Strong coincidence between slow wave sleep and low AHI is explainable by the high instability of slow wave sleep to obstructive apnoea exposure

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Summary

It is well known that in patients with obstructive sleep apnoea syndrome (OSAS) the apnoea-hypopnoea index (AHI) is significantly decreased during slow wave sleep (SWS). It used to be explained by the ability of SWS to stabilize the upper airways against collapse. Another explanation, which is the focus of the current study, is that it is just a result of high instability of SWS to obstructive apnoea exposure, i.e. high susceptibility of SWS to transition into lighter sleep stages during exposure to obstructive apnoeas. A retrospective chart review was performed on 560 males who underwent an overnight polysomnography. Two hundred and eighty-seven patients were eligible for the study. They were divided into 3 groups according to different AHI level. All three groups had a higher SWS occurrence in the lateral position than in the supine position. A special fourth group of patients was created with severe OSAS in the supine position but with very mild OSAS in the lateral position. This group had, in the lateral position, (A) higher AHI in NREM sleep (4.1±3.1/hour vs. 0.7±1.2/hour, $p < 0.001$) as well as (B) higher SWS occurrence (27.7±15.0% vs. 21.4±16.2% of NREM sleep, $p < 0.05$), than the group with the lowest AHI in the study, i.e. AHI ≤ 5/hour. These data suggest that strong coincidence between SWS and low AHI is the result of the high instability of SWS to obstructive apnoea exposure. The data also support the presence of SWS-rebound in OSAS patients in the lateral body position.

Key words

Obstructive sleep apnoea, NREM sleep, Slow-wave sleep, Body position, Position of upper airways

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common disorder characterized by repetitive upper-airway collapse during sleep. It has important consequences such as increased risk of

cardiovascular disease or motor vehicle accidents (Garvey *et al.* 2015). The presence and severity of OSAS is typically determined by frequency of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index, AHI). It is well known that AHI is significantly decreased during slow wave sleep (SWS) (Ratnavadivel *et al.* 2009, Koutsourelakis *et al.* 2016, Bittencourt *et al.* 2001). There is an attempt to explain it by higher upper-airway muscle activity and/or by lower upper-airway collapsibility during this stage of sleep (McSharry *et al.* 2013, Carberry *et al.* 2016). However, it is possible to simply explain it just by increased instability of SWS to obstructive apnoea exposure, i.e. high susceptibility of SWS to transition into lighter sleep stages during exposure to obstructive apnoeas. As it is well known, severe OSAS decreases occurrence of SWS and continuous positive airway pressure (CPAP) treatment of OSAS causes SWS rebound (Brillante *et al.* 2012, Issa and Sullivan 1986). This suggests that disadvantageous shapes of the upper airways for breathing during sleep, due to some body positions (especially supine) (Oksenberg *et al.* 2000) as well as of head or bite (Isono *et al.* 2005, Isono *et al.* 2004, Zhu *et al.* 2017), result in higher AHI (and more severe obstructive episodes) and finally in lower occurrence of SWS and on the other hand, beneficial shapes of upper airways result in lower AHI (and less severe obstructive episodes) and rebound of SWS. The aim of this study was, therefore, to investigate the relationship between SWS occurrence and different body positions in patients with different OSAS severity and thus to detect both (A) low occurrence of SWS in supine body position (which represents disadvantageous shapes of the upper airways for breathing during sleep) and (B) rebound of SWS in lateral body position (which represents beneficial shapes of the upper airways for breathing during sleep).

