Negative Expiratory Pressure (NEP) Technique and Anthropometric Derived Indices as Surrogate Markers for Predicting Obstructive Sleep Apnea Syndrome (OSAS)

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Abstract: *Introduction:* We wondered whether anthropometric, lung function, arterial blood gas (ABG), tidal volume (V_T), and Negative Expiratory Pressure (NEP) Technique data could be utilized alone or collectively for predicting the presence of obstructive sleep apnea syndrome (OSAS).

Methods: Thirty-eight consecutive subjects (29% females) were referred for symptoms suggestive of OSAS. They had no respiratory or any other system failure. Anthropometric data, V_T and lung function measurements were obtained. All subjects underwent overnight polysomnogaphy (PSG). They were also subjected to the NEP technique (-5 cm H_2O) in seated and supine positions, specifically investigating the usefulness of known NEP-acquired indices (EFL %, $\Delta \dot{V}$ %, V, NEP $_{0.5}$, V0.2%). PSG classified subjects according to Apnea/Hypopnea Index (AHI).

Results: Eleven patients had AHI<15, whilst 27 had AHI≥15. Only $\Delta \dot{V}$ % and V,$NEP_{0.5}$ correlated with AHI in both positions. A Multiple Linear Regression (MLR) model using V,NEP 0.5 in the seated position (V,NEP 0.5_{se}), Neck Circumference (NC), arterial oxygen tension (Pa02), Expiratory Reserve Volume (ERV,% pred), improves AHI prediction (R^2_{adj} =0,814).

Conclusions: V,$NEP_{0.5}$, could identify moderate and severe OSAS in stable patients. MLR models using additional parameters substantially improve AHI prediction.

Keywords: Negative expiratory pressure, obstructive sleep apnea syndrome, apnea hypopnea index, expiratory flow limitation, anthropometric data.

1. INTRODUCTION

OSAS is a syndrome caused by intermittent pharyngeal obstruction during sleep, resulting in interruption of normal breathing and disruption of sleep, leading to hypoxemia, and cerebral arousal [1]. It is probably one of the most frequent syndromes of the respiratory system [2] with severe consequences.

The increased prevalence of OSAS in the general population, the OSAS severity, the coexistence of overlap syndrome in some patients, and the cost for performing a full overnight PSG make screening of the disease a difficult task. Consequently, efforts to early and easily diagnose OSAS with alternative methods are justified. Some of the known methods used are the ones derived from the NEP technique [3] and several anthropometric data. We also investigated whether lung function testing, arterial blood gas (ABG) analysis and inspiratory tidal volume (V_T) can help in OSAS prediction.

Each alternative method appears to have limited usefulness for OSAS diagnosis in comparison to the gold standard PSG [4, 5]. Therefore, the aim of this study was to investigate the usefulness of the indices derived from NEP technique, anthropometric data, lung function and ABG analysis data to predict the diagnosis of OSAS. Finally, we assessed if all these methods can be collectively used as surrogate markers of screening OSAS.

2. MATERIALS AND METHODS

2.1. Materials

Thirty-eight consecutive general population subjects (29% females) were referred to “Sotiria” Chest Disease Hospital for symptoms suggestive of OSAS. These were recruited by our respiratory out-patient clinic. The study was approved by the Hospital’s Ethics Committee (No. 13259). All subjects gave informed consent. Patients’ inclusion criteria were: age≥18, sufficient cooperation during the examination, stable clinical status. Exclusion criteria were: respiratory, heart, other organ system failure, recent major operation, and neuromuscular disorders.

2.2. Methods

2.2.1. Polysomnography

Epworth Sleepiness Scale (ESS) [6] was used in all subjects for assessment of daytime sleepiness prior to

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PSG. Overnight polysomnography (Alice 4, Respironics, Inc, Murryville, PA, USA) was performed between 11 pm to 6 am. Apnea was defined by a 90% decrease or absence in the thermistor signal of airflow for 10 sec. Hypopnea was defined by a 50% reduction of nasal pressure signal lasting for 10 sec associated with a decrease of 3% in oxygen saturation or an EEG arousal according to the American Academy of Sleep Medicine new scoring rules [7]. An event was defined as *obstructive* in the presence of respiratory efforts and *central* in their absence. AHI was defined as the number of obstructive and central apneas and hypopneas per hour of sleep. It was calculated by dividing the total number of events by the total sleep time.

2.2.2. Arterial Blood Gas Analysis

ABG were analyzed with GEM 3000 blood gas analyzer (Model GEM 3000: Instrumentation Laboratory, Orangeburg, NY, USA).

2.2.3. Assessment of Lung Function

An appropriate device (*V*max Encore 22: Sensor Medics, Yorba Linda, CA, USA) was used for lung function testing. Simple spirometry was performed using the "fast maneuver" [8]. Static lung volumes were measured by the Nitrogen Washout Technique. Diffusion Capacity for carbon monoxide was measured by the single breath method. The predicted values for spirometry, lung volumes, and diffusion capacity originate from the European Coal and Steel Community [9].

2.2.4. Experimental Setup to Assess EFL

Figure **1** depicts the experimental set-up used to apply the Negative Expiratory Pressure technique (NEP) in order to assess expiratory flow limitation during tidal breathing (EFL), and hence derive the NEP indices. Briefly, a flanged plastic mouthpiece is connected to a pneumotachograph (Screenmate-Box; Erich Jaeger GmbH & Co.) and a T-tube. One side of the T-tube is open to the atmosphere, whilst the other side is equipped with a one-way pneumatic valve (Series 9300; Hans Rudolph, Inc., Kansas City, MO, USA). This allows for the subject to be rapidly switched (Hans Rudolph control switch 9301) to negative expiratory pressure (NEP) generated by a vacuum cleaner (Model S204; Miele Electronic de Lux, Miele, Germany). The NEP (-5 cmH2O) could be adjusted with a potentiometer incorporated into the vacuum cleaner. Flow ($\dot{V}$) was measured with the heated pneumotachograph and pressure at the airway opening was measured through a side port on the mouthpiece using a differential pressure transducer ($\pm$50 cmH2O, Screenmate-Box; Erich Jaeger Gmbh & Co). The NEP test compares the tidal expiratory flow-volume curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied (Figure **2a**). Subjects in whom application of NEP did not elicit an increase of flow during part or all of the tidal expiration were considered flow-limited (EFL). In contrast, subjects in whom flow increased with NEP throughout the control tidal volume range were considered as non flow-limited (NFL). Using the NEP technique, EFL was assessed in the patients randomly in seated and supine positions.

