PROCEEDINGS REPORT

Does the energy expenditure status in obstructive sleep apnea favour a positive energy balance?

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Abstract

Purpose: The effect of the obstructive sleep apnea syndrome on energy expenditure is controversial. The objective of this study was to assess the relationship between 24-hr energy expenditure or sleeping metabolic rate and features of the obstructive sleep apnea. **Methods:** Twenty-four apneic men took part in this cross-sectional study and were classified in quartiles of nocturnal desaturation severity, *i.e.* of percentage total sleep time with $\text{SaO}_2 < 90\%$ determined with polysomnography. 24-hr energy expenditure and sleeping metabolic rate were measured with a whole body indirect calorimetry (respiratory chamber), and body composition by hydrodensitometry. During the stay in the respiratory chamber, urine was collected to assess catecholamine concentration and percentage recording time with $\text{SaO}_2 < 90\%$ (%TRT $\text{SaO}_2 < 90\%$) was measured with nocturnal oximetry.

Results: Mean fat free mass and fat mass were greater in quartile 4 than in quartile 1 ($P < 0.05$). %TRT $\text{SaO}_2 < 90\%$ was higher in quartile 4 than in other quartiles ($P < 0.0001$). 24-hr energy expenditure and sleeping metabolic rate were

similar among quartiles. However, when expressed on a per kg body weight basis (kcal/kg), these variables were negatively correlated with the %TRT $\text{SaO}_2 < 90\%$ in the whole group ($r = -0.46$ and -0.48 , respectively, $P < 0.05$). %TRT $\text{SaO}_2 < 90\%$ was found to be a predictor of sleeping metabolic rate which explained, together with fat mass and fat free mass, 86% of this variance ($P < 0.05$).

Conclusion: In apneic men energy expenditure relative to body weight decreases with increasing severity of oxygen desaturation which could favour a positive energy balance.

The obstructive sleep apnea syndrome (OSAS) is paradoxically regarded as a consequence of obesity and body weight gain as well as being associated with a greater propensity to weight gain just before or since its associated symptoms onset.¹⁻⁶ Recently, an adaptive decrease in thermogenesis, *i.e.* an energy expenditure lower than predicted by body weight or its components, has been shown to be associated with the severity of nocturnal desaturation⁷ that occurs following repetitive episodes of apnea and hypopnea during sleep. This suggests that apneic individuals with pronounced nocturnal desaturation might be characterised

by lowered energy expenditure which could predispose to positive energy balance and body weight gain, thus partly explaining the apparent paradox.

The effect of OSAS on energy metabolism has been a controversial issue in scientific literature. It has been shown that patients with OSAS have a higher energy expenditure per kilogram of fat free mass than patients with a less severe degree of the disease,⁶ and that sleep energy expenditure is greater in apneic than in healthy individuals.⁸ Although these results are concordant with the increase in energy expenditure associated with sleep-disordered breathing disturbance (such as sympathetic nervous system activation, sleep deprivation, sleep fragmentation, increase in breathing effort and motor activity),⁹⁻¹¹ other studies found no difference in resting, daily, and sleeping energy expenditure in OSAS patients compared to controls after corrections for lean body mass.^{7,11}

Taken together, these results indicate that the effects of OSAS on energy metabolism are not straightforward. Accordingly, this study was conducted to test the hypothesis that, beyond apparent normal or increased energy expenditure, OSAS is associated in individuals characterised by pronounced nocturnal desaturation with lower energy expenditure relative to body weight, suggesting the presence of an adaptive decrease in thermogenesis.

Methods

Eighty-seven men coming from the greater Québec region area answered the advertisement for this study whose protocol was approved by the Ethical Review Board of Hôpital Laval and Université Laval. In total, 32 men corresponded to inclusion criteria which were as follows: age between 20 and 65 yr, stable body weight (body weight change < 3kg for three months prior to intervention), body mass index (BMI) of 25 to 40kg/m², < 3 periods of 20 min physical exercise/week, general good health, non smoking, low coffee consumption (≤ 4 cups/d), normal thyroid hormone

levels (measured at screening), unknown sleep apnea status or absence of sleep apnea treatment, and not receiving medication that could affect body weight or energy metabolism. Following the first screening appointment and medical examination, two men were excluded since they did not meet the inclusion criteria. Thus, 30 men were initially enrolled in the study from whom five dropped-out for personal reasons and one was diagnosed with central apnea and excluded from analyses. All participants, except two African/American, were Caucasian. A second visit to the laboratory was organised during which body weight and composition and resting metabolic rate were measured, and on a third occasion 24-hr energy expenditure was measured. Finally, the fourth visit was held in the Sleep Laboratory for a polysomnography.