Methods

A retrospective chart review was performed on 560 males who underwent an overnight polysomnography from March 2009 to June 2017. Polysomnography included three-channel electroencephalogram, two-channel electrooculogram, electrocardiogram, submental and leg electromyogram, thoracic and abdominal inductance plethysmography, nasal cannula, pulse oximeter,

body position sensor (capable to determine 8 different body positions: supine, prone, right-lateral, left-lateral and 4 boundary positions, i.e. right-supine, left-supine, right-prone, left-prone), snore microphone and infrared camera (Alice 3 Diagnostic Sleep System, Phillips Respironics). Records were scored manually according to the standard criteria (Iber *et al.* 2007, Berry *et al.* 2015) using Alice Sleepware software. Patients with total sleep time duration under 200 min, with a higher amount of central apnoeas than obstructive apnoeas during NREM sleep (NREMs) and those with NREMs duration in supine position under 15 minutes as well as those with NREMs duration in lateral body position (the sum of right-lateral, left-lateral, right-prone and left-prone position) under 15 minutes were excluded from the study (n = 273). The rest of the patients were eligible for the study (n = 287). Patients were divided into three groups: 1) those with AHI in NREM sleep (AHI-NREMs) under 5/h, 2) those with AHI-NREMs 5/h and higher but less than 30/h and 3) those with AHI-NREMs 30/h and higher. Females were not included in the study because they typically show a lower severity of OSAS (at least in NREMs) (Garvey *et al.* 2015, Peregrim *et al.* 2013), and, independently of this, also a higher occurrence of SWS (Redline *et al.* 2004). Each value in the study is written as a mean ± SD. Wilcoxon signed ranks test or Mann-Whitney U test were used for statistical analysis. Moreover, an analysis of covariance (ANCOVA) using the general linear model procedure was performed to test the effect of both age and BMI (covariates) for SWS occurrence. $P < 0.05$ was considered significant. All statistics were made using SPSS statistics 17.

Results

Both the first (AHI-NREMs < 5/hour) and the second (5/hour ≤ AHI-NREMs < 30/hour) group of patients reached in both lateral (i.e. right-lateral, left-lateral, right-prone and left-prone position together) and supine body position higher SWS occurrence when compared to the third (AHI-NREMs ≥ 30/hour) group of patients; however, after taking both age and BMI into account, the statistical significance was not reached between the first and the third group in the lateral position (Table 1). All three groups had a higher SWS occurrence in the lateral position than in the supine position. This

relationship was stronger in groups with higher AHI as follows 1.58 vs. 2.55 and vs. 2.90 (Table 1, green numbers). The patients of the third group, during NREMs, in the lateral position, reached both (A) higher AHI (47.4±31.4/hour vs. 32.4±18.3/hour, $p < 0.001$) and apnoea index (AI, i.e. frequency of apnoeas per hour of sleep; 33.2±28.7/hour vs. 18.8±17.7/hour, $p = 0.001$) as well as (B) higher SWS occurrence (14.4±16.0% vs. 9.0±11.8% of NREMs, $p < 0.01$), than the patients of the second group reached during NREMs in the supine position (Table 1, blue numbers).

A special fourth group of patients was created with severe OSAS in the supine position but with very mild OSAS in the lateral position as follows: The second and third group were merged together and those patients were removed who reached AHI-NREMs < 30/hour in supine position, arousal index (ArI, frequency of arousals per hour of sleep) < 10/hour during NREMs in supine position or AHI-NREMs > 10/hour in lateral position. This group had, in the lateral position, (A) higher both AHI-NREMs (4.1±3.1/hour vs. 0.7±1.2/hour, $p < 0.001$) and AI-NREMs (2.0±2.4/hour vs. 0.3±0.6/hour, $p < 0.001$) as well as (B) higher SWS occurrence (27.7±15.0% vs. 21.4±16.2% of NREMs, $p < 0.05$), than the first group of patients had in the lateral position (Table 2, red numbers). The fourth group also reached the highest ratio of SWS occurrence between lateral and supine position (Table 1 and Table 2, green numbers).

