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The Effect of Non-invasive Mechanic Ventilation Treatment on Lactate Level in Sleep-Related Breathing Disorders

Uykuyla İlişkili Solunum Bozukluklarında Non-invaziv Mekanik Ventilasyon Tedavisinin Laktat Düzeyi Üzerine Etkisi

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Abstract

Objective: Lactate, as an indicator of hypoxia, may be useful in sleep-related breathing disorders to identify higher risk groups and monitor the effectiveness of positive airway pressure (PAP) treatment. We aimed to investigate the change in arterial lactate level in blood after PAP treatment in patients with obstructive sleep apnea (OSA) and sleep-related hypoventilation and hypoxemic syndromes and its applicability for monitoring this change regarding the effectiveness of the treatment.

Materials and Methods: PAP titration was applied to 64 OSA patients diagnosed with polysomnography. Measurements included pulmonary function testing, overnight PAP titration, arterial blood gases, and analysis of arterial lactate before and after titration. Overnight lactate level change was calculated.

Results: Of the 64 patients in the study, 49 were in the OSA group and 15 were in the Obesity Hypoventilation syndrome plus OSA group. No statistically significant difference was detected among the patients in terms of lactate levels before and after PAP treatment [1.97 (±0.7) - 1.98 (±0.6)] (p>0.05). In the OSA patient group, we detected an inverse relationship between Lactate and pre-treatment non-rapid eye movement 1-2% (r=-0.328, p=0.021), T 90% (r=-0.356, p=0.012), and total apnea hypopnea index (AHI) (r=-0.424, p=0.002). Lactate is found to be positively correlated with pre-treatment measured oxygen saturation (r=0.396, p=0.005), and with minimum oxygen saturation (r=0.361, p=0.011).

Conclusion: Our study showed that there is a relationship between AHI, average and minimum oxygen saturation and T 90% and lactate difference, which are severity indicators for OSA. These results suggest that PAP treatment may prevent possible lactate increase.

Keywords: Apnea, hypoxia, obstructive sleep apnea, polysomnography, positive airway pressure treatment

Öz

Amaç: Hipoksinin bir göstergesi olan laktat, uyku ile ilişkili solunum bozukluklarında yüksek risk taşıyan grupları belirlemede ve pozitif hava yolu basıncı (PAP) tedavisinin etkinliğini izlemede faydalı olabilir. Bu çalışmada obstrüktif uyku apnesi (OUA) ve uyku ile ilişkili hipoventilasyon ve hipoksemi sendromları hastalarında PAP tedavisinin ardından kandaki arteriyel laktat seviyesi değişimini ve tedavinin etkinliği açısından bu değişimi izlemenin uygulanabilirliğini araştırmayı amaçladık.

Gereç ve Yöntem: Polisomnografi ile tanı konulan 64 OUA hastasına PAP titrasyonu uygulandı. Solunum fonksiyon testi, tüm gece PAP titrasyonu, arteriyel kan gazı ve titrasyon öncesi ve sonrasında arteriyel laktat analizi ölçümleri yapıldı. Gecelik laktat değişimi hesaplandı.

Bulgular: Çalışmada yer alan 64 hastadan 49'u OUA grubunda, 15'i ise Obezite Hipoventilasyon sendromu artı OUA grubundaydı. PAP tedavisinden önce ve sonra hastaların laktat seviyelerinde istatistiksel açıdan anlamlı bir fark bulunamadı [1,97 (±0,7) - 1,98 (±0,6)] (p>0,05). OUA hasta grubunda laktat değişimi ile tedavi öncesi hızlı göz hareketi olmayan %1-2 (r=-0,328, p=0,021), T %90 (r=-0,356, p=0,012) ve toplam apne hipopne indeksi (AHİ) (r=-0,424, p=0,002) arasında ters bir ilişkinin söz konusu olduğu belirlendi. Laktat değişiminin tedavi öncesinde ölçülen oksijen satürasyonu (r=0,396, p=0,005) ve minimum oksijen satürasyonu (r=0,361, p=0,011) ile pozitif korelasyon sergilediği tespit edildi.

Sonuç: Çalışmamız, OUA için hastalık şiddeti göstergeleri olan AHİ, ortalama ve minimum oksijen satürasyonu ve T %90 ile laktat değişimi arasında bir ilişki olduğunu göstermiştir. Bu sonuçlar PAP tedavisinin muhtemel laktat artışını önleyebileceğini düşündürmektedir.

