Neuroscience & Medicine, 2012, 3, 187-191
http://dx.doi.org/10.4236/nm.2012.32024 Published Online June 2012 (http://www.SciRP.org/journal/nm)

Obstructive Sleep Apnea Syndrome in Two Subjects with Down Syndrome: Continuous Positive Airway Pressure Contribution on Exercise Tolerance

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Received February 17th, 2012; revised March 12th, 2012; accepted April 28th, 2012

ABSTRACT

In subjects with Down syndrome the obstructive sleep apnea is the cause of many disorders (cognitive and cardiovascular disorders, premature exhaustion, increase of daytime sleepiness). The standard treatment in the obstructive sleep apnea is continuous positive airway pressure, which eliminates the respiratory events, allows recovery of a satisfactory quality of sleep, and suppresses daytime sleepiness and cognitive dysfunction. The aim of this study was to verify the effects of continuous positive airway pressure on aerobic performance, as well as on hormonal and metabolic parameters during exercise, in two young adults with Down syndrome and with obstructive sleep apnea, treated or not, after an interval of 5 years. The main result observed is the beneficial effect on the ability to achieve a longer submaximal exercise with higher intensity in subject receiving the treatment. Obstructive sleep apnea syndrome treatment in people with Down syndrome could improve aerobic capacity and reduce daytime sleepiness.

Keywords: Trisomy 21; OSAS; Muscular Exercise; Metabolic Responses; Hormonal Responses

1. Introduction

Related to the presence of a chromosome 21 in triplicate, Down syndrome is a congenital aneuploidy whose prevalence is still high. Gene overexpression associated with chromosomal triplication affects almost every system and leads to a numerous phenotypic physical consequences [1].

Some of these abnormalities predispose Down syndrome patient to present obstructive sleep apnea syndrome (OSAS). The prevalence of OSAS is higher in these individuals (30% to 50%) [2] than in the general population. In individuals with Down syndrome, a macroglossia, a decrease in upper airway associated with generalized hypotonia, a high risk of hypothyroidism and obesity, are risks factors for OSAS [2] and also cause a decrease in effort tolerance and an increase in cardiovascular risks.

In general population, sleep apnea can lead to more or less pronounced consequences as those observed on the cardiovascular system (coronary heart disease, arrhythmias, decreased cardiac output and hypertension) [3].

In Down syndrome with OSAS, sleep fragmentation, nocturnal awakenings with nocturia, considerable snoring, morning asthenia, and daytime sleepiness are symptoms more frequently reported than in control subjects [4].

The standard treatment for sleep apnea is continuous positive airway pressure (CPAP) [5]. On a long term basis CPAP eliminates respiratory events, and suppresses daytime sleepiness. Normalization of ventilation suppresses sympathetic discharge at the end of respiratory-related events leading to a reduced rate of catecholamines [6]. CPAP treatment also appears to provide beneficial effects on cardiorespiratory fitness. Several studies have reported similar results: increased VO_{2peak}, higher QR_{peak}, improved exercise capacity, reduced sympathetic activity during exercise, increased baroreflex response, and better recovery of the resting HR [7,8].

However, at the present time, there is no data available on any possible links between CPAP set up, aerobic performance and hormonal adaptations to exercise in subjects with Down syndrome. Thus, the aim of this study

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was to explore the long term effects of CPAP treatment on the ability to maintain prolonged muscular exercise by comparing two young men with Down syndrome suffering from OSAS, one of which received CPAP treatment while the other was untreated.

2. Methods

During an interval of 5 years (2005 and 2010), two young men with trisomy 21 (age 23/28 years vs. 20/25 years and BMI 24.4/26.2 vs. 24.3/25.5 $kg \cdot m^{-2}$, respectively) were followed during clinical research on the limitations to muscular exercise. Both participants and their representatives were well informed, and then signed a consent form to take part in this study. Each protocol is based on three separate evaluations:

1) A maximal treadmill test (TT). It started at 3 $km \cdot h^{-1}$ and 0%, then speed and slope were alternately increased by 1 $km \cdot h^{-1}$ or 2% every minute, to reach VO_{2max}. Subjects were familiarized before the sessions to be able to reach their maximum. This TT was based on results previously published [9].