The transducers were calibrated before and after each study with a water manometer. With this system, there was no appreciable shift or alteration in pressure amplitude up to 20 Hz [10]. The flow and pressure signals were sampled simultaneously at a rate of 100 Hz, using a computer data acquisition system with a built-in 16-bit analog-to digital converter (AT-Codas;

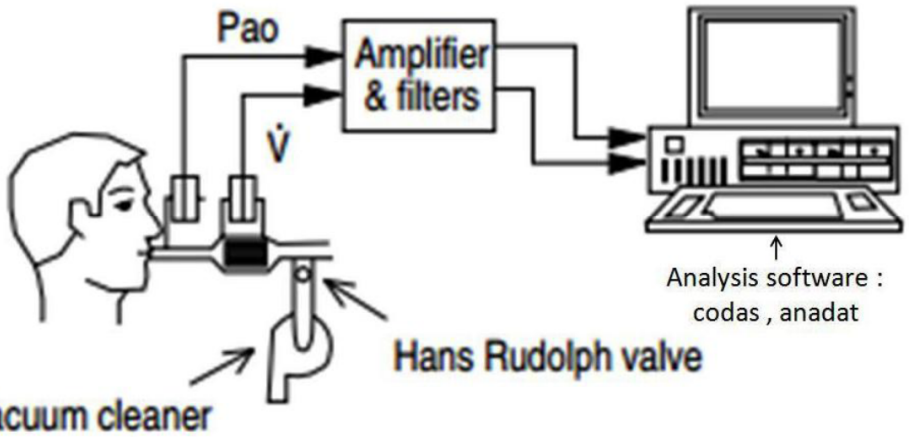

Figure 1: Schematic diagram of equipment set-up [modified from ref. 3]. Pao: pressure measured at the airway opening; $\dot{V}$: flow.

DATAQ instruments, Inc., Akron, OH, USA). Collected data were stored on computer disk for subsequent analysis. Volume (V) was obtained by numerical integration of the flow signal. The flow signal was corrected for any offset, using the assumption that inspired and expired volume of the control breaths preceding the test breaths were the same [11]. This analysis was made using ANADAT data analysis software (version 5.1; RHT-InfoDat Inc., Montreal, Quebec, Canada).

2.2.5. Anthropometric Data

Neck Circumference (NC) was measured in a horizontal plane extending transversely from immediately downstream of the Adam's apple anteriorly, to the posterior surface of the neck [12]. Waist Circumference (WC) was measured in a horizontal plane as the greatest abdominal diameter [13]. Body Mass Index (BMI) was calculated in kg/m^2. Visual Analogue Score (VAS)[14], as well as, Borg's modified CR10 scale [15] for subjective grading of acute dyspnea were used for the assessment of acute dyspnea presence in seated and supine positions. Chronic dyspnea score was assessed by the 6 grade mMRC scale [16].

2.2.6. Maximum Static Mouth Expiratory (Pemax) and Inspiratory (Pimax) Pressures

A differential pressure transducer (±350, Validyne MP45, Validyne Co., Northridge, CA) was used to measure Pemax and Pimax mouth pressures. They were measured with a plastic semi-rigid flanged mouthpiece fitted to a metallic stem incorporating a 3-way tap manufactured according to the design of Ringqvist [17]. All measurements were performed with a nose clip on, with the patients sitting comfortably on a chair with a tall and comfortable back. Pemax was measured at Total Lung Capacity (TLC), whilst Pimax was measured at Residual Volume (RV).

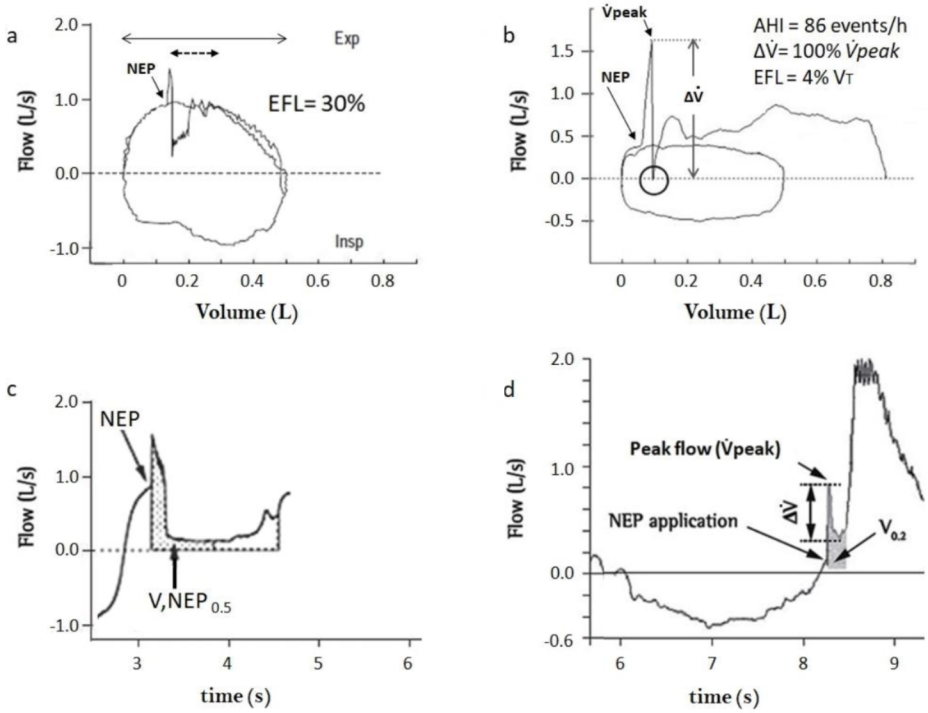

Figure 2: Flow-time and flow-volume graphs during NEP technique data acquisition.

a: EFL% is expressed as the percentage of the tidal volume of the test breath over which flow is equal to or smaller than the flow of the previous control breath; Exp: expiration; Insp: inspiration; [ref. 18, modified].

b: Δ V̇ % is defined as (Δ V̇ / V̇ peak)*100 % [19] of the test breath. V̇ peak is the highest flow developed at the beginning of the negative pressure application. Δ V̇ = the immediate drop in flow due to pharyngeal partial or total collapse; AHI: Apnea/Hypopnea Index; [ref. 19, modified].

c: V, $NEP_{0.5}$ is the volume of air expired during the first 0.5 second (shaded part in the flow-time graph) from the beginning of negative pressure application; [ref. 5, modified].

d: V0.2% is the % ratio of the volume of air expired during the first 0.2 seconds from the beginning of negative pressure application (shaded part in the flow-time graph), divided by the mean of the 3 inspiratory tidal volume breaths that precede negative pressure application; [ref. 22, modified].

NEP: Negative Expiratory Pressure.

2.2.7. Indices Derived from the NEP Technique

The Negative Expiratory Pressure was manually exerted, starting from peak expiratory flow and lasting until the end of expiration. EFL% [3, 18] is expressed as the percentage of the tidal volume of the test breath over which flow is equal to or lower than the flow of the previous control breath (Figure **2a**). $\Delta\dot{V}$ % is defined as *$(\Delta\dot{V}/\dot{V}$ peak)*100 %* [19] of the test breath. $\dot{V}$ *peak* is the highest flow developed at the beginning of the negative pressure application. $\Delta\dot{V}$ = the immediate drop in flow due to pharyngeal partial or total collapse (Figure **2b**). V,$NEP_{0.5}$ [5, 20] is the volume of air expired during the first 0.5 second from the beginning of negative pressure application (Figure **2c**). V0.2% [21-23] is the % ratio of the volume of air expired during the first 0.2 seconds from the beginning of negative pressure application, divided by the mean of the 3 inspiratory tidal volume breaths that precede negative pressure application (Figure **2d**).