Anahtar Kelimeler: Apne, hipoksi, obstrüktif uyku apne, polisomnografi, pozitif basınçlı hava yolu tedavisi

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Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by apneas and hypopneas caused by repetitive airway narrowing and associated sleep fragmentation, increased sympathetic drive and intermittent hypoxia (1). Sleep-related hypoventilation and hypoxemic syndromes (SRHHS) include diseases characterized by abnormal gas exchange that occur or get worse during sleep, such as Obesity Hypoventilation syndrome (OHS) (2). Studies have demonstrated that cardiovascular mortality and morbidity increase in sleep-related breathing disorders (SRBD) (3,4). Reduced pyruvate, which is the end product of glycolysis through anaerobic mechanism, generates lactate. In many diseases accompanied by deep hypoxia, lactate-the end product of anaerobic carbohydrate metabolism increases and such increase is found to be in parallel with poor prognosis in some studies. Studies conducted in intensive care units have demonstrated that blood lactate measurements constitute an independent indicator of mortality (5-7). Hypoxia triggers a number of pathophysiological impairments in OSA and OHS cases as well. Again, in OSA, impaired muscle metabolism and excessively increased lactate levels during exercise have been demonstrated in previous studies (8,9).

A study conducted in our clinic found that arterial lactate levels measured with polysomnography (PSG) in the morning were higher in OSA patients compared to the non-OSA patient group. However, there is not enough data on lactate levels in SRBD patients measured after positive airway pressure (PAP) titration. For this reason, in this study we aimed to investigate arterial blood lactate change as an indicator of tissue hypoxia after PAP treatment in OSA and SRHHS patients.

Materials and Methods

Selection of Patients

This prospective study was conducted on a total of 64 patients with OSA; 49 with OSA (grouped as 1) and 15 with both OSA and OHS (grouped as 2) who were referred to the sleep outpatient clinic in our hospital over the period from 27.04.2011 to 01.10.2011. A total of 312 patients had an overnight PSG during this period in our clinic that 234 of them diagnosed as OSA. One hundred eighty two of these OSA patients had the indication for PAP treatment. The subjects who met the criteria for inclusion in the study (n=64) were also diagnosed with overnight PSG. All the participants' had indication for PAP [continuous PAP (CPAP), bi-level PAP (BPAP) and auto PAP (APAP)] treatment. The study protocol was approved by the Institutional Review Board of the research hospital (Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee No: 279 01.09.2010). Patients included in the study completed an informed written consent form.

OSA and SRHHS diagnoses were based on the International Classification (ICSD-2) of the American Academy of Sleep Medicine (AASM) (10). PAP treatment was offered to those scoring equal to or higher than 30 in the apnea hypopnea index (AHI), independent of the subjects' complaints (11). Further, subjects with documented cardiovascular diseases such as hypertension, ischemic coronary disease and stroke and/or symptoms like increased daytime sleepiness, cognitive dysfunction, mood disorders, sleeplessness with AHI score between 5 and 30 per hour were also given PAP treatment (12-17).

BPAP was applied to the OSA cases with intolerance to CPAP treatment because of high nasal airflow, air leak or poor exhalation under positive pressure as well as those with a co morbidity accompanying OSA (cases with nocturnal respiratory problems such as morbid obesity or nocturnal hypoventilation) (18-22). Physicians specialized in sleep disorders have preferred APAP treatment for cases who failed treatment with fixed pressure (23,24).

All patients were evaluated according to their co morbidities such as hypertension, hyperlipidemia, diabetes mellitus, cardiac disease, thyroid diseases, etc. Hypertensive patients were those whose blood pressure is determined to be higher than 135/85 mmHg after two independent measurements (25). Patients diagnosed with hyperlipidemia display increased levels of cholesterol and/or triglyceride in their plasma (26). Cardiac patients constitute the patient group who received treatment with arrhythmia or ischemic cardiac disorder in their medical history, and with ejection fraction higher than 50%. Finally, the group diagnosed with diabetes mellitus covers those who received antidiabetic medication (except metformin) and whose fasting glucose levels after PSG recording equals to 7.0 mmol/L (126 mg/dL) (27).

Exclusion Criteria

Patients with comorbidities that may alter lactate metabolism, such as severe renal failure, chronic hemodialysis treatment, hepatic failure, acidosis, diabetes requiring insulin, deep anemia, hemoglobinopathy, congestive cardiac failure, as well as those with chronic alcohol consumption, those receiving metformin, methyldopa, oral contraceptives, statin/3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, acetaminophen, diclofenac, amoxicillin, amiodarone, chlorpromazine, ciprofloxacin, erythromycin, fluconazole, isoniazid, ripamfin, and valproic acid, were excluded from the study. We also excluded chronic obstructive pulmonary disease (COPD) patients from the study.