2) A submaximal TT divided into 3 levels (30% VO_{2max} 10 minutes - 50% VO_{2max} 10 minutes - 70% VO_{2max} until exhaustion) realized one week after the maximal TT.

During these two TT, measurement of gas exchange was performed using a metabograph (Brainware, Toulon, France). Heart rate was monitored continuously (ECT-WAS2000, Cardioline, Remco, Italy). In addition, a sampling catheter was placed in the fold of the elbow to carry out blood samples at rest, at the end of exercise and during recovery to allow evaluation of metabolic and hormonal variables.

3) A polysomnography was performed, 3 weeks after the submaximal TT, during a night at the hospital, according to international recommendations, to diagnose OSAS [5].

These two Down syndrome patients also took part in regular physical activity in sports clubs, where they regularly participated in adapted sports competitions (**Table 1**).

3. Results

The characteristics of these patients are presented in **Table 1**.

An OSAS was diagnosed in these young with Down syndrome following polysomnographic examination in 2005 (**Table 1**). Since diagnosis, the first subject (S.I) has an appropriate device every night and tolerates his treatment, while as the second subject (S.II) did not support the CPAP treatment, and remained untreated for his OSAS.

In S.I, the establishment of CPAP permitted an improvement of the total sleep time (335 min vs. 500 min), a reduction of total respiratory events (73.8 to 12.0/h), apnea index (23.7 to 12.0/h) and respiratory micro-awakenings events (43 to 6/h). In comparison, in S.II the absence of treatment led to a sharp rise in the number of total respiratory events (44.7 to 51.4/h), the apnea index (17.5 to 44.0/h) and micro-awakenings events (33 to 47/h).

The comparison between the two maximal TT after a 5 year interval showed (**Table 1**):

1) The maximal oxygen uptake in S.I was 36.0 in 2005 vs. 35.2 $ml \cdot min^{-1} \cdot kg^{-1}$ in 2010 (−2.2%) and for S.II it fell from 30.4 to 28.8 $ml \cdot min^{-1} \cdot kg^{-1}$ (−5.3%). The maximal heart rate values (HRmax) were similar for both subjects between the two TT after a 5 year interval.

2) The lactate concentration at 2 minutes post-exercise was significantly higher in S.I in the second TT whereas it remained stable in S.II.

The comparison between the two submaximal TT after an interval of 5 years showed (**Table 2**):

1) The total distance increased between TT 1 and 2 for S.I (+37.5%) while for S.II it decreased (−5.6%).

2) The HR recorded over the two tests overlapped in S.I whereas there was a HR decrease in S.II, when the effort was prolonged and intensified.

3) The values of ventilation are greater in S.I during the second test.

As for the hormonal results, we noted (**Table 2**):

1) The evolution in epinephrine kinetic between the two TT after an interval of 5 years was similar in S.II. For S.I the elevation of plasma epinephrine which existed at the first submaximal TT is no longer found 5 years later. The norepinephrine kinetic was also similar between the two TT, but with a lower amplitude in S.II.

2) A significant increase in cortisol concentration was found for S.I in the second submaximal TT, a result not observed in S.II.

4. Discussion

Individuals with Down syndrome exhibit a combination of factors predisposing them to develop more frequently an OSAS [2]. However, the consequences of OSAS on exercise capacity in subjects with intellectual disability have never been published in the literature. To our knowledge, this is the first time that are reported the effects of CPAP treatment on the ability of persons with Down syndrome to perform long muscular effort and on the metabolic and hormonal adaptations during those tests.

In this work, the results obtained after a 5 year interval showed that under the influence of CPAP treatment, it may exist in S.I, who is under treatment, a significant

Table 1. Subjects characteristics, maximal treadmill test and polysomnography results.