2.2.8. Procedure

A full medical file was created and clinical examination was performed for each subject. NC, WC, ABG and lung function parameters were measured. The subjects then underwent nocturnal PSG and after that, NEP Technique was performed in both seated and supine positions using a negative pressure of ~ 5 cm H20 in random order. Expiratory flow limitation (EFL) was assessed using the (NEP) Technique as described in detail by Koulouris *et al.* [3]. The procedure and results are summarized in a flowchart (Figure **3**).

2.2.9. Statistical Analysis

Data were analyzed using appropriate statistical software (IBM-SPSS v.19, Chicago, Illinois, USA) and (Medcalc v 14.8 software Ostend, Belgium, Europe). Values were expressed as mean ± standard deviation. The level of statistical significance was defined as p<0, 05. We used t-test, Mann-Whitney U-test, logistic regression analysis, best subset regression analysis, Passing-Bablok analysis, and Factor Analysis where appropriate.

3. RESULTS

The subjects were divided into group A (4 controls and 7 mild OSAS with AHI<15) and group B (10 moderate and 17 severe OSAS with AHI≥15), according to the AHI results of overnight PSG. Anthropometric and functional characteristics of the 2 groups are shown in Table **1**.

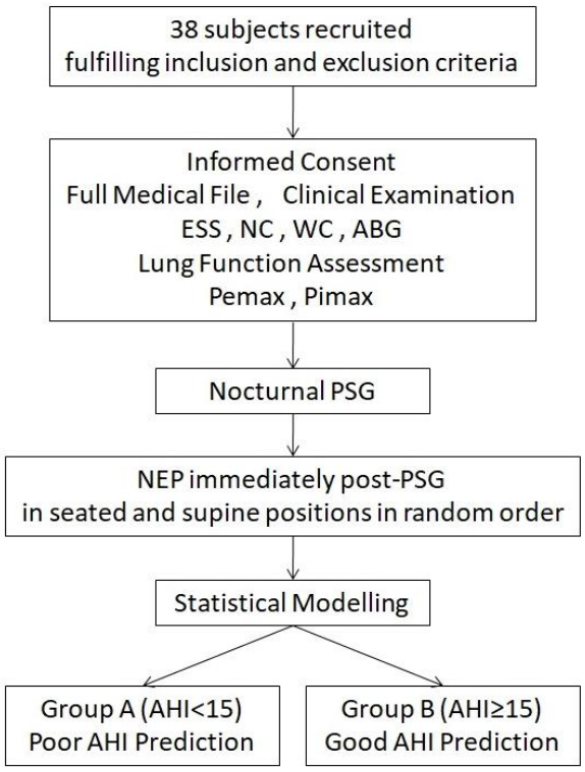

Figure 3: Flowchart of the procedure and results.

ESS: Epworth Sleepiness Scale; NC: Neck Circumference (in cm); WC: Waist Circumference (in cm); ABG: Arterial Blood Gas Analysis; Pemax, Pimax: maximum static mouth expiratory and inspiratory pressures (in cm H20); PSG: Polysomnography; NEP: Negative Expiratory Pressure Technique; AHI: Apnea/Hypopnea Index.

3.1. Position

There was no statistically significant difference between most seated and supine NEP parameter measurements. Only mean V0.2 % was significantly lower (n=37, p=0,028) in the supine position in comparison to the seated one.

3.2. Data Analysis

Respiratory variables correlating to AHI are depicted in Table **2**. NEP-acquired parameters: $\Delta\dot{V}\%_{se}$, V,$NEP_{0.5se}$, $\Delta\dot{V}\%_{su}$, V, $NEP_{0.5su}$ correlated to AHI. Whilst $EFL\%_{se}$, $V0.2\%_{se}$, $EFL\%_{su}$, $V0.2\%_{su}$ did not correlate with AHI.

3.2.1. Logistic Regression Analysis

Logistic regression analysis was used in order to find out which independent variable(s) may predict the presence of clinically significant OSAS. An AHI value ≥ 15 was considered as clinically significant OSAS. If the NEP method is not included in the model, then the best model included the independent variables WC and Pa02, resulted in $R^2_{Nagelkerke}$=0,714 (Table **3**). If the

Table 1: Anthropometric and Lung Function Data of Study Patients

	All Patients	Group A	Group B	
Subjects (n)	**38**	**11**	**27**	
Gender(M/F)	**27/11**	**5/6**	**22/5**	
	mean±SD	**mean±SD**	**mean±SD**	**p***
Age (years)	50 ± 13	40 ± 11	54 ± 12	0,003
Weight (kg)	94 ± 17	82 ± 18	98 ± 15	0,007
BMI (Kg/m^2)	32 ± 7	29 ± 7	33 ± 6	0,039
AHI (events/h)	33 ± 26	7 ± 5	43 ± 23	<0,001
NC (cm)	40,3 ± 3,8	37,0 ± 2,7	41,6 ± 3,3	<0,001
WC (cm)	110 ± 14,5	96,4 ± 10,7	115 ± 12,2	<0,001
$Sa0_2\%_{se}$	97 ± 2	97 ± 1	96 ± 2	0,06
Pa02 (mm Hg)	84 ± 12	95 ± 11	79 ± 10	<0,001
AaD02 (mm Hg)	20 ± 11	13 ± 8	23 ± 11	0,03
Pimax (cm H20)	98 ± 32	92 ± 36	101 ± 31	0,479
Pemax (cm H20)	168 ± 57	158 ± 64	173 ± 54	0,280
DLCO/VA% adj	96 ± 15	92 ± 11	97 ± 17	0,347
ERV,% pred	77 ± 40	103 ± 42	67 ± 35	0,014
FEV1,% pred	98 ± 15	98 ± 17	98 ± 14	0,641
FVC,% pred	103 ± 16	106 ± 17	102 ± 16	0,556
FEV1/FVC,%	78 ± 6	78 ± 8	78 ± 6	0,777

BMI: Body Mass Index; AHI: Apnea/Hypopnea Index; NC: Neck Circumference; WC: Waist Circumference; $Sa0_2\%_{se}$: $Sa0_2\%$ (arterial oxygen saturation) in the seated position; $Pa0_2$: Arterial Oxygen Tension; AaD02: Alveolar-arterial gradient; Pimax: maximum static mouth inspiratory pressure; Pemax: maximum static mouth expiratory pressure; DLCO/VA% adj: Adjusted diffusion for ventilation, %; ERV,% pred: Expiratory Reserve Volume % predicted; FEV1,% pred: Forced expiratory volume in 1 second as a percentage of predicted normal values; FVC,% pred: Forced vital capacity as a percentage of predicted normal values; FEV1/FVC,%: the percentage of FEV1/FVC.
Group A: Controls and Mild OSAS.
Group B: Moderate and Severe OSAS.
*p<0,05 (between groups A and B).

