 (0.01) 1.01–1.03
Lactate (mM)		5.4 (2.3)[##] 2.9–9.0	7.1 (3.0) 5.0–9.2
Heart rate (beats/min)		177 (17) 153–208	178 (13) (168–187)
Blood pressure (mm/hg)	Systolic	168 (21)[#] 151–209	226[#] –
	Diastolic	83 (17)[##] 64–107	112[#] –
Borg scale, median (min–max)		19 (19–20)	19[#] –

[#]n = 1 missing, [##]n = 2 missing.
For abbreviations see Materials and Methods.

the smoking women (1.45 l/min) was slightly lower than the mean for the group. However, her peak VO_2 measured in ml/kg/min was similar to the results in Table IIIa (26.25 ml/kg/min). The peak VO_2 for the second smoker did not differ from the results in Table IIIa. The mean peak heart rate was approximately 90% of predicted maximal heart rate for both sexes (n = 7 women and n = 2 men). The mean R-value was above 1.15 in 7 subjects and below 1.00 in only 2. The median reported perceived exertion was 19 (19–20) for the women and 18 (17–19) for the men on the Borg scale. The systolic blood pressure rose significantly ($p < 0.01$) from rest to exhaustion without changes in the diastolic pressure ($p = 0.19$) in the women with Marfan syndrome. This is similar to responses found in the normal population (15). The mean Ve_{max}/MVV ratio during exercise is normally 60–70% in healthy subjects, and all but 1 non-smoking subject with Marfan syndrome obtained values within this limit.

The peak VO_2 for 3 of the 4 subjects using β-blockers (Table IIIb) were comparable to the results in Table IIIa. The peak VO_2 for the fourth subject, a woman, was slightly lower. As for the women with Marfan syndrome who were not using β-blocking medication; the systolic blood pressure rose significantly ($p = 0.03$) while the diastolic pressure remained unchanged ($p = 0.52$) for the 3 women using β-blockers.

Subjectively reported exhaustion may not correlate with the physiological limitation of endurance, particularly in patient populations and in untrained subjects (16, 18). We therefore performed subgroup analysis. Seven subjects (5 women and 2 men) reached lactate concentrations in the blood of 6 mM or more, and were thus considered to be close to maximal oxygen uptake. This subgroup (La >6 mM) reached peak heart rates above 90% of predicted, and 4 subjects reached R-values above 1.15 (Table IIIb). One woman and 1 man in the subgroup used β-blockers, and their peak heart rates were 194 and 169 beats/min, respectively.

For the rest of the Marfan group, i.e. five women and one man, who reported maximal performance but obtained lactate concentrations below 6 mM ("La <6 mM and Borg score ≥19"), the mean peak heart rate was approximately 85% of predicted maximal values. The R-values were above 1.15 in 3 subjects

Table IIIB. *Bicycle ergometer exercise test, peak values, in 2 subgroups of patients with Marfan syndrome. Data are given as mean (SD) min–max. For women with β-blockers "La <6 mM, Borg score ≥19", subject 1 values are given with subject 2 values in brackets []*

	1. La >6 mM				2. La <6 mM, Borg sore >19			
	Women (n = 4)	Men (n = 1)	Women (n = 1)	Men (n = 1)	Women (n = 3)	Men (n = 1)	Women (n = 2)	Men (n = 0)
β-blockers			+	+			+	+
Age	24 (6)	29	21	30	21 (3)	22	26 [23]	–
$VO_{2\ peak}$ (l/min)	1.88 (0.12) 1.76–2.01	2.56	1.74	2.47	1.58 (0.35) 1.31–1.98	2.3	1.46 [1.75]	–
$VO_{2\ peak}$ (ml/kg/min)	26.8 (2.0) 24.3–28.8	24.10	31.6	27	23.4 (3.0) 20.2–26.3	24.7	24.5 [22]	–
VE_{peak}/MVV (%)	60 (13) 47–77	48	44	63	61(11) 52–66	–	65 [41]	–
R value	1.13 (0.16) 0.95–1.33	1.03	1.23	1.33	1.12 (0.2) 0.96–1.34	1.01	1.17 [1.18]	–
Lactate (mM)	7.6 (2.0)[##] 6.2–9.0	9.2	6.2	7.4	3.9 (0.9) 2.9–4.7	5.0	– [5.3]	–
Heart rate (beats/min)	186 (16) 175–208	187	194	169	165 (12) 153–177	168	138 [188]	–
Borg scale, median min–max	19 19	19	–	17	20 19–20	–	19 [19]	–
Cardiac surgery		+		+				
Charcot Marie Tooth		+						

[##]n = 2 missing subjects. For abbreviations see Materials and Methods.