Polysomnography

PSG was performed with a PSG running Somnologica, version 4.0 (Embla Systems®, Broomfield, CO) and included four electroencephalography channels (C3-A1, C4-A2, O1-A2, O2-A1), right and left electrooculography channels, one chin electromyography (EMG) channel and four tibialis anterior EMG channels, finger pulse oximeter, strain gauges for thoraco-abdominal movements, one electrocardiography lead, a nasal airflow (pressure cannula), and a digital microphone for snoring detection. PSG recordings were scored in 30-second periods for sleep, breathing, and oxygenation according to the standard criteria of AASM (24). "Obstructive apneas" were defined as a complete cessation of oronasal airflow for at least 10 seconds in the presence of chest-wall motion. "Hypopneas" were defined as a reduction in respiratory airflow of 50% or more or a clear reduction in airflow related with more than 3% arterial oxygen desaturation or an arousal lasting for at least 10 seconds. The AHI was calculated as the total number of apneas and hypopneas per hour of sleep. Sleep was staged manually using the standard criteria of AASM (24,25). According to ICSD-2 classification, the diagnosis of SRBD is based on PSG and includes:

- OSAS: AHI -5 per hour of sleep.
- Obesity hypoventilation syndrome:

Obese patients [body mass index (BMI) -30 kg/m^2] with one of the following (10):

- SpO_2 during sleep of less than 90% for more than five minutes with a minimum of at least 85%;
- More than 30% of total sleep time with an SpO_2 of less than 90%;
- Sleeping arterial blood gas with $PaCO_2$ that is abnormally high or disproportionately increased relative to levels during wakefulness.

Bi-Level Positive Airway Pressure, Continuous Positive Airway Pressure and Auto Positive Airway Pressure Titration

PAP titration was performed by a sleep technician at night under expiration pressure with 1 cmH_2O pressure increases until the sufficient pressure was reached for all apneas, flow limitations and snoring to disappear, and under inspiration pressure with 1 cmH_2O pressure increases until the sufficient pressure was reached for hypopnea, hypoxia, and hypoventilation to disappear. Manual CPAP titration was performed by a sleep technician at night with 1 cmH_2O pressure increases until all apneas, hypopneas, flow limitations and snoring disappeared. We performed APAP titration with rapid eye movement sleep (REM) star Auto (Respironics, Germany). We analyzed the average pressure required through the night after BPAP, Manual CPAP and APAP titration, maximum pressure required for 90% of the night, and average mask leak data.

Arterial Blood Gas Lactate Measurement

The first 2 mL arterial blood gas sample was taken before manual PAP titration in the night in supine position while the subject is asleep and awake, and the second was taken after titration in the morning in the same position, from the radial artery via heparinized tubes. We evaluated samples immediately via Rapidlab Analyzer 860 (Bayer Health Care Systems-Siemens, USA). Laboratory reference value for lactate was 0.5-2 mmol/lt. Overnight lactate change was calculated based on the following formula: $\Delta lactate=(\text{blood gas lactate})_{Morning} - (\text{blood gas lactate})_{Night}$

Other Measurements

Fasting blood samples were taken in the following morning for an evaluation of biochemical parameters such as hemogram and fasting glucose, lipid profile, and thyroid function tests. Pulmonary function test (PFT) measurements were conducted with a ZAN 100, (Flow Handy, Germany) device in standing position and by using nasal clips in order to exclude COPD (28). At least three and up to five forced expiratory maneuvers were performed to obtain three technically acceptable blows. The highest forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were recorded. We used Epworth sleepiness scale (ESS) to measure daytime sleepiness and ESS >10 was defined to indicate excessive daytime sleepiness (29).

Statistical Analysis

Analyses were conducted by using SPSS 17 package software. Variables for classification were described in frequency and percentage, continuous variables in average and standard deviation or median and min-max values. Mode and frequency values were used for describing the first and second titration pressures. We tested lactate differences between groups and changes in lactate levels with median testing. In comparing average values, we used the Mann-Whitney U test for independent samples, and Wilcoxon test for dependent samples. We investigated the relationship between other parameters and lactate difference as well as change of lactate with respect to initial condition through partial correlation analysis (adjusted according to BMI). All analyses were conducted with 95% level of confidence and $p<0.05$ was considered to indicate statistical significance.

Results

Forty-nine patients diagnosed with OSA syndrome out of 64 included in the study constituted group 1, and 15 patients with OHS constituted group 2. Age and gender characteristics were found to be similar between two groups (Table 1). Average BMI value was 34.2 in group 1 and 42.2 in group 2 (p=0.001). Hypertension was the co-morbidity with the highest frequency observed in both groups (n=31, 48.4%) in which it was found to be 51% in group 1, and 40% in group 2 (Table 1).

Both groups had similar hemogram, biochemical parameters, thyroid functioning test scores and lipid profiles. When we compared the PFT parameters of both groups, average values for FEV1 in group 1 (2.6 L vs. 2.07 L, respectively, p=0.02) and FVC (3.1 L vs. 2.3 L, respectively, p=0.006) were found to be higher than group 2 on a statistically significant level. ESS average values for group 1 and group 2 were determined to be above ESS >10, which is accepted as a threshold value for daytime sleepiness (11.4 and 12.4, respectively, p>0.005).