Table 2: Pearson Correlation (r) and Determination (r^2) Coefficients of AHI with Respiratory Variables

Variable	Seated				Supine			
	n	r	r^2	p*	n	r	r^2	p*
Age (years)	38	0,486	0,237	0,002				
Weight (Kg)	38	0,606	0,367	<0,001				
BMI (Kg/m^2)	38	0,440	0,194	0,006				
NC (cm)	38	0,662	0,438	<0,001				
WC (cm)	38	0,684	0,467	<0,001				
$Sa0_2\%$	38	-0,472	0,223	0,003	38	-0,453	0,205	0,004
Pa02 (mm Hg)	33	-0,572	0,328	<0,001				
AaD02 (mm Hg)	31	0,442	0,195	0,013				
Pimax (cm H20)	38	0,0141	0,0002	0,933				
Pemax (cm H20)	38	0,0223	0,000498	0,894				
DLCO/VA% adj	36	0,519	0,269	0,001				
ERV,% pred	35	-0,409	0,167	0,015				
V_T (l)	38	0,535	0,286	<0,001	38	0,557	0,310	<0,001
$\Delta \dot{V}$ %	38	-0,328	0,107	0,045	38	-0,338	0,114	0,038
$V,NEP_{0.5}$ (l)	38	0,436	0,190	0,006	38	0,457	0,209	0,004
EFL%	38	0,246	0,06	0,136	38	0,185	0,0344	0,265
V0.2%	37	0,0315	0	0,853	37	-0,04	0,001	0,814

*p<0, 05.
AHI: Apnea/Hypopnea Index; BMI: Body Mass Index; NC: Neck Circumference; WC: Waist Circumference; $Sa0_2\%$: Arterial oxygen saturation respectively in the seated and supine positions; $Pa0_2$: Arterial Oxygen Tension; AaD02: Alveolar-arterial gradient; Pimax: maximum static mouth inspiratory pressure; Pemax: maximum static mouth expiratory pressure; DLCO/VA% adj: Adjusted diffusion for ventilation, %; ERV,% pred: Expiratory Reserve Volume % predicted; V_T: inspiratory Tidal Volume respectively in the seated and supine positions; $\Delta \dot{V}$ %, $V,NEP_{0.5}$, EFL%, V0.2% : Parameters (indices) measured and calculated from the application of Negative Expiratory Pressure Technique, either in the seated ($_{se}$) or in the supine($_{su}$) position.

Table 3: Best Model without NEP Method Inclusion in the Logistic Regression

	B	S.E.	Wald	df	p	Exp (B)
Constant	0,357	7,908	0,002	1	0,964	1,429
WC (cm)	0,141	0,063	5,097	1	0,024	1,152
Pa02 (mm Hg)	-0,167	0,08	4,388	1	0,036	0,846

WC: Waist Circumference (in cm); $Pa0_2$: Arterial Oxygen Tension (in mm Hg); Constant: the constant term of the regression model; B: the values for the logistic regression equation for predicting the dependent variable from the independent variable; S.E.: the standard errors associated with the coefficients; Wald: the Wald chi-square value used in testing the null hypothesis that the coefficient (parameter) is zero; df: the number of degrees of freedom for each of the tests of the coefficients; p: 2 tailed p-value of the Wald statistics; Exp (B): the odds ratios for the predictions.

Table 4: Best Model with NEP Method Inclusion in the Logistic Regression

	B	S.E.	Wald	df	p	Exp (B)
Constant	0,356	10,743	0,001	1	0,974	1,427
$V0.2\%_{su}$	-0,316	0,197	2,586	1	0,108	0,729
WC (cm)	0,289	0,191	2,277	1	0,131	1,335
Pa02 (mm Hg)	-0,265	0,173	2,340	1	0,126	0,767

$V0.2\%_{su}$: V0.2% in the supine position; WC: Waist Circumference (in cm); $Pa0_2$: Arterial Oxygen Tension (in mm Hg); Constant: the constant term of the regression model; B: the values for the logistic regression equation for predicting the dependent variable from the independent variable; S.E.: the standard errors associated with the coefficients; Wald: the Wald chi-square value used in testing the null hypothesis that the coefficient (parameter) is zero; df: the number of degrees of freedom for each of the tests of the coefficients; p: 2 tailed p-value of the Wald statistics; Exp (B): the odds ratios for the predictions.

NEP method is included in the model, then the best model included the independent variables $V0.2\%_{su}$ (V0.2% in the supine position), WC and Pa02, resulted in $R^2_{Nagelkerke}$=0,824 (Table **4**).

3.2.2. ROC Curves Analysis

ROC curve analysis was performed for $\Delta\dot{V}\%$, and V, NEP0.5, with a cut-off value of AHI=15. Evaluation of the predictive accuracy of the best models that were derived from the logistic regression analyses was made by assessing the power of the model's predicted values to discriminate between positive and negative cases as quantified by the area under the curve (AUC). Predicted probabilities of disease were used as a new variable in ROC curve analysis, with a cut-off value of AHI=15. The results are shown in Table **5**.

3.2.3. MLR Models

Best subset regression analysis was used in order to find the combination of independent variables that best predict AHI. If the NEP method is not included in the model, then the model leading to the best AHI prediction, included the independent variables NC, Pa02, V_{Tsu}, DLCO/ VA% adj, designated as model A, resulting in p<0,001, R^2_{adj} =0,776 (Table **6**). If the NEP method is included in the model, then the model leading to the best AHI prediction, included the independent variables $V,NEP_{0.5\,se}$, NC, Pa02, ERV,%

Table 5: ROC Curves Analysis

	AUC	Se	Sp	CC%
ROC curve for each NEP-derived parameter				
$\Delta\dot{V}\%_{se}$	0,525	0,407	0,818	50,00%
$V,NEP_{0.5\,se}$ (l)	0,620	0,704	0,636	65,79%
$\Delta\dot{V}\%_{su}$	0,650	0,889	0,455	73,68%
$V,NEP_{0.5\,su}$ (l)	0,690	0,636	0,909	68,42%
ROC curves derived from Logistic Regression Analysis #				
WC (cm),Pa02 (mm Hg)	0,948	0,800	0,913	87,88%
$V0.2\%_{su}$, WC (cm) and Pa02 (mm Hg)	0,965	0,900	0,913	90,91%

WC: Waist Circumference (in cm); $Pa0_2$: Arterial Oxygen Tension (in mm Hg); $\Delta\dot{V}\%_{se}$, $\Delta\dot{V}\%_{su}$: $\Delta\dot{V}\%$ in the seated and supine positions respectively; $V,NEP_{0.5\,se}$, $V,NEP_{0.5\,su}$: $V,NEP_{0.5}$ in the seated and supine positions respectively (in l); $V0.2\%_{su}$: V0.2 % in the supine position.
AUC: Area under the curve; Se: sensitivity; Sp: specificity; CC%: percentage of correct classification.
ROC curves derived from the logistic regression analysis, were calculated by using the predicted probabilities of disease as a new variable in ROC curve analysis (and a classification variable of AHI with a cut-off value of 15).