Table IIIC. *Working capacity, peak values, in 4 subjects, who interrupted the test*

	Subject 1 Woman	Subject 2 Woman	Subject 3 Woman	Subject 4 Man
Reason for interruption	Pathological changes in ECG	Pathological changes in ECG	BP > 160	BP > 160
β-blockers				+
Age (years)	21	29	31	26
$VO_{2\ peak}$ (l/min)	1.9	–	1.2	1.1
$VO_{2\ peak}$ (ml/kg/min)	26.7	–	17.6	12.1
VE_{max}/MVV (%)	36	–	32	19
R value	1.05	–	0.95	0.91
Lactate (mM)	3.6	–	2.06	1.2
Heart rate (beats/min)	181	167	90	87
Borg scale (6–20)	18	15	11	11
Cardiac surgery		+	+	

For abbreviations see Materials and Methods.

(Table IIIb). Two subjects used β-blockers, and their peak heart rates were 188 and 138 beats/min, respectively. Both obtained R-values above 1.15. The peak oxygen uptake was slightly higher in "La >6 mM group" compared with the "La <6 mM and Borg ≥19 group".

Four subjects interrupted the bicycle test; 2 were stopped because of irregularities in ECG during the bicycling, and 2 reached the predetermined medical limitations (see method). Data for these 4 subjects are given in Table IIIc.

Peak torque

The mean peak torque (Nm) for knee flexion was slightly lower in women with Marfan syndrome compared with healthy age-matched women at low velocities, i.e. 60 °/s ($p = 0.15$ and $p = 0.11$ for the right and the left leg, respectively). The reduced peak torque became significant for the right knee when the velocity increased to 240 °/s ($p = 0.03$ and $p = 0.12$ for the right and the left leg, respectively). Data for the right leg are given in Table IV. No differences were found between the mean peak torques for extension in the 2 groups ($p > 0.24$). In the small group of men with Marfan syndrome the values for knee flexion and extension peak torque were close to values found in healthy subjects.

DISCUSSION

The present study showed that in a Marfan population of 17, approximately 80% were able to complete a symptom limited exercise test until exhaustion. The main difference between the subjects with Marfan syndrome and the reference population was a marked reduction in peak oxygen uptake in the subjects with Marfan syndrome. The subjects with Marfan syndrome also showed increased total and residual lung volume values compared with predicted values. The isokinetic knee peak extension and flexion torque were reduced only for flexion at the highest velocity of 240 °/s in the women with Marfan syndrome.

Pulmonary function

Although we found slightly obstructive lung function in approximately 30% of the subjects and increased TVC and RV in all but 1 subject, there were no indications of pulmonary function as the limiting factor. The Ve_{max}/MVV did not indicate ventilatory restriction during exercise, and the diffusion capacity (DLCO) was within normal limits, however in the lower range of predicted. The pulmonary function in the smokers was no worse than the pulmonary function in the non-smokers. However, the population was small, and the subjects were young.

Using sitting height to calculate the expected spirometric values, normal spirometric values were reported in subjects with

Table IV. *Peak torque (Nm) for knee flexion and extension in the right leg at 2 velocities (60 °/s and 240 °/s) in 13 patients with Marfan syndrome compared with a Norwegian reference group. Data are given as mean (SD) min–max*

		Women		Men	
Peak torque (Nm)		Subjects with Marfan syndrome ($n = 10$)	Healthy controls ($n = 13$)	Subjects with Marfan syndrome ($n = 3$)	Healthy controls ($n = 5$)
Flexion 60 (°/s)	Right	68 (25) 20–98	82 (22) 48–120	113 (6) 107–119	122 (24) 102–154
Flexion 240 (°/s)	Right	33 (17) 5–62	49 (16) 29–81	66 (29) 41–98	77 (15) 61–93
Extension 60 (°/s)	Right	128 (40) 50–172	140 (37) 84–232	214 (15) 197–226	229 (43) 166–269
Extension 240 (°/s)	Right	73 (28) 33–112	77 (19) 46–122	118 (25) 94–143	133 (25) 104–168