When PSG findings were compared between the groups, in group 2, the percentage of time spent at O_2 saturation under 90% (T90%) (33.7 min. vs. 120 min., respectively, $p<0.001$) was longer, minimum O_2 saturation value (74.9% vs. 61.6%, respectively, p=0.012) was lower, and average O_2 saturation value (90.3% vs. 87.1%, respectively, p=0.003) was lower (Table 2). No difference was detected between the groups in terms of REM latency and percentage, non-REM (NREM) percentage, AHI, total sleep time and sleep effectiveness (p>0.05) (Table 2).

After PAP titration, all patients displayed, on statistically significant levels, increased REM% ($p<0.001$), decreased NREM 1-2% ($p<0.001$), decreased T90% ($p<0.001$), increased minimum O_2 saturation (from 71.8% to 85.5%, $p<0.001$) and average O_2 saturation (from 89.6% to 94.1%, $p<0.001$), and decreased total AHI ($p<0.001$) (Table 3). Further, we detected a statistically significant increase in arterial blood gas partial oxygen pressure (PaO_2) after PAP titration (from 70.6% to 78.4%, $p<0.001$) (Table 3).

No statistically significant difference was detected among the patients in terms of lactate levels before and after treatment [1.97 (±0.7) - 1.98 (±0.6)] (p>0.05) (Table 4). There was a negative correlation between BMI and lactate difference (Δlactate) across the entire group (r=-0.277 p=0.027). We found BMI-adjusted pre- and post-treatment lactate levels (lactate difference) of patients to be positively correlated with REM latency (r=0.37 p=0.03), positively correlated with sleep effectiveness (r=0.38, p=0.026), and negatively correlated

with ESS score (r=-0.389, p=0.025). Changes in lactate levels and post-treatment AHI were inversely related on a statistically significant level (r=-0.5, p=0.003) (Table 5).

No statistically significant difference was detected between pre- (1.88±0.6) and post-treatment (1.98±0.6) lactate levels in the OSA patient group (group 1) (p>0.05). In the OSA patient group, we detected an inverse relationship between Δlactate and pre-treatment NREM 1-2% (r=-0.328, p=0.021), T90% (r=-0.356, p=0.012), and total AHI (r=-0.424, p=0.002). We found Δlactate to be positively correlated with pre-treatment average O_2 saturation (r=0.396, p=0.005), and with minimum O_2 saturation (r=0.361, p=0.011) in group 1. This patient group also displayed an inverse relation between post-treatment total AHI and Δlactate, which was statistically significant on a reasonable level (r=-0.320, p=0.0025). Again, we determined that the difference between pre- and post-treatment AHI (Δtotal AHI) and the lactate difference was positively correlated (r=0.394, p=0.005) (Table 6).

There was not any statistically significant difference between pre- (2.24±1.1) and post-treatment (1.98±0.6) lactate levels in patients diagnosed with OSA plus OHS (group 2) (p>0.05). This group displayed a statistically significant positive correlation between pre-treatment lactate levels and minimum pre-treatment O_2 saturation, an inverse relationship between post-treatment lactate levels and post-treatment T90% (r=-0.539, p=0.038), and a statistically significant positive correlation between post-treatment lactate levels and average post-treatment O_2 saturation (r=0.558, p=0.031). No statistically significant correlation was found between Δlactate and PSG parameters in this patient group (Table 7).

Discussion

This study revealed no significant difference between nocturnal lactate levels and lactate levels after PAP treatment in patients diagnosed with OSA and OHS. Besides, in the OSA patient group, we found a relationship between the lactate level difference and AHI, minimum and average O_2 saturation and T90%, which are indicators of disease severity. We found a statistically significant correlation between AHI difference and lactate difference measured before and after PAP treatment.

In a previous study conducted in our clinic, morning lactate levels were significantly higher in the SRBD group than the No-SRBD group (1.65 +/- 0.48 and 1.35 +/- 0.57 mmol/L, respectively) (p=0.003) (30). After an adjustment for age, gender, and BMI, lactate levels before PSG were related to the

Table 1. Patient characteristics

	Total		OSA (n=49)		OSA+OHS (n=15)		p
Age (Mean, SD)	53.4	9.5	52.4	9.2	57.0	9.8	0.052
Sex (n, %)							
Male	40	62.5	33	67.3	7	46.7	0.148
Female	24	37.5	16	32.7	8	53.3	
BMI kg/m^2 (Mean, SD)	36.1	7.9	34.2	6.3	42.3	9.4	**0.001**
Hypertension (n, %)	31	48.4	25	51.0	6	40.0	NS
Comorbidity (n, %)							
No	33	51.6	28	57.1	5	33.3	0.106
Yes	31	48.4	21	42.9	10	66.7	
DM (n, %)							
No	55	85.9	41	83.7	14	93.3	0.672
Yes	9	14.1	8	16.3	1	6.7	
CHD (n, %)							
No	53	82.8	41	83.7	12	80.0	0.710
Yes	11	17.2	8	16.3	3	20.0	
Titration (n, %)							
Auto CPAP	24	37.5	22	44.9	2	13.3	<**0.001**
Continuous PAP	29	45.3	26	53.1	3	20.0	
Bi-level PAP	11	17.2	1	2.0	10	66.7	
Pulmonary function test (n, %)							
FEV1/FVC (%)	84.6	6.8	84.4	6.5	85.1	7.8	1.000
FEV1 (L)	2.5	0.8	2.7	0.8	2.1	0.7	**0.020**
FVC (L)	3.0	1.0	3.1	1.0	2.4	0.8	**0.006**