Table 6: Model A

Model A	B	S.E.	t-test	p
Constant	-97,201	37,577	-2,587	0,015
NC (cm)	3,618	0,777	4,659	0,000
Pa02 (mm Hg)	-0,738	0,200	-3,695	0,001
V_{Tsu} (l)	24,004	10,212	2,350	0,026
DLCO/VA% adj	0,361	0,166	2,174	0,038

NC: Neck Circumference (in cm); $Pa0_2$: Arterial Oxygen Tension (in mm Hg); V_{Tsu}: inspiratory Tidal Volume in supine position; DLCO/VA% adj: Corrected Diffusion for ventilation % adjusted; Constant: the constant term of the regression model; B: the values for the regression equation (unstandardized coefficients); S.E.: the standard errors associated with the coefficients; t: the t-statistics; p: the 2 tailed values of the t-statistics.

Table 7: Model B

Model B	B	S.E.	t-test	p
Constant	-63,249	31,266	-2,023	0,053
V,NEP $_{0.5\,se}$ (l)	71,616	21,184	3,381	0,002
NC (cm)	3,662	0,656	5,583	<0,001
Pa02 (mm Hg)	-0,694	0,179	-3,871	<0,001
ERV,% pred	-0,186	0,0573	-3,240	0,003

NC: Neck Circumference (in cm); $Pa0_2$: Arterial Oxygen Tension (in mm Hg); ERV,% pred: Expiratory Reserve Volume % predicted; V,NEP $_{0.5\,se}$: V,NEP $_{0.5}$ in the seated position (in l).
Constant: the constant term of the regression model; B: the values for the regression equation (unstandardized coefficients); S.E.: the standard errors associated with the coefficients; t: the t-statistics; p: the 2 tailed values of the t-statistics.

pred, designated as model B, resulting in R^2_{adj} =0,814 (Table **7**).

3.2.4. Factor Analysis

Factor analysis was used in order to create a linear combination of the variables that were found to be statistically significant during the best subset regression analysis. Two variables were created: Variable 1, which was created from the variables of Model A and Variable 2, which was created from the variables of Model B. Therefore, we calculated the approximate sensitivity and specificity of these models, for a cut-off value of AHI being either 5 or 15, as shown in Figure **4**.

4. DISCUSSION

The main finding of the present study is that each one of these parameters has limited usefulness in OSAS diagnosis in comparison to the gold standard PSG. Therefore, the solution to this problem is to combine NEP technique, V_T, anthropometric, lung function and ABG analysis data in order to predict the diagnosis of OSAS. MLRs substantially improve AHI prediction. Both model A (without the use of the NEP technique, r=0,896, p<0,001) and model B (with the use of the NEP technique, r=0,915, p<0,001) can be used as surrogate markers for predicting sleep apnea syndrome (OSAS). ROC curves, provide an approximate Se=78,3% and Sp=90% for model A and Se=87% and Sp=100% for model B respectively, for a cut-off AHI value of 15.

There are a number of secondary findings that emerge from this study. Firstly, we noted a lack of a statistically significant difference between most seated and supine NEP parameter measurements. In fact, supine measurements do show slightly better coefficients of determination. Secondly, $\Delta\dot{V}$ % and V, $NEP_{0.5}$, correlated to AHI in both positions. To our knowledge, there is no study directly comparing the 2 parameters. In our study V, $NEP_{0.5}$ correlated to AHI better than $\Delta\dot{V}$ % (Table **2**). Furthermore, V, $NEP_{0.5su}$, had similar coefficients of correlation to the ones reported (r=-0,46, p<0,05 only in the severe OSAS group) by Ferretti *et al.* [5]. Whilst $\Delta\dot{V}$ % coefficient of determination in our study was worse than the one reported by Insalaco *et al.* [19] in the seated (n=37, p=0,0102, R^2=0,174) and supine (n=37, p=0,0037, R^2=0,217) positions. ROC curves show a greater Area Under the Curve (AUC) for V, $NEP_{0.5}$ relationship to AHI than to $\Delta\dot{V}$ % relationship to AHI, in both positions, for a cut-off AHI value of 15 (Figure **5**). Furthermore, Passing-Bablok regression reveals that despite all methods being useful, V,$NEP_{0.5}$ and V0.2 % are better in order to predict AHI (Figure **6A** & **B**).

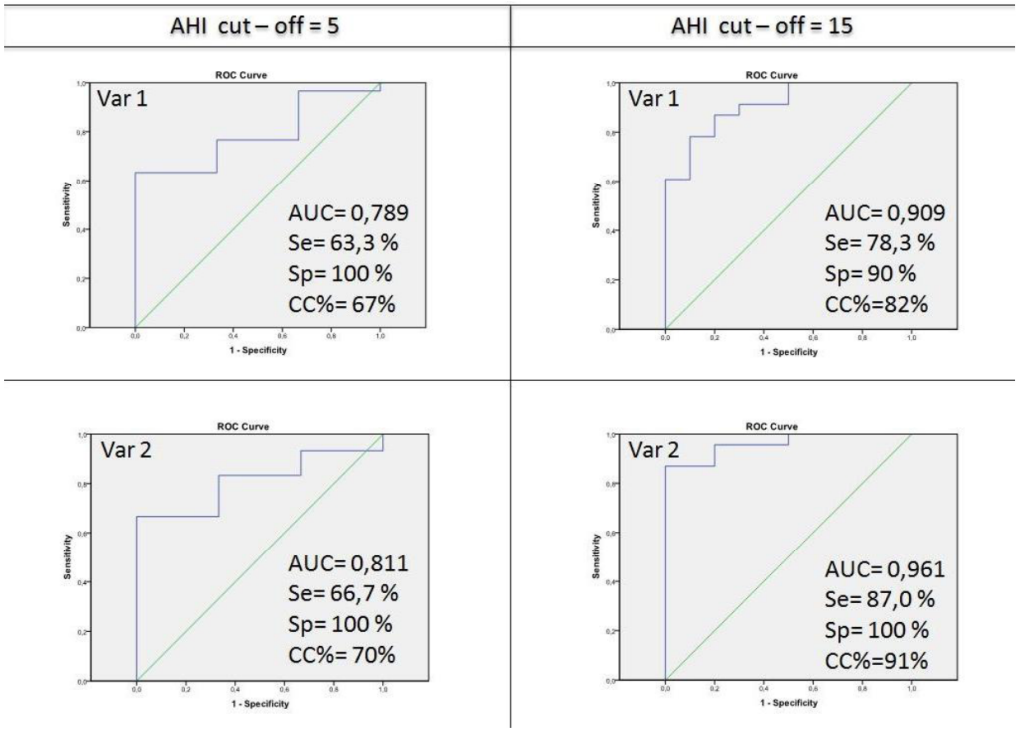

Figure 4: ROC curves for the linear combinations.

AHI: Apnea/Hypopnea Index; Var 1: Variable 1; Var 2: Variable 2; AUC: Area Under the Curve; Se: Sensitivity; Sp: Specificity; CC%: percentage of correct classification.