Marfan syndrome free of severe thoracic cage deformity (19). The same study found lower than expected values of TVC and FVC when they used the subjects with Marfan syndrome standing height, and claimed that abnormalities in pulmonary function could often be explained by thoracic cage deformity or by inappropriate use of standing height. In our study the standing height was used in the calculation. Subjects with Marfan syndrome often have longer legs than healthy and thus shorter chest length at the same height. Hence, the measured enlargement of the lung volumes in our study are probably underestimated rather than overestimated. The increased TVC and RV found in the present study may not give any functionally symptoms, but could be interpreted as reduced elasticity of the lung walls. The DLCO was low normal range for the majority of the subjects in spite of increased lung volumes. Increased TVC and RV have not been verified in other studies. However, pathological changes of the pulmonary function have been found. One study described fragile lungs and decreased lung elastic recoil in 2 cases of the Marfan syndrome, and suggested that weakness in the pulmonary connective tissue framework caused pneumothorax and bullous emphysema (20). Another study described obstructive lungs and bronchial hyperreactivity in most if not all of the patients in a group of 11 children with Marfan syndrome compared with healthy children (21).

In our study the subjects were young, and functional consequences of slight obstruction, large TVC and RV and lower range of DLCO with ageing, and thus co-morbidity, cannot be excluded. However, further investigations of the pulmonary function are needed, especially with the prolonged life span in subjects with Marfan syndrome (22).

Muscle strength

Peak torque measured at high velocities may be more sensitive measurements of disease related changes than peak torque at lower velocities (23). Altered elasticity of connective tissue may influence muscle torque production. Also anthropometrical differences, cardiac affection and modified physical activity may influence peak torque (4). We have, however, no plausible explanation to the selective influence at flexion torque. To our knowledge muscle strength in patients with Marfan syndrome has not previously been characterized. Peak torque ought to be measured in larger populations of subjects with Marfan syndrome and supplemented with muscle physiological measurements to elucidate the mechanisms of reduced flexion torque.

Working capacity

The present study showed that 13 out of 17 subjects with Marfan syndrome could exercise at their maximal experienced level without having cardiovascular complications. Only in 2 subjects the test was stopped because of pathological changes in ECG. Two other subjects were stopped when they reached the predetermined levels in blood pressure (160 mmHg).

The main result in the bicycle test to exhaustion was a marked reduction in peak oxygen uptake in 13 subjects with Marfan syndrome completing the test. The results did not differ between Marfan smokers and non-smokers. None of the subjects with Marfan syndrome reached a plateau level by the levelling off criterion (15). However, several studies have shown that this is difficult to reach even in healthy persons (13, 14). Seven subjects with Marfan syndrome were close to maximal values in oxygen uptake by reaching lactate concentration in the blood above 6 mM, and 6 other subjects reported maximal effort.

Impairment of the cardiovascular system is one of the core manifestations in Marfan syndrome, and may be one of the main limiting factors in oxygen uptake. Despite this, the working capacity and cardiovascular function in subjects with Marfan syndrome is scarcely described in the literature. Because of changes in the elastic fibres the blood distribution to the muscles during exercise may be reduced. In the 17 subjects with Marfan syndrome in our study the echocardiography did not indicate cardiac failure or insufficient pump capacity. Furthermore, the ECG did not show any abnormalities during exercise in the 13 subjects who completed the test. In the subjects without β-blockers the peak heart rate was comparable to predicted values in both sexes, the diastolic pressure both at rest and at exhaustion were comparable to values reported in the normal population, and the systolic blood pressure rose as in healthy subjects during exercise (15). Thus, as far as we could evaluate, the cardiovascular function during exercise was normal, and could not explain the reduced peak oxygen uptake.

Impaired pulmonary function might reduce oxygen uptake, but the spirometric measurements did not indicate any limitations in the subjects with Marfan syndrome during exercise. We found no restrictions in mechanical ventilation measured by Ve_{max}/MVV, and no flow limitations either by airway resistance or muscle impairment, measured by FVC, FEV1 and MVV. A DLCO in the lower range of predicted, is not expected to result in reduced gas exchange ability during exercise. Thus, the lung function was probably not the cause of reduced oxygen uptake in the Marfan group. Furthermore, muscle strength was probably not a limiting factor during the exercise test, since the peak extension torque was normal.