OSA: Obstructive sleep apnea, OHS: Obesity hypoventilation syndrome, BMI: Body mass index, DM: Diabetes mellitus, CHD: Coronary heart disease, SD: Standard deviation, PAP: Positive airway pressure, CPAP: Continuous positive airway pressure, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity

apnea-hypopnea index (β: 0.004, 95% CI: 0.000-0.008) and percentage of time spent at O_2 saturation under 90% (T90%). The following morning lactate level was correlated with the T 90% (β: 0.005, 95% CI: 0.000-0.010). After an adjustment for lactate levels before PSG, lactate in the morning was correlated with T90% (β: 0.004, 95% CI: 0.000-0.008). This

Table 2. The comparison of sleep characteristics of polysomnograhy night scores and positive airway pressure titration night scores in between two groups

	Total (n=64)		OSA (n=49)		OSA+OHS (n=15)		p
	Mean	SD	Mean	SD	Mean	SD	
REM (%) pre	10.3	7.4	10.8	7.9	8.9	5.9	0.573
REM (%) post	22.4	10.8	21.0	11.1	26.7	8.5	**0.022**
NREM1-2 (%) pre	79.1	25.1	79.9	27.5	76.6	15.5	0.775
NREM1-2 (%) post	61.4	17.6	65.4	16.1	48.2	16.3	**0.001**
NREM3 (%) pre	16.5	30.2	17.2	33.8	14.5	13.8	0.741
NREM (%) post	16.0	13.7	13.6	12.8	23.9	14.1	**0.011**
T90% (%) pre	54.0	63.6	33.7	41.0	120.0	79.8	**<0.001**
T90% (%) post	12.8	43.8	4.2	15.0	41.0	82.1	**<0.001**
Minimum O_2 saturation (%) pre	71.8	14.9	74.9	11.6	61.6	19.9	**0.012**
Minimum O_2 saturation (%) post	85.5	8.1	87.8	4.4	78.1	12.4	**<0.001**
Average O_2 saturation (%) pre	89.6	5.3	90.3	5.2	87.1	5.0	**0.003**
Average O_2 saturation (%) post	94.1	2.1	94.5	1.7	92.8	2.7	**0.023**
TAHI pre	48.2	23.3	46.5	20.4	53.6	31.3	0.428
TAHI post	4.6	3.3	4.5	3.2	5.1	3.5	0.437
ESS	11.7	6.0	11.5	6.0	12.5	6.1	0.535

OSA: Obstructive sleep apnea, OHS: Obesity hypoventilation syndrome, REM: Rapid eye movement sleep, NREM: Non rapid eye movement sleep, T90%: Percentage of time spent at O_2 saturation under 90%, TAHI: Total apnea hypopnea index (events/hr), ESS: Epworth sleep scale (points), pre: The polysomnography night scores, post: After positive airway pressure titration (posttreatment) polysomnography scores, SD: Standard deviation

Table 3. The comparison of polysomnography scores before and after positive airway pressure treatment inside the two groups

	Total			OSA			OSA+OHS		
	Mean	SD	p	Mean	SD	p	Mean	SD	p
REM latency (MINS) pre	109.7	88.2	0.073	103.3	87.8	0.403	130.7	89.2	**0.041**
REM latency (MINS) post	81.2	63.8		90.1	63.4		51.9	57.6	
REM (%) pre	10.3	7.4	**<0.001**	10.8	7.9	**<0.001**	8.9	5.9	**0.001**
REM (%) post	22.4	10.8		21.0	11.1		26.7	8.5	
NREM1-2 (%) pre	79.1	25.1	**<0.001**	79.9	27.5	**0.001**	76.6	15.5	**0.003**
NREM1-2 (%) post	61.4	17.6		65.4	16.1		48.2	16.3	
NREM3 (%) pre	16.5	30.2	0.247	17.2	33.8	0.912	14.5	13.8	0.050
NREM (%) post	16.0	13.7		13.6	12.8		23.9	14.1	
T90% (%) pre	54.0	63.6	**<0.001**	33.7	41.0	**<0.001**	120.0	79.8	**0.003**
T90% (%) post	12.8	43.8		4.2	15.0		41.0	82.1	
Minimum O_2 saturation (%) pre	71.8	14.9	**<0.001**	74.9	11.6	**<0.001**	61.6	19.9	**0.005**
Minimum O_2 saturation (%) post	85.5	8.1		87.8	4.4		78.1	12.4	
Average O_2 saturation (%) pre	89.6	5.3	**<0.001**	90.3	5.2	**<0.001**	87.1	5.0	**0.001**
Average O_2 saturation (%) post	94.1	2.1		94.5	1.7		92.8	2.7	
TAHI pre	48.2	23.3	**<0.001**	46.5	20.4	**<0.001**	53.6	31.3	**0.001**
TAHI post	4.6	3.3		4.5	3.2		5.1	3.5	