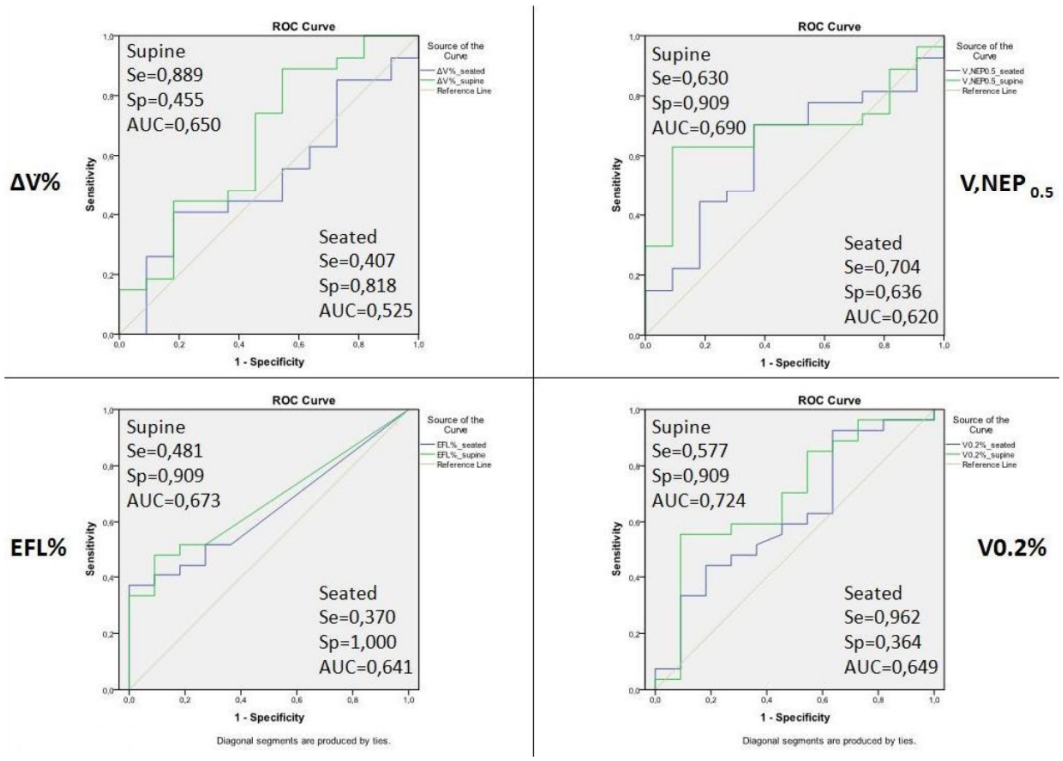

Figure 5: ROC curves of the NEP parameters for an AHI cut-off value of 15.

AUC: Area Under the Curve; Se: Sensitivity; Sp: Specificity; Seated: values of Se, Sp and AUC in the seated position; Supine: values of Se, Sp and AUC in the supine position.

Se and Sp results are different from the ones [23] of the other studies, for EFL% (Se=81,9%, Sp=69,1%).

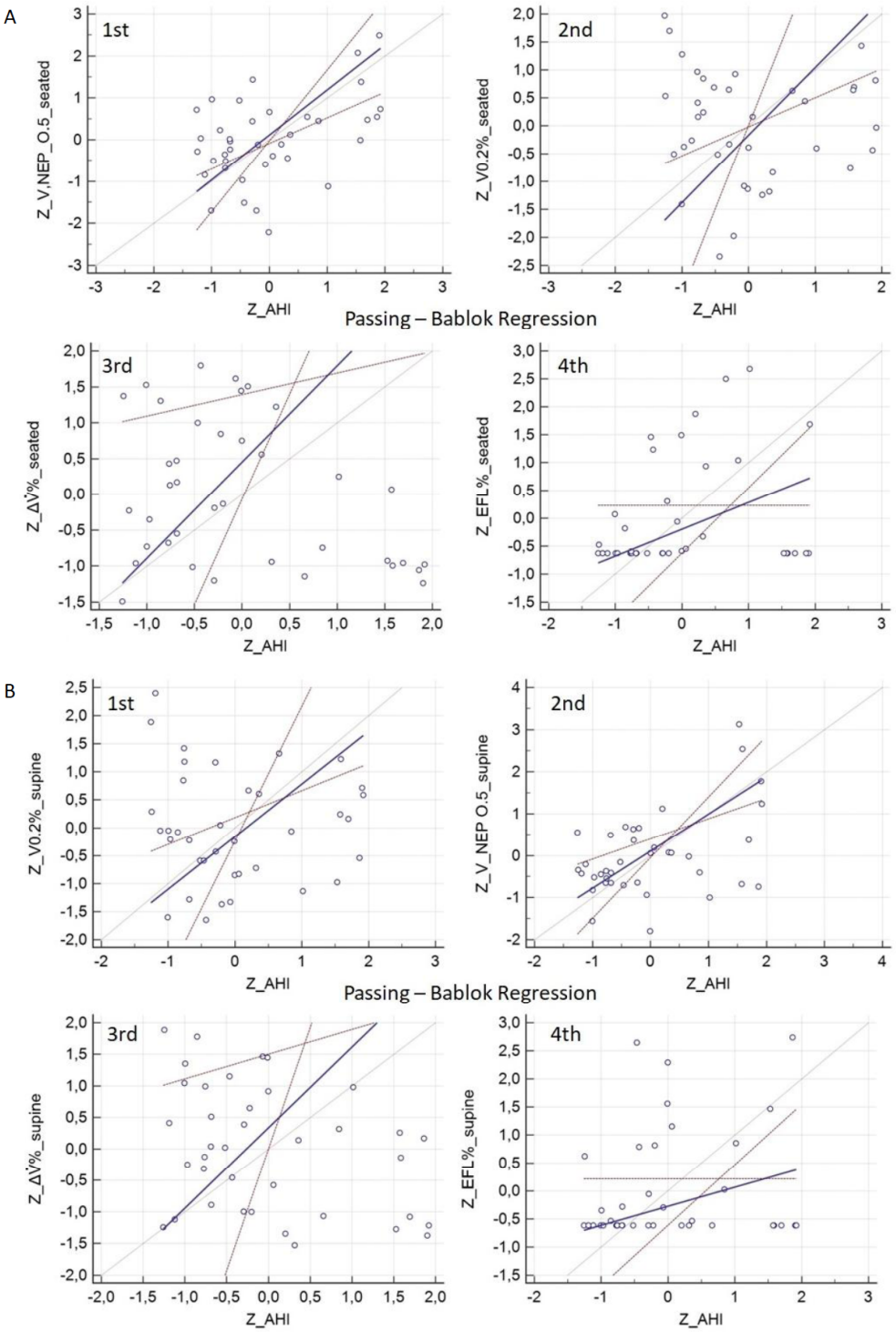

Figure 6: Passing – Bablok Regression in the seated (**A**) and supine (**B**) position.

Z_AHI, Z_EFL%, Z_$\Delta\dot{V}$%, Z_V,NEP0.5, Z_V0.2%: are the z-values of AHI and of the respective NEP-related parameters. Because the NEP technique acquired parameters have a different scale of results than AHI parameter, a typical transformation was necessary, in order to find the z-values. Solid continuous line signifies the Passing and Bablok regression equation. The longest continuous line in every chart, corresponds to the regression equation of the gold standard method (the polysomnography). The two dashed-lines correspond to the confidence interval (95% CI) of the Passing-Bablok regression line.