Discussion

It was found that higher AHI-NREMs is associated with lower SWS occurrence; this is true not only generally for OSAS patients, but also for their different body positions (i.e. the supine position is associated with both higher AHI and lower SWS occurrence compared to the lateral position). Our results also suggest that SWS-rebound occurs in severe OSAS patients in cases of accidental beneficial shapes of the upper airways for breathing during sleep. OSAS patients with higher AHI-NREMs (third group, AHI-NREMs ≥ 30/hour) reached in the lateral position (A) higher AHI-NREMs as well as (B) higher SWS occurrence, than OSAS patients with lower AHI-NREMs (second group, 5/hour ≤ AHI-NREMs < 30/hour) reached in the supine position (Table 1, blue numbers). Similarly, the fourth group of patients (severe OSAS in the supine position but very mild OSAS in the lateral position) had in the lateral position

both (A) higher AHI-NREMs and (B) higher SWS occurrence, than the first group, i.e. patients with AHI-NREMs < 5/hour (Table 2, red numbers).

It should be emphasized that lower SWS occurrence is associated with higher age (at least in men) (Redline *et al.* 2004) and probably also with other factors such as higher BMI (Rao *et al.* 2009) or diabetes mellitus (Pallayova *et al.* 2010). Despite this, patients with higher AHI in the current study (3rd group, 4th group), who are also associated with higher BMI, age (Garvey *et al.* 2015) as well as diabetes mellitus (Reutrakul and Mokhlesi 2017), were able to reach higher SWS occurrence under certain conditions than patients with lower AHI. Surprisingly, although patients with the highest AHI (3rd group) showed a lower occurrence of SWS in the supine position than patients with the lowest AHI (1st group) even after considering covariates (age and BMI), it was not the case in the lateral position (Table 1). This reflects the effort of OSAS patients to compensate the lack of SWS by its rebound during beneficial shapes of the upper airways.

The current study supports the following relationship: the body position (more precisely, the shape of the upper airways) influences the AHI level (as well as the severity of obstructive episodes) which subsequently influences the occurrence of SWS in NREMs. More specifically, these data suggest two effects: (A) during disadvantageous body positions (i.e. disadvantageous upper-airway shapes) for breathing, higher AHI interrupts SWS which occurrence in NREMs subsequently decreases and (B) during beneficial body positions (i.e. beneficial upper-airway shapes) for breathing, lower AHI supports SWS-rebound which imitates the effect of CPAP.

One may find the results of SWS occurrence in groups with different AHI (Table 1) somewhat strange. For example, in the group with the highest AHI, the AHI is nearly 70-times (47.4/0.7) higher in the lateral position and nearly 20-times (75.1/4.5) higher in the supine position than in the group with the lowest AHI, however, the SWS occurrence in NREMs is only 1.5-times (21.4/14.4) lower in the lateral position and 2.7-times (13.6/5.0) lower in the supine position. However, this apparent mismatch between the "rapid" increase in AHI and the "slow" decline in SWS is consistent with the existence of

a rebound phenomenon. Even in the group of patients with the highest AHI, there are still some sections of sleep with normal breathing, alternatively with only snoring or mild hypopneas, which do not interrupt SWS. Naturally, these sections occur more frequently in the lateral position. Rebound phenomenon means that in patients with higher and higher AHI, SWS appears more and more in these still shorter and shorter sleep sections.

One might doubt that they are obstructive upper-airway episodes that reduce SWS in sleep and not vice versa, i.e. that SWS reduces the occurrence of obstructive episodes. Differences in details exist, but there is a general opinion that it is gravity which affects the shape of the upper airways in different ways in different body positions, and this is also the cause of the higher occurrence of obstructive apnoeas in the supine position compared to the lateral position (Elliott *et al.* 2001, Joosten *et al.* 2015, Marques *et al.* 2017). Our data show that there are both high AHI and low occurrence of SWS in the supine position in all our groups. This can be explained as follows: The supine position increases, due to gravity, the occurrence of apnoea episodes and these interrupt SWS; or to put it another way, SWS is unstable (i.e. it turns into lighter NREMs stages) when exposed to obstructive apnoeas.

Theoretically, there may also be an inverse mechanism of causal relationships. This means that during sleep, as well as subconsciously when falling asleep or awakening in the night, body position is selected to prefer lateral position for SWS instead of for lighter NREMs stages. If so, the question arises why it is necessary to protect SWS in this way against obstructive episodes. The answer seems to be that SWS is 1) more susceptible to obstructive episodes than lighter NREMs stages and/or 2) highly unstable to obstructive apnoea exposure.