	S.I			S.II		
	S.I (1)	**S.I (2)**	**Variations**	**S.II (1)**	**S.II (2)**	**Variations**
Age (y)	23	28	+5 ans	20	25	+5 ans
Height (cm)	159	159	/	153	153	/
Weight (kg)	62.0	66.1	+6.6%	57.0	59.7	+4.8%
BMI ($kg \cdot m^{-2}$)	24.4	26.2	+7.2%	24.3	25.5	+5.0%
Fat mass (%)	22.9	22.3	−0.6%	16.8	18.5	+1.7%
Lean mass (%)	77.1	77.7	+0.6%	83.2	81.5	−1.7%
Sports (h/week)	2.0	3.0	+1 hour	2.5	4.0	+1.5 hour
HR_{rest} (bpm)	64	63	−1 bpm	69	71	+2 bpm
SAP_{rest} (mmHg)	130	135	+3.8%	110	105	−4.5%
Maximal HR (bpm)	183	183	/	164	160	−4 bpm
VO_{2max} ($mL \cdot min^{-1} \cdot kg^{-1}$)	36.0	35.2	−2.2%	30.4	28.8	−5.3%
VE ($L \cdot min^{-1}$)	64.8	93.0	+43.6%	60.8	54.6	−10.2%
VE/VO_2	29.2	40.4	+38.4%	35.1	31.7	−9.7%
RF (cycles/min)	39.8	48.8	+22.6%	42.8	35.3	−17.5%
VE/RF	1.6	1.9	+18.7%	1.4	1.5	+7.1%
RER	1.07	1.32	+23.4%	1.02	0.99	−2.9%
Blood lactate Rec + 2' ($mmol \cdot L^{-1}$)	4.4	10.6	+141%	7.0	7.3	+3.6%
Total sleep time (min)	335	500	+49%	289	348	+20%
Total respiratory events (event/h)	73.8	12.0	−83.7%	44.7	51.4	+15%
Apnea index (event/h)	23.7	12.0	−49.4%	17.5	44.0	+151.4%
Micro-awakenings events (event/h)	43	6	−86%	33	47	42%

S.I: subject 1, S.II: subject 2, (1): first TT in 2005, (2): second TT in 2010, BMI: body mass index, Resting HR: resting heart rate (beats/minute), Resting SAP: resting systolic arterial pressure (mmHg), VO_{2max}: maximal oxygen uptake ($mL \cdot min^{-1} \cdot kg^{-1}$), VE: ventilation ($L \cdot min^{-1}$), RF: respiratory frequency, RER: respiratory exchange ratio, Blood lactate Rec + 2': blood lactate concentration ($mmol \cdot L^{-1}$), 2' after TT stop.

Table 2. Cardio-respiratory and hormonal results during the submaximal treadmill tests (1) and (2) after an interval of 5 years.

	S.I					S.II				
	S.I (1)		**S.I (2)**		**Variations**	**S.II (1)**		**S.II (2)**		**Variations**
	Start	**End**	**Start**	**End**	**End**	**Start**	**End**	**Start**	**End**	**End**
Total distance (m)	1456		2002		+37.5%	1667		1573		−5.6%
Ventilation (L/min)	8.1	47.9	14.2	62.6	+30.7%	7.4	60.1	10.1	33.2	−44.7%
Heart rate (bpm)	81	177	98	177	0 bpm	84	167	72	129	−38 bpm
Plasma concentration of epinephrine (pmol/L)	181	439	185	179	−59.2%	328	434	378	545	+25.6%
Plasma concentration of norepinephrine (pmol/L)	1628	4540	2185	4849	+6.8%	3385	3140	4643	4602	+46.6%
Plasma concentration of cortisol (nmol/L)	432	456	412	550	+20.6%	347	434	432	431	−0.7%

S.I (1): subject 1 during submaximal TT 1; S.I (2): subject 1 during submaximal TT 2; S.II (1): subject 2 during submaximal TT 1; S.II (2): subject 2 during submaximal TT 2; Start: beginning of the submaximal TT; End: end of the submaximal TT.

improvement in various OSAS indexes, and in parallel, the results obtained during the maximal and submaximal exercise tests confirmed that the physical condition of the subject S.I, not only did not deteriorate with age, but it was improved for some parameters (*i.e.* aerobic capacity, ventilation).