Evidently, V0.2 % can better separate disease from health than V, $NEP_{0.5}$ or $\Delta\dot{V}$ % in our study. V0.2 % is also better than $\Delta\dot{V}$ % to separate disease from health in other studies [23]. In contrast, there is no statistical significant difference between V0.2 % and AHI, in our study [21-23].

Apart from that, other factors could affect NEP Technique's ability to predict AHI. The authors assume

that there could be a difference between pre- and post-PSG NEP measurements due to the "swelling" because of snoring of the pharyngeal walls during sleep. This would cause severe instability of the pharynx immediately after waking up than at pre-PSG. A number of indirect data from other studies lead us to this hypothesis. Redistribution of the extracellular fluid in the supine position may also cause airway narrowing in the awake subject with OSAS and the non-obese subject without OSAS [24-25]. Diuretic use in OSAS with a coexisting diastolic heart failure improves AHI, as well as, the oropharyngeal junction area during tidal breathing in the awake state [26]. Overnight rostral fluid shift [27] in both heathly non-obese and OSAS non-obese men correlates strongly with AHI by increasing the neck circumference (NC) during sleep. Time spent sitting in the awake state, correlates positively with AHI [27].

Interestingly, subgroup analysis has shown that V0.2 % does correlate in our study to AHI in non-obese subjects, in both seated (r =-0,504, p=0,039) and supine (r =-0,518, p=0,033) positions but not in obese subjects. Inversely, $\Delta\dot{V}\%_{se}$ (r=-0,470, p=0,032), V, $NEP_{0.5se}$ (r=0,648, p=0,001), V,$NEP_{0.5su}$(r=0,434, p=0,049) correlated with AHI only in the obese patients in this study. From the perspective of OSAS severity, group B patients correlated V0.2 % to AHI (r=0,390, p=0,049) in the supine position. Whilst, V0.2 % in the seated position, correlated to AHI (r=0,595, p=0,012), only when severe OSAS was considered (AHI>30).

From the present data it is evident that $\Delta\dot{V}$%, V, $NEP_{0.5}$ and V0.2 % had opposite direction of the correlation coefficients compared to the ones described in the other studies [5, 21-23]. In the non-obese subjects in the seated position $\Delta\dot{V}$% and V, $NEP_{0.5}$ did not correlate to AHI. However, these parameters do have correlation coefficients of the same direction as the ones reported in previous various studies [5, 19]. Specifically, V0.2% has the same negative correlation to AHI in non-obese subjects alone as in a previous study [21]. Whilst, when all (both obese and non-obese) subjects are analyzed, V0.2% has a non statistically significant positive correlation to AHI. These observations are unique to our study.

Therefore, we deduce that in our study obesity might be partially responsible for the change of the direction of the correlation coefficients. Firstly, obese controls have an increased expiratory braking due to persistent diaphragmatic activity into early expiration [28], probably in order to compensate for a decreased EELV (End-Expiratory Lung Volume) [29-30]. Secondly, OSAS patients (even the obese ones) have a decreased expiratory braking [31-32] probably because of a decreased cross-sectional area of the pharynx and larynx [33-35] in the awake state. Expiratory braking then decreases, despite the presence of a decreased EELV.

The obese OSAS subjects in our study (as expected) have an increased OSAS (AHI) severity. When OSAS severity (pharyngeal obstruction) increases, decreased expiratory braking causes maximal resting flows to be attained earlier in expiration (as a fraction of the resting breathing total expiratory time). This effect is similar to the one that occurs in case of intrathoracic airway obstruction such as asthma and COPD [36-37]. In this case, earlier maximal resting flows attainment, correlated to the severity of airway obstruction.

Despite the upper airway obstruction, the increase of neural drive in OSAS, causes a normal [38] or increased tidal volume inspired [39]. Hence, the neural drive increases the volume expired up to the time of the peak expiratory flow. Concurrently the decrease of expiratory braking that is found in OSAS causes the pharynx to reach peak expiratory flow earlier. Consequently, peak expiratory flow increases and expiratory flow reserve decreases. An earlier in time and greater in magnitude peak expiratory flow is a sign of pharyngeal stabilization. Therefore in the awake state, it would probably be more difficult to induce EFL by negative pressure application in obese OSAS (because of an increased AHI) in comparison to non-obese OSAS.

We believe that the predominant reason for the change in direction of the correlation coefficients reflects the difference in methods. There are at least 3 differences compared with the other studies. Firstly, the measurements were made immediately post-PSG. Secondly, we used a pneumatic valve with a 60 msec opening time, in comparison to the faster solenoid valve of all other studies [5, 18-23]. And thirdly, all other authors measuring NEP-derived parameters [5, 18-23], apply the negative pressure in the beginning of expiration, when the pharynx is still partially unstable, directly causing EFL [40]. Instead, we manually applied this pressure, starting at the peak expiratory flow, or just before the peak flow.

In the awake state, we suspect that OSAS adults have a stabilized pharynx, partly because of the increased mean inspiratory flow rates (V_T/Ti), tidal

volume (V_T) and total ventilation ($\dot{V}E$) [39]. In our study, there are correlations between $\Delta\dot{V}\%_{su}$ (r=-0,595, p<0,001), V,$NEP_{0.5se}$ (r=0,385, p=0,017), V, $NEP_{0.5su}$ (r=0,719, p<0,001) and V_T, but not between $\Delta\dot{V}\%_{se}$ (r=-0,279, p=0,09) and V_T. In other words, an increase in V_T tends to increase V,$NEP_{0.5}$ and AHI and decrease $\Delta\dot{V}$%, in our study.

Moreover, obesity tends to either not affect or reduce V_T [41-44]. V_T is increased in obese patients with OSAS proving that the impact of OSAS on V_T increase is greater than the impact of obesity on V_T decrease [44]. As a result, all OSAS subjects in the awake state [39] have an increased mouth occlusion pressure ($P_{0.2}$) and a compensatory increase in V_T and in total ventilation ($\dot{V}E$). Thus, expiratory flow reserve (EFR) decreases due to an increase neural drive (which in turn increases V_T), probably in order to maintain the airway patent. Expiratory flow reserve (EFR) also decreases in morbid obesity [45] during resting breathing. It is caused by an increase of expiratory flow, despite a possible decrease in tidal volume. In this case, we speculate that flow increases because the subjects breathe at lower lung volumes (a lower EELV). However, EFL does occur during resting tidal breathing [46-47] in obese subjects with ERV<20% pred, because of tidal small airway closure.

Additionally, OSAS decreases EELV and ERV both dependently and independently of BMI, at least in the pre-obese and obese groups [48-49]. Furthermore, EELV and ERV negatively correlate with AHI [50]. In our study, resting ERV is an important factor for AHI prediction. There is a correlation between ERV,% pred and AHI (n=15, r =-0,526, p=0,044) in non-obese subjects. When ERV,% pred decreases, AHI increases. However, there was no correlation between ERV,% pred and AHI (n=20, r=-0,162, p=0,495) in obese subjects.