Koutsourelakis et al. (2016) found an extremely low AHI in OSAS patients during SWS compared to previous studies, i.e. 0.3±0.9 and 0.4±1.7/hour in supine and lateral position, respectively. They explain the difference by somewhat different study management: all patients had "at least 15 consecutive minutes of SWS". One other study (Bittencourt *et al.* 2001) found similarly low levels of

AHI in SWS. One might suggest that such an extremely low AHI during SWS may be the result of higher upper-airway muscle activity and/or lower upper-airway collapsibility during this stage of sleep. There is probably lower genioglossus (GG) activity (McSharry *et al.* 2013, Carberry *et al.* 2016, Jordan *et al.* 2009) and higher upper-airway collapsibility (Carberry *et al.* 2016) during stage 2 of NREMs (S2-NREMs) compared to SWS, however, during REM sleep (REMs), GG activity is clearly much lower (Carberry *et al.* 2016, Jordan *et al.* 2009, McSharry *et al.* 2014) and upper-airway collapsibility is clearly much higher (Carberry *et al.* 2016) compared to both SWS and S2-NREMs, which would suggest that AHI is clearly the highest during REMs. In the study of Koutsourelakis et al. (2016), mean AHI was higher in S2-NREMs (36.5±29.1/h) than in REMs (35.1±31.2/h) at the supine position (without statistical significance testing). This may be explained by longer apnoeas in REMs (i.e. by coincidence of these long apnoeas and high AHI in supine position) than in NREMs; as showed in our previous study (Peregrim *et al.* 2013). At the lateral position, the mean AHI was, on the contrary, higher in REMs (13.5±20.1/h) than in S2-NREMs (12.1±19.8/h), however, statistical significance was not reached (personal communication). These AHI data of REMs suggest that extremely low AHI during SWS can not be explained by high upper-airway muscle activity or low upper-airway collapsibility. It is possible to conclude that Koutsourelakis et al. (2016) took into account the position of the body but did not take into account (nor could take into account) all beneficial upper-airway positions (e.g. the result of beneficial positions of head or bite) which seem to result in low or even very low AHI and finally in deep NREMs, i.e. SWS.

Some other data offer different relationship between AHI and sleep stages, more specifically, that the highest AHI is in REMs, lower AHI is in S2-NREMs and the lowest AHI is in SWS (Ratnavadivel *et al.* 2009). However, the highest AHI in REMs is possible to explain by general body, i.e. also upper-airway, hypotonia which seems to be a prevention against motoric manifestations of dreams as dreams are typical for REMs (for example, prevention against sleep-talking or biting a tongue). On the contrary, deeper NREMs stages show typically higher body hypotonia than lighter NREMs stages (Berry *et al.* 2015), which would suggest lower upper-airway muscle tone during SWS than S2-NREMs. Some studies have indeed shown the tendency of tensor palatini or even geniohyoid, i.e. upper-airway dilator

muscles, to decrease in EMG activity when transitioning from lighter to deeper NREMs stages (Wiegand *et al.* 1990, Tangel *et al.* 1991, Tangel *et al.* 1992, Edwards and White 2011, Hicks *et al.* 2017). This would explain detection of higher resistance in the upper airways during SWS compared to S2-NREMs (Trinder *et al.* 1997). Higher upper-airway resistance causes higher negative pressure in the upper airways which together with hypercapnia stimulates the activity of the upper-airway dilator muscles but especially the GG, the muscle that is able to reach EMG activities in NREMs similar to those in wakefulness or even higher (Tangel *et al.* 1992, Edwards and White 2011, Hicks *et al.* 2017, Malhotra *et al.* 2004). This explains the high activity of GG during SWS.