Anthropometric measurements

Body weight was measured to the nearest 0.1 kg with a standard beam scale and height was measured to the nearest 0.1 cm with a stadiometer. Waist and hip circumferences were taken according to Harrison et al¹² and the BMI and waist-to-hip ratio were then calculated. Body density was determined by hydrodensitometry.¹³ The closed-circuit He dilution method¹⁴ was used to assess residual lung volume. The Siri formula¹⁵ was then used to estimate the percentage of body fat from body density, while fat mass and fat-free mass were calculated from the derived percentage of body fat and total body weight.

24 hr energy expenditure, sleeping metabolic rate and substrate oxidation measurements

Twenty-four hour total energy expenditure (24-hEE) was measured with a whole-body indirect calorimeter, which provides highly reproducible data in our laboratory.¹⁶ A more complete description of this measurement methods have previously been published by our group.¹⁷ Sleeping metabolic rate (SMR) was also measured in the whole-body indirect calorimeter and was determined as the mean of the two consecu-

tive hours of the night when the subject had the lowest oxygen consumption. This value was then extrapolated over 24 hr. Thus, 24-hEE represented the mean score of measured energy expenditure over 24 hr, whereas SMR was extrapolated over the same time. The determination of substrate oxidation was assessed through the calculations previously described by Frayn¹⁸ while assuming that protein oxidation contributes 10% of total energy expenditure measured under these conditions.

Urinary nitrogen and catecholamine excretion

While in the metabolic chamber, patients were asked to collect urine for 24 hr and a sample was taken for analysis to measure urinary nitrogen and catecholamine excretion. The extraction and separation of urinary catecholamines was done using C₁₈ solid-phase extraction sorbent and HPLC.¹⁹

Nocturnal oximetry

Continuous nocturnal arterial oxygen saturation from transcutaneous sensing (*i.e.* SpO₂ monitoring) with a pulse oximeter using a finger probe was recorded with the MASIMO oximeter (Irvine, CA) during the night in the calorimetric chamber. Profox Oximetry Software Version: PO MASIMO was used for data interpretation. Desaturation events were defined as a decrease $\geq 4\%$ of SpO₂ and ≤ 3 min and the oxygen desaturation index (ODI) as the number of desaturations per hour of the nocturnal oximetry recording period. The mean percentage of total *recording* time with SaO₂ below 90% (%TRT SaO₂<90%) was also determined.

Polysomnography

Participants were admitted to Hôpital Laval at 8:00PM and were taken to the sleep laboratory unit to undergo polysomnography as described elsewhere.²⁰ They were instructed not to consume alcohol for 24 hr prior to the test. Desaturation severity was deter-

mined, with the mean percentage total *sleep* time with SaO₂ below 90%. The apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep. Sleep-wake state and arousals were scored according to standardized criteria,^{20,21} and respiratory and total micro-arousals index were calculated as the number of respiratory and respiratory plus spontaneous micro-arousals per hour of sleep.

Statistical analysis

Statistical analyses were performed using software from the SAS Institute, Cary, NC (9.1.2 version). Participants were divided by quartiles of desaturation severity obtained during polysomnography. Comparisons between quartiles were made by ANOVA using the general linear model, and the Duncan *post hoc* test was used in situations in which a statistically significant group effect was observed. Simple Pearson correlations were computed between 24-hEE and SMR absolute (kcal) and relative to body weight (kcal/kg) values and the nocturnal oximetry and polysomnography variables. Body weight was used to express energy expenditure in relative term since regression analyses described hereafter revealed a greater contribution of fat mass and fat free mass in explaining energy expenditure variables than fat free mass alone (83 vs 75 and 79 vs 70%, $P < 0.05$ for 24-hEE and SMR, respectively). Stepwise multiple regression analyses were performed to identify predictors of 24-hEE and SMR. Variables entered in these models included age, fat mass, fat free mass, % TRT SaO₂<90%, ODI and urine noradrenaline concentration. Probability to enter the models was set at $P < 0.05$. Values were considered significant at $P < 0.05$.

Results

Differences between quartiles for anthropometric, energy expenditure, oximetry and polysomnography variables mean values are presented in Table 1. The % of total sleep time spent $< 90\%$ SaO₂, as measured during polysomnography, was $0, 0.58 \pm 0.38, 3.60 \pm$

TABLE 1. Differences between quartiles of desaturation severity* for anthropometric, energy expenditure, oximetry and polysomnography variables.