OSA: Obstructive sleep apnea, OHS: Obesity Hypoventilation Syndrome, REM: Rapid eye movement sleep, NREM: Non rapid eye movement sleep, T90%: Percentage of time spent at O_2 saturation under 90%, TAHI: Total apnea hypopnea index (events/hr), pre: The polysomnography night scores, post: After positive airway pressure titration (posttreatment) polysomnography scores, SD: Standard deviation

study revealed no statistically significant difference between night lactate before PSG and morning lactate after PSG in the SRBD patient group (30). Another recent study considered uric acid and lactate levels as indicators of hypoxia, and as a result, suggested that lactate might prove to be a better parameter than uric acid since lactate values are higher in the morning (31). Our study supported these findings. We determined a relationship between lactate difference and indicators of disease severity. Further, the fact that morning lactate levels of patients receiving treatment displayed no increase in comparison to the night levels might be related with the effectiveness of PAP treatment.

Increased lactate production and reduced excretion might be associated with intermittent hypoxia and sleep disruptions, which are the two significant outcomes of OSA. Sleep disruptions result in reduced sleep quality and NREM 3 phase (32). Sleep disruptions reduce sleep quality, together with significant decreases in NREM 3 phase and distort the oxidative metabolism by causing abnormal secretion of hormones such as catecholamine and growth hormone (33,34). Sleep disruption indicator NREM 3 is shorter in patients with sleep-related respiratory disorders (SRDs) than in healthy individuals. As defined in the literature, the time spent in the REM sleep is significantly reduced in OSA and SRHHS (32). Since all striated muscles except the diaphragm are at rest during the REM sleep, lactate production is expected to fall. High lactate levels in patients with SRD might be associated with increased sympathetic activity, sleep disruptions and/or intermittent hypoxemia. PAP treatment increases oxygenation and thus ameliorates peripheral and myocardial oxygen supply. This reduces anaerobic stress in peripheral tissues, results in lactate clearance and decreases systemic stress response. Further, CPAP treatment reduces increased sympathetic activity in the morning and at night in patients with OSA (35). Cooper et al. (36) evaluated the effect of nasal continuous PAP treatment on venous lactate in six obese patients. Although lactate levels were not different after continuous PAP treatment as compared to baseline levels, higher baseline lactate/pyruvate ratios suggested glycolytic flux during a hypoxic night. There was no significant relationship between the severity of hypoxemia and the lactate/pyruvate ratio, which may be due to the small sample size of the study. Our study also revealed no change in lactate level after PAP treatment.

Vanuxem et al. (9) reported an association between night desaturation, AHI and lactate elimination during exercise in patients with OSA. However, in contrast to Vanuxem et al. (9) data, Bonanni et al. (37) did not find any relationship between AHI and blood lactate level, and refused the role of sympathetic activity in the increased lactate production in muscles of OSA patients. Bonanni et al. (37) suggested the primary defect in the muscle oxygen metabolism through adaptation to chronic nocturnal hypoxemia as an explanation for excessive lactate production. Another study found morning plasma lactate levels to be related with AHI and T90% in the patients with OSA (31). It is known that apnea, hypopnea and hypoventilation cause chronic intermittent hypoxemia, which was compensated by increasing the rate of breathing in SRD (38). The study conducted by Ucar et al. (30) determined both night and morning lactate levels to be correlated with AHI and T90% in the SRD group with respect to the control group. In the OSA patient group, we found a relationship between the arterial lactate level differences measured before and after PAP

Table 4. Comparison of lactate differences and changes in lactate levels

	Total (n=64)		OSA (n=49)		OSA+OHS (n=15)		p
Lactate Difference (Median, minimum-maximum)	0.06	(-4.34)-(1.17)	0.03	(-0.81)-(1.17)	0.11	(-4.34)-(0.71)	0.880
Change in Lactate Levels (Median, minimum-maximum)	0.03	(-0.76)-(0.82)	0.02	(-0.50)-(0.82)	0.04	(-0.76)-(0.50)	0.733
Lactate pre (mmol/L) (Mean, SD)	1.97	0.77	1.88	0.60	2.24	1.16	0.358
Lactate post (mmol/L) (Mean, SD)	1.98	0.63	1.98	0.62	1.98	0.68	0.855