Boudewyns et al. (2000) determined both the collapsibility and the resistance of the upper airways during NREMs in both supine and lateral body position in 10 obese patients with severe OSAS. When they focused on subgroup of six patients with subatmospheric critical-upper-airway closing pressure in lateral position, they found higher AI in supine position compared to lateral position ($p = 0.03$). Surprisingly, these patients reached higher resistance of the upper airways in lateral position than in supine position (24.8±14.0 cm H_2O/L/s vs. 13.6±6.0 cm H_2O/L/s, $p = 0.034$, Wilcoxon signed ranks test). This could be partly explained by high resistance of the upper airways during SWS (Trinder *et al.* 1997) and by an abundance of this stage of sleep in lateral position as was found in the current study. Generally, this could be due to higher occurrence of deeper NREMs (i.e. also "deeper" S2-NREMs) in lateral position and higher occurrence of lighter NREMs (i.e. also "lighter" S2-NREMs) in supine position.

One might consider contradictory that together with higher upper-airway resistance (Trinder *et al.* 1997), the lower upper-airway collapsibility (Carberry *et al.* 2016) has been found in SWS compared to S2-NREMs. The same surprising results were also reached in the above-mentioned study of Boudewyns et al. (2000). The special subgroup of six patients had both (A) higher upper-airway resistance and (B) lower upper-airway collapsibility in the lateral position compared to the supine position (the critical-upper-airway closing pressure was 1.25±1.05 cm H_2O and -2.80±1.27 cm H_2O in

supine and lateral position, respectively; p = 0.028, Wilcoxon signed ranks test). As seen in Fig.1, SWS itself is likely to increase both upper-airway resistance as well as upper-airway collapsibility, however, this influence is accompanied by the opposite effect of beneficial upper-airway positions. Suppose now that SWS increases the resistance more than collapsibility of the upper airways. Theoretically, the hypotonia of the upper-airway dilator muscles (except GG) during SWS (see the red rectangle in Fig. 1, the only one which continues with two arrows) could result in higher increase of upper-airway resistance than upper-airway collapsibility, i.e. despite the generally low upper-airway muscle activity (except GG) during SWS, the ability to achieve high muscle activity levels during imminent threats of upper-airway collapse could be quite well preserved. After adding both influences (A) the SWS and (B) the beneficial upper-airway positions it is possible to reach seemingly contradictory results (A) higher upper-airway resistance and (B) lower upper-airway collapsibility. However, this explanation is only theoretical with no supporting data.

There are some drugs, such as, sodium oxybate (SXB) or some antidepressants (e.g. trazodone, fluoxetine) which seem to be more beneficial for NREMs than REMs in OSAS patients (George *et al.* 2011, Veasey *et al.* 1999, Smales *et al.* 2015, Hanzel *et al.* 1991). These drugs can decrease whole-night AHI and also increase occurrence of SWS but they do not increase or even sometimes decrease occurrence of REMs. This may suggest that their primary effect is the increase of SWS which subsequently leads to decrease of AHI. However, for example, protriptyline, one of the activating antidepressants, has a primary inhibitory effect on SWS (Wichniak *et al.* 2017) and yet is able to decrease AHI in OSAS patients (Hanzel *et al.* 1991). Moreover, both SXB and antidepressants are used for treatment of cataplexy (Lopez and Dauvilliers 2013); this supports the view that higher upper-airway muscle tone, or the decrease of AHI, is achieved directly without any relationship with SWS. In an animal model of OSAS (English Bulldog), the combination of trazodone and L-tryptophan lowers AHI in both REMs and NREMs, however, the occurrence of REMs tends to decrease (Veasey *et al.* 1999), probably because of the adverse effect of L-tryptophan to REMs (Bakalian and Fernstrom 1990). The same inhibitory effect on REMs is attributed to many antidepressants (e.g. also fluoxetine or

protriptyline) (Wichniak *et al.* 2017). It is also worth mentioning that CPAP, which clearly acts on the upper airways, may also appear to have a stronger beneficial effect on NREMs than REMs, as the rebound of SWS is higher than the rebound of REMs in the first CPAP night (Brillante *et al.* 2012).