Variables	Q 1 (n = 7)	Q 2 (n = 5)	Q 3 (n = 6)	Q 4 (n = 6)	p values
Age (yrs)	46 ± 9	49 ± 8	50 ± 5	51 ± 13	0.86
Weight (kg)	90.06 ± 5.35	103.44 ± 10.46	99.40 ± 15.78	110.07 ± 16.43	0.06
BMI (kg/m ²)	30.6 ± 2.3	32.2 ± 3.4	33.0 ± 4.0	35.5 ± 2.6	0.07
FFM (kg)	65.83 ± 4.68	70.60 ± 3.54	66.35 ± 7.47	71.90 ± 13.28 ¶	0.05
FM (kg)	24.22 ± 5.81	32.84 ± 7.37	33.05 ± 8.51	38.16 ± 6.30 ¶	0.01
Fat mass (%)	26.75 ± 5.71	31.46 ± 3.79	32.80 ± 3.51	34.88 ± 5.36 ¶	0.04
Waist circum (cm)	107.4 ± 9.2	112.2 ± 10.1	115.8 ± 9.8	120.4 ± 5.4	0.09
24-h EE (kcal/24h)	2861 ± 207	3127 ± 505	3012 ± 555	3189 ± 335	0.52
24-hEE/weight (kcal/kg/24h)	31.9 ± 2.9	30.1 ± 2.4	30.3 ± 2.2	29.2 ± 2.0	0.27
SMR (kcal/24h)	2219 ± 220	2438 ± 40	2435 ± 489	2571 ± 437	0.46
SMR/weight (kcal/kg/24h)	24.7 ± 2.8	23.5 ± 2.2	24.4 ± 2.2	23.4 ± 2.2	0.70
SaO ₂ mean (%) [†]	96.14 ± 2.00	95.12 ± 0.92	94.77 ± 0.65	88.30 ± 5.00 §	0.0003
SaO ₂ min (%) [†]	90.11 ± 2.60	82.16 ± 5.23 ¶	81.35 ± 3.30 ¶	58.12 ± 8.52 §	<0.0001
ODI, (events/h) [‡]	2.8 ± 2.7	8.0 ± 7.2	13.0 ± 9.9	51.7 ± 16.0 §	<0.0001
AHI (events/h) [†]	15.5 ± 19.3	26.1 ± 5.3	33.8 ± 24.3	64.5 ± 24.5 §	0.003
TRT SaO ₂ < 90% (%) [‡]	0.04 ± 0.005	0.78 ± 1.48	1.84 ± 1.18	35.86 ± 33.06 §	0.01
Norepinephrine (nmol/d)	177.2 ± 68.6	164.8 ± 85.3	194.0 ± 123.2	391.7 ± 139.1§	0.01

Values are means ± SD; Q = quartile; FFM = fat free mass; FM = fat mass; EE = daily energy expenditure; SMR= sleeping metabolic rate; Waist circum = waist circumference; SaO₂ = arterial blood oxygen saturation; SaO₂ mean = mean for SaO₂; SaO₂ min = minimal SaO₂; AHI = Apnea/hypopnea index; % TRT SaO₂< 90% = mean % total *recording* time spent with arterial oxygen saturation below 90%; * % total *sleeping* time with arterial oxygen saturation below 90% assessed with polysomnography; [†]Measured with polysomnography; [‡]Measured with oximetry in the respiratory chamber. §Significantly different from quartiles 1-3 values; ¶Significantly different from Quartile 1 value.

FIGURE 1. Relationship between the % TRT SaO₂ < 90% and the 24-hEE and SMR/ body weight ratios in participants.

* $r = -0.46$, $P < 0.05$; † $r = -0.48$, $P < 0.05$.

1.86 and 48.35 ± 20.69 % for quartiles 1 to 4, respectively (difference among quartiles, $P < 0.0001$). Not shown in this table are mean values for 24-hr and sleeping respiratory quotients that were found to be similar among quartiles, indicating no difference in the mix of substrate oxidized.