Although the assessment of physical activity level in subjects with Marfan syndrome are not explicitly described in the literature, recommendations and guidelines given by health personnel indicate restrictions and caution rather than boldness, especially according to the dangers of aorta dissection (24–26). Patients with Marfan syndrome also report that they modify their physical activity due to consequences of their diagnosis and experienced subjective fatigue (4). Hence, the results indicate that cardiovascular deconditioning may be one important reason for the reduced peak oxygen uptake obtained in the present study. Furthermore, subjects with Marfan syndrome report that modifying exercise activities have significant negative consequences for their life (4). Exercise has therefore been recommended, without knowing the benefit, for subjects with Marfan syndrome (24). Physical activity is well known to improve both physical and mental health in the general population (27, 28). Thus, we suggest that subjects with Marfan syndrome may also

benefit from physical training. The field concerning physical activity and working capacity is probably unexplored because of the previously lethal character of the syndrome. Currently, there is little knowledge regarding the effects of long-term aerobic exercise on the development or progression of Marfan syndrome, and prospective studies need to be undertaken.

Recommendations about physical activity in subjects with Marfan syndrome

Some authors claim that in the absence of cardiovascular disease and compromising ophthalmologicl or musculo-skeletal abnormalities, subjects with Marfan syndrome should not avoid participation in sport (3). The exception is contact sports (3). The guidelines for "physical activities in children with coronary diseases" recommend that subjects with Marfan syndrome not to participate in contact sports, "high to moderate dynamic and static demands" or sports with "low dynamic and high to moderate static demands" (25, 26). In one article the author advised patients with Marfan syndrome not to exceed 50% of their aerobic capacity and to keep the heart rate below 110 beats/min. If they used β-blockers the heart rate should not exceed 100 beats/min (24). A reasonable upper limit for physical work during an 8-hour day is a workload of 30–40% of an individual's peak oxygen uptake (15). The peak oxygen uptake in the subjects with Marfan syndrome in our study was 1.7 ± 0.2 l/min for the women and 2.5 ± 0.1 l/min for the men (Table IIIa). Light work requires an oxygen uptake up to 0.5 l/min and a heart rate of 90 beats/min in healthy subjects at the age of 20–30 years. Moderate work requires oxygen uptake from 0.5 to 1.0 l/min and heart rate of 90–110 beats/min (15). If the guidelines for heart rates are followed, this indicates no work above moderate level for subjects with Marfan syndrome (24). Moderate work will also exceed 30–40% of the peak oxygen uptake for the subjects with Marfan syndrome in this study. This is above the upper limit of a reasonable workload during an 8-hour day. The consequences of limited physical activity might be a vicious circle with increasing heart rates and oxygen uptake at the same absolute workload (15).

Several studies have shown that patients with coronary diseases and cystic fibrosis, respectively, benefit from physical training (29, 30). One of the most important variables to show improvement of the cardiac function was lowering of the heart rate at a given submaximal work rate (15). We do not know if moderate endurance training reduce or enhance cardiovascular mortality in subjects with Marfan syndrome. Neither do we know the effects of exercise on activities of daily living and quality of life in patients with Marfan syndrome. However, several studies have shown that exercise improves function and quality of life in the general population and in many patient groups including chronic pain patients and patients with neuromuscular diseases (31, 32). However, the consequences of exercise programs for subjects with Marfan syndrome need to be investigated further, both in relation to quality of life as well as to cardiovascular complications and mortality.

In conclusion, the results from the present study show that 13 out of 17 subjects with Marfan syndrome were able to perform a dynamic bicycle test until exhaustion without having cardiovascular complications, while the remaining 4 subjects interrupted the test due to predetermined precautions or pathological ECG changes. The subjects with Marfan syndrome had decreased aerobic capacity, probably due to deconditioning, and increased total and residual lung volumes. Due to the increased lifespan of subjects with Marfan syndrome, future problems related to living with the syndrome may change. Research is needed to explore the long-term consequences of endurance training on the cardiovascular system, quality of life and mortality in subjects with Marfan syndrome.

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