OSA: Obstructive sleep apnea, OHS: Obesity hypoventilation syndrome, SD: Standard deviation, pre: The polysomnography night scores, post: After positive airway pressure titration (posttreatment) polysomnography scores

Table 5. Correlations of lactate difference and change in lactate levels corrected for body mass index with polysomnography parameters

	Lactate difference		Change in lactate levels	
	r	p	r	p
Sleep start-up latency (Mins)	-0.262	0.141	-0.393	**0.024**
Rem latency (Mins)	0.377	**0.030**	0.476	**0.005**
ESS	-0.389	**0.025**	-0.426	**0.013**
Sleep efficacy (%) post	0.388	**0.026**	0.229	0.200
TAHI post	-0.335	0.057	-0.501	**0.003**

REM: Rapid eye movement sleep, TAHI: Total apnea hypopnea index (events/hr), ESS: Epworth sleep scale (points), post: After positive airway pressure titration

treatment and AHI, average O_2 saturation, and T90%, which are indicators of disease severity. Again, we found a statistically significant correlation between AHI difference and lactate difference measured before and after PAP treatment. In patients with OSA accompanied by OHS, we determined similar lactate levels and post-treatment lactate difference.

Studies have demonstrated that OSA poses a risk for obesity, hypertension, CHD, and DM. The prevalence of OSA is 25% in the non-obese population, and 45% in the obese population, whereas prevalence of obesity is 70% among patients with OSA (39). Güven et al. (40) assumed obesity threshold to be BMI >29 kg/m^2 in a series of 67 cases, and determined 69% obesity among the cases with mild OSA, and 77% obesity in those with medium and severe OSA. Ursavaş et al. (41) assumed BMI >26 kg/m^2 and found obesity ratio to be 77%. In our study, BMI average was 34.2 kg/m^2 for OSA, and 42.3 kg/m^2 in OSA and inattention-hyperactivity score; and BMI average were higher than 30 kg/m^2 in all patient groups. Further, BMI was higher on a statistically significant level in group 2 than the group 1.

It has been shown that obese individuals display high lactate levels, which are reduced by weight loss (42). Chen et al. (43) found lactate levels to be low in low-weight individuals, high in non-diabetic individuals, and high in both diabetic and obese individuals. Most lactate production is caused by fat tissue in obese individuals (44). Reduced blood flow in fat tissue causes local hypoxia and results in increased lactate production in obese individuals. Consequently, lactate production in the fat tissue increases as the fat tissue grows due to limited oxygen diffusion (45). Our study found a negative correlation between BMI and lactate difference in patients with OSA. This finding has been detected in the other group that might be due to the limited number of sample size. In addition, we found BMI to be higher on a statistically significant level in the OSA and OHS group in comparison to the OSA group, although no statistically significant difference was detected among all groups in terms of night and morning lactate levels. In this study, a relationship was demonstrated between ΔLactate level and BMI, but multiple regression analysis was conducted to control the potential confounding effect of BMI.

This study is one of the first studies to investigate lactate changes after PAP treatment in the OSA and OHS patient groups. The small sample size and cross-sectional design were the main limitations of this study, making it difficult to interpret the findings. Along with this, arterial lactate level

Table 6. The correlation of lactate levels and change in lactate levels with pre-treatment polysomnography night scores before positive airway pressure titration

	OSA (n=49)					
	Lactate (mmol/L) pre		**Lactate (mmol/L) post**		**ΔLactate**	
	r	**p**	**r**	**p**	**r**	**p**
REM (%)	-0.030	0.840	0.035	0.810	0.237	0.100
NREM1-2 (%)	0.053	0.716	-0.051	0.728	**-.328***	**0.021**
NREM3 (%)	-0.038	0.798	-0.009	0.952	0.191	0.189
T90% (%)	0.092	0.531	-0.141	0.334	**-.356***	**0.012**
Minimum O_2 saturation (%)	0.070	0.632	0.259	0.072	**.361***	**0.011**
Average O_2 saturation (%)	-0.093	0.524	0.133	0.362	**.396****	**0.005**
TAHI	0.092	0.528	-0.068	0.644	**-.424****	**0.002**
ESS	0.128	0.380	0.046	0.755	-0.170	0.242
	OSA+OHS (n=15)					
	Lactate (mmol/L) pre		**Lactate (mmol/L) post**		**ΔLactate**	
	r	**p**	**r**	**p**	**r**	**p**
Rem latency (Mins)	0.036	0.899	.611*	**0.016**	**.625***	**0.013**
REM (%)	0.093	0.742	0.157	0.576	0.193	0.491
NREM1-2 (%)	0.139	0.621	0.375	0.168	0.132	0.639
NREM3(%)	-0.091	0.747	**-.522***	**0.046**	-0.315	0.253
T90% (%)	-0.432	0.108	0.007	0.980	0.304	0.271
Minimum O_2 saturation (%)	**.643****	**0.010**	0.066	0.815	-0.500	0.057
Average O_2 saturation (%)	0.380	0.163	-0.004	0.990	-0.249	0.371
TAHI	0.018	0.950	0.327	0.234	0.288	0.298
ESS	0.302	0.274	0.063	0.824	-0.140	0.618