CPAP is regarded as a gold standard for OSAS treatment. Pharmacological intervention can be used occasionally, especially when there is CPAP intolerance together with depression comorbidity. However, effectiveness is highly variable, some patients do not respond to the treatment and some of them even show worsening of OSAS (Smales *et al.* 2015, Hanzel *et al.* 1991, Mendelson *et al.* 1991). For example, Hanzel et al. (1991) found a slight decrease in AHI-NREMs in 12 OSAS patients after 4 weeks with fluoxetine as well as with protriptyline (from 57±9/hour to 34±6/hour and 33±8/hour, respectively), however, one patient decreased AHI-NREMs from 46/hour to 2/hour with fluoxetine, other one decreased AHI-NREMs from 51/hour to 7/hour with protriptyline and there was also one patient who reached significant increase in AHI-NREMs with fluoxetine as well as with protriptyline (from 18/hour to 49/hour and 69/hour, respectively). Therefore, an individual patient approach is important here and it may be assumed that this will also be the case of potential new drugs specifically designed to treat OSAS in the future. Along with the falling cost of genome sequencing, it suggests the rise of personalised pharmacological treatment of OSAS in the future.

The current study does not take into account the presence of depression, the diet or the use of drugs which are potential confounding factors as they may affect SWS occurrence (Pillai *et al.* 2011, Wichniak *et al.* 2017, Afaghi *et al.* 2008). Depression occurs more frequently in both obese and OSAS patients. Reduced SWS was suggested as a genetic biomarker, i.e. predisposition, for major depressive disorder (Pillai *et al.* 2011). During depression, SWS is significantly longer than during remission (Pillai *et al.* 2011).

In conclusion, the current study found that SWS occurs more in the lateral body position than in supine position, i.e. in the position which is less prone to obstructive apnoea exposure. This suggests that strong coincidence between SWS and low AHI is the result of the high instability of SWS to

obstructive apnoea exposure. The data also support the presence of SWS-rebound in OSAS patients in the lateral body position. Generally, the current study does not consider the effort to increase the occurrence of SWS by drugs as beneficial for OSAS patients, on the contrary it supports the increase of the upper-airway muscle tone as beneficial.

Conflict of interest

There is no conflict of interest.

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Table 1.

Group	L-SWS/NREM	S-SWS/NREM	Ratio	AHI in L in NREMs	AHI in S in NREMs	AI in L in NREMs	AI in S in NREMs
1st	21.4±16.2% Θ	13.6±16.9% # Θ	1.58	0.7±1.2 OOO	4.2±5.9 ### OOO	0.3±0.6 OOO	1.7±2.9 ### OOO
2nd	23.0±16.2% ◇◇◇[1] ☆☆☆[1]	9.0±11.8% ### ☆[1]	2.57	5.7±6.7 ⟐ ☆☆☆	32.4±18.3 ### ☆☆☆	2.5±4.0 ⟐ ☆☆☆	18.8±17.7 ### ☆☆☆
3rd	14.4±16.0% △△[1] □□[2]	5.0±8.0% ### □□[1]	2.90	47.4±31.4 △△△ □□□	75.1±19.2 ### □□□	33.2±28.7 △△ □□□	62.2±23.0 ### □□□