In S.I, the distance covered during submaximal TT was more important, he was able to walk-run up to the same VO_{2max} percentages than 5 years before, while maintaining the same heart rate values. On the contrary, in S.II, there was a marked decrease in numerous variables characterizing cardiorespiratory fitness level. In particular, during the third stage of the submaximal test, S.II could not carry on his effort (70% VO_{2max}) with the same result than 5 years before: ventilation dropped significantly (−44.7%) and the increase in HR was lesser (167 vs. 129 bpm). These observations are consistent with those reported by other authors concerning the improvement of the aerobic component following the introduction of CPAP treatment in patients with OSAS but without intellectual disability [7,8]. The lack of treatment for OSAS was accompanied by a significant decrease in exercise tolerance, as described herein for subject S.II and confirmed by the results of the study of Guillermo *et al*. [10].

Several hypotheses have been proposed to support these observations. The first suggested that patients receiving CPAP showed better cardiovascular and respiratory adaptations. However, because this one is not systematic in all patients, it does not seem possible to keep the cardiovascular function improvement as the only component of the enhancement of VO_{2max} [11].

The second hypothesis is relative to the ventilatory responses. Hypoxia, hypercapnia, awakenings, sleep fragmentation and increased inspiratory effort, all of which characterize OSAS, simultaneously contribute to the degradation of cardiovascular and pulmonary functions. Patients with OSAS show a reflex inspiratory effort increase during periods of obstruction [12] and increased ventilation during exercise, which produces an exaggerated sympathetic discharge [12]. The well-known increase in sympathetic tone and catecholamine secretion in patients with OSAS may mediate chronic changes in muscle metabolism (altered use of energy substrates and muscle mitochondrial function). Also, when patients are treated with CPAP, and treatment compliance is respected, ventilation is significantly improved [8]. Furthermore, the sympathetic nervous hyperstimulation is improved, even if it does not completely normalize [13]. It seems likely that these two parameters are actually vectors of improvement in the exercise capacity in OSAS patients with or without Down syndrome.

Moreover, the hormonal changes observed during the submaximal TT showed two differences. In S.II, plasma catecholamine concentrations were always very high, even at rest, and quite above normal values, reflecting a probable sympathetic overactivity, as mentioned previously in patients with OSAS.

For the subject S.I, the plasma epinephrine concentration rose under the effect of exercise in year 2005, but this was not the case in the second submaximal TT in 2010. This observation, although unconventional with regards to the hormonal changes that occur in healthy subjects, is similar to that observed in subjects with Down syndrome without OSAS during a prolonged exercise [9] that actually seem to slow down their catecholaminergic response to stress. Fernhall *et al*. [14] have linked this inadequate adrenergic response with chronotropic incompetence which is well described in this population. So, a link between chronotropic incompetence and lower exercise capacity, with weakest VO_{2max} value could reflect the existence of a possible dysautonomia [15].

Moreover, the cortisol concentration during the second submaximal TT showed a clear difference between S.I and S.II. In S.I, the cortisol kinetic measured in 2010, after the implementation of CPAP therapy was the only one among the four to follow a normal trend, with an enhancement when the exercise was prolonged and became intense. Therefore we can assume that there may be a possible pertinent hormonal adaptation, which reflects an increased metabolism demand by a longer and intense effort. This result was not observed in S.II, so we can propose that the adjustments permitted by the elevation of cortisol concentrations (especially on gluconeogenesis and the mobilization of free fatty acids during exercise) did not occur and consequently limited the ability to perform an exercise in this subject [9].

However, several limitations about these results must be done. First, this is a preliminary study which included only two subjects, therefore the observations need to be validated in a larger sample. Secondly, the problems of intellectual disability associated with Down syndrome are among numerous obstacles preventing such studies from taking place. Here, these two subjects have done without difficulty the submaximal TT, including clearly the instructions. Nevertheless, it would have been interesting to evaluate quality of sleep with the Epworth scale, but, this scale has not been validated in persons with intellectual disability.

5. Conclusion

In subjects with Down syndrome, sleep apnea syndrome is frequent and the link with lowered exercise capacity might partly be explained by the anomalies found in one

hand in OSAS and secondly, by gene overdose linked to the supernumerary chromosome 21. Treatment of OSAS by CPAP might show a significant improvement in submaximal exercise capacity in individuals with Down syndrome. Nevertheless, these results must be confirmed on a larger sample.

6. Acknowledgements

This study was supported by Lejeune Foundation (Paris, France). The authors have no conflict of interest to declare.

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