Figure 1 shows simple correlations analyses between 24-hEE/kg as well as between SMR/kg and %TRT SaO₂<90%. 24-hEE/kg was also positively correlated with SaO₂ minimal values ($r=0.44$, $P<0.05$) and negatively correlated with AHI and ODI (-0.41, -0.51, respectively $P<0.05$), but no correlation was observed between respiratory and total micro-arousals index and 24-hEE/kg and SMR/kg. Correlation

analyses were repeated in each quartile, and it was found that % TRT SaO₂< 90% correlated negatively with SMR/kg in quartile 4 only ($r=-0.93$, $P<0.05$). When a similar strategy was used and participants were classified in quartiles of AHI, ODI or total micro-arousals index, no correlation was observed in each quartile between these variables and 24-hEE or SMR/kg.

Stepwise multiple regression analyses showed that fat-free mass and fat mass were the only two predictors of 24-hEE explaining together 82% of the variance ($P=0.03$). These two variables also explained 79% of the variance of SMR ($P = 0.004$), but when %TRT SaO₂<90% measured with oximetry was added to the model, it explained an additional negative 7% of the variance in SMR ($r^2 = 0.86$, $P=0.04$).

Discussion

This study characterised the energy expenditure profile in men with different degrees of OSAS severity tested in a whole-body indirect calorimeter under standardized conditions of energy intake and activity. The important finding was a negative correlation between the time spent at <90% SaO₂ during the night and 24-hEE and SMR expressed on a per kg body weight basis. This shows that apneic patients, characterised by a more pronounced recurrent transient desaturation profile, have a lowered energy expenditure relative to their body weight which, in accordance with others,⁷ suggests the presence of an adaptive decrease of thermogenesis with increasing desaturation severity of OSAS. Indeed, the correlation between %TRT SaO₂< 90% and SMR/body weight in our study was more pronounced in quartile 4, which was composed of men spending, on average, nearly half of their sleeping time with SaO₂<90% (48.35 ± 20.69 %). This might also indicate that the severity of nocturnal desaturation has a stronger influence on energy expenditure than do higher ODI, AHI and micro-arousals index. This could explain, at least partly, the association between OSAS and obesity as well as a

tendency towards weight gain in some newly diagnosed patients.^{1,2} Indeed, despite strong evidence linking obesity to the development of OSAS,⁵ our results and those of others,^{1,2} suggest that the causality between obesity and OSAS may not be unidirectional and that a severe form of the disease could be a factor, in itself, favouring a positive energy balance and weight gain. This is a relevant issue to be considered in a clinical context where the high prevalence of OSAS in obesity might complicate weight loss interventions, and conversely complicate OSAS treatment for which weight loss appears to be an effective therapy.⁵

Our results also show, in accordance with other recent studies,^{6,8} that men in quartile 4 had a greater 24-hEE and SMR than men in other quartiles but not to a statistically significant extent. This is most likely attributable to their greater fat free mass and fat mass²² which together were found to explain 83 and 79% of 24-hEE and SMR, respectively. It could also be partly explained by their greater AHI and ODI which are factors associated with an increased energy expenditure.⁹⁻¹¹ Increased desaturation severity as well as micro-arousals index are also expected to increase energy expenditure^{6,8} through stimulation of peripheral chemoreceptors, and sympathetic nervous system activity.²³⁻²⁷ The higher norepinephrine excretion in men of quartile 4 suggests that 24-hr sympathetic activity was higher in this group²³. However, it has been shown, in apneic individuals, that sympathetic activity is not only increased during sleep, but also during awakening state,^{25,28,29} in addition to the sympathetic stimulation already induced by obesity^{28,30,31} which characterizes a majority of apneic patients. In this regard, a reduced vascular response to α , β -1, and β -2 receptor stimulation was shown to be associated with OSAS,³² which suggests that the continuous increased exposure to sympathetic flux in OSAS could lead to the development of a compensatory resistance to sympathetic nervous system stimulation. As β -1 and β -2 adrenoceptors are involved in the sympathetically-mediated variations in thermogene-

sis,³³ resistance to these adrenoceptor stimulation could represent, at least partly, the rationale behind the lower energy expenditure per kg body weight observed with increasing desaturation severity. In agreement with this observation, % TRT $\text{SaO}_2 < 90\%$ was found to be a significant negative predictor of SMR in our participants, explaining 7% of this variable's variance.

Conclusion

Our results demonstrated that, in men with OSAS, the nocturnal desaturation severity, *i.e.* the time spent during the night with $\text{SaO}_2 < 90\%$, is negatively correlated with 24-hEE and SMR expressed on a per kg body weight basis. This lowered energy expenditure in severe form of OSAS suggests the presence of an adaptive decrease in thermogenesis that could favour a positive energy balance and complicate, in some individuals, obesity treatment.

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