Group 1st: AHI-NREMs < 5/h, n (number of patients) = 59, BMI = 28.1±3.6, age = 41.3±11.6; **Group 2nd:** 5/h ≤ AHI-NREMs < 30/h, n = 105, BMI = 30.7±4.9, age = 47.2±12.3; **Group 3rd:** AHI-NREMs ≥ 30/h, n = 123, BMI = 33.1±5.0, age = 48.9±11.6; BMI comparison between groups always reached $p < 0.001$; age of patients in 1st group (age1) vs. age2 reached $p < 0.01$; age2 vs. age3 reached $p > 0.05$; age1 vs. age3 reached $p < 0.001$; **L-SWS/NREM:** the % of SWS from NREMs in lateral body position; **S-SWS/NREM:** the % of SWS from NREMs in supine position; **Ratio:** the ratio between L-SWS/NREM and S-SWS/NREM; **AHI in L in NREMs:** apnoea-hypopnoea index (AHI) during NREMs in lateral body position; **AHI in S in NREMs:** AHI during NREMs in supine position; **AI in L in NREMs:** apnoea index (AI) during NREMs in lateral body position; **AI in S in NREMs:** AI during NREMs in supine position; **#** means the comparison of variables in one group (i.e. L-SWS/NREM vs. S-SWS/NREM, AHI in L in NREMs vs. AHI in S in NREMs, AI in L in NREMs vs. AI in S in NREMs); **O** means the comparison of the same variables between 1st group and 2nd group (e.g. L-SWS/NREM of 1st group vs. L-SWS/NREM of 2nd group); ☆ means the comparison of the same variables between 2nd group and 3rd group; □ means the comparison of the same variables between 1st group and 3rd group; ◇ means the comparison of variables between 1st group in supine position and 2nd group in lateral body position (e.g. S-SWS/NREM of 1st group vs. L-SWS/NREM of 2nd group); △ means the comparison of variables between 2nd group in supine position and 3rd group in lateral body position; one mark (e.g. ◇) means $p < 0.05$; two marks (e.g. ◇◇) mean $p < 0.01$, three marks (e.g. ◇◇◇) mean $p < 0.001$; crossed mark (e.g. ⟐) means $p > 0.05$

[1]Statistical significance was also reached after taking the covariates (age and BMI) into account (ANCOVA).

[2]Statistical significance was not reached after taking the covariates into account (ANCOVA). The effect of both age ($p < 0.001$) and BMI ($p = 0.047$) was significant.

Table 2.

Group	L-SWS/NREM	S-SWS/NREM	Ratio	AHI in L in NREMs	AHI in S in NREMs	AI in L in NREMs	AI in S in NREMs
1st	21.4±16.2% O[1]	13.6±16.9% # OO[1]	1.58	0.7±1.2 OOO	4.2±5.9 ### OOO	0.3±0.6 OOO	1.7±2.9 ### OOO
4th	27.7±15.0%	4.1±8.1% ###	6.81	4.1±3.1	56.4±14.8 ###	2.0±2.4	39.0±22.4 ###

Group 1st: AHI-NREMs < 5/h, n (number of patients) = 59, BMI = 28.1±3.6, age = 41.3±11.6; **Group 4th:** AHI-NREMs ≥ 5/h, AHI-NREMs ≥ 30/hour in supine position, arousal index ≥ 10/hour during NREMs in supine position, AHI-NREMs ≤ 10/hour in lateral body position, n = 46, BMI = 30.7±4.5, age = 48.0±11.9; BMI of patients in 1st group (BMI 1) vs. BMI 4 reached p = 0.001; age of patients in 1st group (age1) vs. age4 reached p < 0.01; **L-SWS/NREM:** the % of SWS from NREMs in lateral body position; **S-SWS/NREM:** the % of SWS from NREMs in supine position; **Ratio:** the ratio between L-SWS/NREM and S-SWS/NREM; **AHI in L in NREMs:** apnoea-hypopnoea index (AHI) during NREMs in lateral body position; **AHI in S in NREMs:** AHI during NREMs in supine position; **AI in L in NREMs:** apnoea index (AI) during NREMs in lateral body position; **AI in S in NREMs:** AI during NREMs in supine position; **#** means the comparison of variables in one group (i.e. L-SWS/NREM vs. S-SWS/NREM, AHI in L in NREMs vs. AHI in S in NREMs, AI in L in NREMs vs. AI in S in NREMs); **O** means the comparison of the same variables between 1st group and 4th group (e.g. L-SWS/NREM of 1st group vs. L-SWS/NREM of 4th group); one mark (e.g. #) means p < 0.05; two marks (e.g. ##) means p < 0.01, three marks (e.g. ###) means p < 0.001

[1]Statistical significance was reached also after taking the covariates (age and BMI) into account (ANCOVA).