OSA: Obstructive sleep apnea, OHS: Obesity hypoventilation syndrome, REM: Rapid eye movement sleep, NREM: Non rapid eye movement sleep, T90%: Percentage of time spent at O_2 saturation under 90%, TAHI: Total apnea hypopnea index (events/hr), ESS: Epworth sleep scale (points), ΔLactate: The change in arterial lactate levels, pre: The polysomnography night scores, post: After positive airway pressure titration (posttreatment) polysomnography scores

Table 7. The correlation of lactate levels and change in lactate levels with post-treatment polysomnography night scores after positive airway pressure titration

	OSA (n=49)					
	Lactate (mmol/L) pre		Lactate (mmol/L) post		ΔLactate	
	r	p	r	p	r	p
REM (%)	0.258	0.073	0.181	0.213	-0.152	0.297
NREM1-2 (%)	-0.216	0.135	-0.154	0.290	0.176	0.228
NREM (%)	0.046	0.755	0.053	0.718	-0.094	0.520
T90% (%)	0.178	0.222	0.055	0.709	-0.241	0.095
Minimum O_2 saturation (%)	-0.217	0.135	-0.109	0.456	0.245	0.089
Average O_2 saturation (%)	-0.128	0.382	0.062	0.674	0.248	0.086
TAHI	0.015	0.920	-0.202	0.165	**-.320***	**0.025**
	OUAS+OHS (n=15)					
	Lactate (mmol/L) pre		Lactate (mmol/L) post		ΔLactate	
	r	p	r	p	r	p
REM (%)	-0.300	0.277	-0.057	0.840	0.036	0.899
NREM1-2 (%)	0.125	0.657	0.250	0.369	0.343	0.211
NREM (%)	-0.096	0.732	-0.339	0.216	-0.371	0.173
T90% (%)	-0.468	0.079	**-.539***	**0.038**	-0.218	0.435
Minimum O_2 saturation (%)	0.427	0.113	0.491	0.063	0.213	0.445
Average O_2 saturation (%)	0.433	0.107	**.558***	**0.031**	0.275	0.320
TAHI	0.259	0.351	-0.123	0.661	-0.232	0.405

OSA: Obstructive sleep apnea, OHS: obesity hypoventilation syndromes, REM: Rapid eye movement sleep, NREM: Non rapid eye movement sleep, T90%: Percentage of time spent at O_2 saturation under 90%, TAHI: Total apnea hypopnea index (events/hr), ΔLactate: The change in arterial lactate levels, pre: The polysomnography night scores, post: After positive airway pressure titration (posttreatment) polysomnography score

measurement in the post-titration morning was the result of a one-night monitoring and may not be sufficient for monitoring the effectiveness of the PAP treatment. Arterial lactate levels measured during follow-ups through long-term and regular PAP treatment may prove to be more valuable.

This study has demonstrated a relationship between lactate difference, which is an indicator of tissue hypoxia and therefore an indicator of prognosis, and severity indicators (AHI, average and minimum oxygen saturation and T90%) for OSA. These results suggest that PAP treatment may prevent possible lactate increase. Further and more comprehensive studies are required on this matter.

Conclusion

Lactate the end product of anaerobic carbohydrate metabolism has not been investigated in OSA for monitoring the effectiveness of treatment. This paper investigates the use of arterial blood lactate change after PAP treatment in patients with OSA and SRHHS. In this study there was no significant difference among the patients in terms of lactate levels before and after PAP treatment. There was a relation between lactate difference and AHI, average and minimum oxygen saturation and percentage of time spent at O_2 saturation under 90% (T90%). These results suggest that PAP treatment may prevent possible lactate increase.

Ethics

Ethics Committee Approval: Dr. Suat Seren Chest Diseases and surgery Education and Training Hospital Ethics Committee No: 279 01.09.2010, **Informed Consent:** It was taken.
Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Zeynep Zeren Uçar, **Design:** Reyhan Gümüşburun, Zeynep Zeren Uçar, **Data Collection or Processing:** Özlem Egemen Tüzel, **Analysis or Interpretation:** Fadıl Murat Gümüşburun, Yelda Varol, Hüseyin Halilçolar, **Literature Search:** Özlem Egemen Tüzel, Erdem Atalay Çetinkaya, **Writing:** Yelda Varol.
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