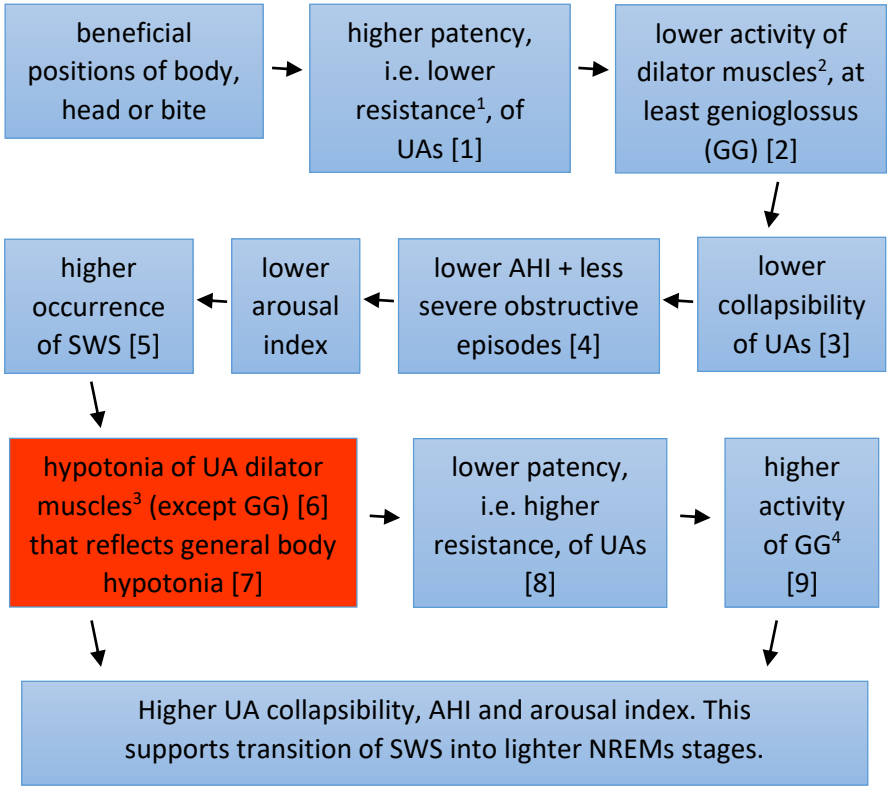

Fig. 1. [1]The study of Boudewyns et al. (2000) shows that during NREMs the resistance of upper airways (UAs) can be higher in the lateral position than in the supine position in some severe OSAS patients, however, we assume that this is the result of higher occurrence of SWS (or generally, deeper NREM sleep) in the lateral position than in the supine position (see our discussion). [2]Lower activity of dilator muscles means lower collapsibility of UAs because in the case of the increase of UA resistance, the dilator muscles still have enough reserve to increase their activity. [3]Due to SWS hypotonia, UA dilator muscles are not able to reach the same maximal activity levels as in lighter NREMs stages which means lower ability to prevent upper-airway collapse. [4]Higher activity of genioglossus means higher collapsibility of UAs because in the case of the increase of UA resistance, the genioglossus has not enough reserve to increase its activity.

[1] Isono *et al.* 2005, Isono *et al.* 2004 [2] Malhotra *et al.* 2004, Otsuka *et al.* 2000 [3] Malhotra *et al.* 2004 [4] Oksenberg *et al.* 2000, *Zhu et al.* 2017 [5] Ratnavadivel *et al.* 2009, Koutsourelakis *et al.* 2016, Bittencourt *et al.* 2001 [6] Wiegand *et al.* 1990, Tangel *et al.* 1991, Tangel *et al.* 1992, Edwards and White 2011, Hicks *et al.* 2017 [7] Berry *et al.* 2015 [8] Trinder *et al.* 1997 [9] McSharry *et al.* 2013, Carberry *et al.* 2016, Hicks *et al.* 2017