In OSAS with/without obesity, the increased elastic load (lung elastic recoil pressure) causes the EELV to decrease, leading to an increased airway resistance (resistive load). Increased resistive load, decreases the EFR. Consequently, it predisposes the lung for tidal small airway closure and EFL [48-49] during resting tidal breathing. Therefore resting breathing mean expiratory flow (V_T/Te) and tidal volume (V_T) are increased in all OSAS subjects in comparison to the control subjects. Whilst, EELV is decreased in OSAS subjects in comparison to the control subjects, during resting breathing.

Concluding, in the first 10% of the expiration, pharyngeal EFL can be elicited by expiratory negative pressure application, due to the decreased pharyngeal cross sectional area (CSA) in OSAS patients in comparison to the controls [40]. EFL results in decreased expired flows and volumes during NEP application. Thus, the correlation coefficients of the regression analysis have a direction as described in the various studies [5, 19, 21-23]. These events occur despite the fact that the subjects have a decreased EFR just before the negative pressure application. Whilst, pharyngeal CSA in OSAS does not differ from the controls, in the rest 80-90% of the expiration [40]. In this case, we presume that expiratory negative pressure application cannot elicit pharyngeal EFL. The lack of EFL results in augmented expired flows and volumes during NEP application because of a decreased EFR during that period. Since there is no EFL, the existence of a decreased EFR during resting breathing is probably the responsible factor for the reversal of the direction of the correlation coefficients of the regression analysis. It may well be that other factors affected our results. It is known that the predominant tidal volume regulator is chemical drive [50]. Chronic exposure to intermittent hypoxia at night, a hallmark of OSAS, might be responsible for the enhanced progressive augmentation (PA) and ventilatory long term facilitation (vLTF) of respiratory motor output likely originating from the carotid bodies [38]. The increased response to hypoxia may be sustained for minutes to hours. The effect is present in both controls and OSAS subjects. There is still observed increased PA and vLTF 30 minutes after the end of the hypoxic episodes.

In comparison to the baseline status (i.e., before the hypoxic episodes begin), there is [38] an increase of total ventilation ($\dot{V}E$) by 56%, of V_T by 78%, and of respiratory frequency (*f*) by 22%. The effect is more potent in OSAS subjects than in control ones ($\dot{V}E$ by 38%, V_T by 30%, *f* by 5%). Also, the ventilatory sensitivity to hypercapnia in the presence of hypoxia was increased in the OSAS subjects compared to control. Increased vLTF is probably the factor responsible for the consistent presence of increased $\dot{V}E$, V_T and *f* in OSAS during resting breathing in the awake state. Therefore, subjects which would undergo NEP technique immediately pre-PSG, should present with decreased tidal volumes, decreased resting peak flows, and $\dot{V}E$ immediately pre-PSG in comparison to being examined immediately post-PSG. Consequently,

the parameters derived from the NEP technique could change values. Furthermore, from the subjects' measurements that would be taken immediately post-PSG, the OSAS subjects should have a greater ventilatory response than control subjects because of vLTF. Thus, NEP technique should be applied in all subjects under the same time frame after waking up and preferably in the morning, because a greater pharyngeal instability is expected in the morning.

The authors attributed the lack of correlation between V0.2% and AHI (n=38) to the timing of negative pressure application. We believe that an early timing of onset (i.e. at less than the first 10% of the expiratory tidal volume) would prove V0.2% to be the NEP parameter with the greatest correlation to AHI. Contrastingly to other studies [18, 51], EFL% had no correlation to AHI in our study. Guillot [4] has proven that EFL was found in only 15% of subjects with OSAS (90% were non-obese). Thus EFL% had low Se (31,4%) and Sp (67,7%) in OSAS prediction. Also [4], EFL% is not a specific to the source of the limitation (intrathoracic or extrathoracic) index. Thus, one of the reasons that we did not find any correlations between EFL% and AHI, could be the fact that we also studied subjects with COPD stage I, asthma, and restrictive lung function testing, which were excluded from the previous studies [5,18-21,23].

Moreover Tamisier [52] revealed that resting breathing EFL during NEP can be either Initial Limitation (IL) corresponding to pharyngeal (extrathoracic) collapse, or End Limitation (EL) corresponding to intrathoracic airway obstruction and/or breathing at a reduced EELV. His method can only be valid if patients with intrathoracic airway obstruction are excluded (lung function with no intrathoracic obstruction). Furthermore, Baydur [53] has demonstrated that EFL quantification using the EFL% and the area under the curve methods, failed to discriminate patients with OSAS from patients with COPD because of interindividual variabilities. Therefore, it seems rational that EFL% had no correlation to AHI in our study.

This study has several drawbacks. Firstly, there were not enough control subjects. Secondly, there were obvious differences in the NEP technique procedure and time of measurement between our study and previous studies. Thirdly, there are no NEP technique studies validating the presence or the absence of OSAS in patients with obstructive and/or restrictive lung function testing. Consequently, more studies are needed to elucidate these points. Nevertheless, MLR models seem to be able to be used as surrogate markers for predicting OSAS.

5. CONCLUSIONS

MLR models including anthropometric data, portable oximetry, ABG analysis, V_T, and NEP technique indices substantially improve Se and Sp. Therefore, they can be used as surrogate markers for predicting the presence of obstructive sleep apnea syndrome.

AUTHORS' CONTRIBUTIONS

N. Koulouris conceived and designed the study. G. Chras conducted the study. G. Chras and N. Koulouris have equally contributed to the thinking, discussing, and finally writing the present paper. M. Alchanatis and C. Roussos contributed in lengthy discussions during the writing of the paper and made constructive criticisms. Alexandra Manolessou performed the statistical analysis.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

ABBREVIATION

ABG	= Arterial Blood Gas Analysis
AHI	= Apnea/Hypopnea Index
AUC	= Area Under the Curve
BMI	= Body Mass Index
COPD	= Chronic Obstructive Pulmonary Disease
DLCO/VA% adj	= Adjusted diffusion for ventilation, %
EEG	= Electroencephalography
EFL	= Expiratory Flow Limitation during tidal breathing

EELV = End-Expiratory Lung Volume

EFR = Expiratory Flow Reserve

ERV,% pred = Expiratory Reserve Volume % predicted

FA = Factor Analysis

NC = Neck Circumference

MLR = Multiple Linear Regression

NEP = Negative Expiratory Pressure Technique

OSAS = Obstructive Sleep Apnea Syndrome

$Pa0_2$ = Arterial Oxygen Tension

PSG = Polysomnography

$Sa0_2\%_{se}$ = $Sa0_2$% (arterial oxygen saturation) in the seated position

$Sa0_2\%_{su}$ = $Sa0_2$% (arterial oxygen saturation) in the supine position

SD = Standard Deviation

Se = Sensitivity

Sp = Specificity

$\dot{V}E$ = Total ventilation

V_{Tse} = inspiratory Tidal Volume in seated position

V_{Tsu} = inspiratory Tidal Volume in supine position

VT/Ti = Mean inspiratory flow rate

WC = Waist Circumference

EFL%, $\Delta\dot{V}$ %, V,NEP $_{0.5}$, V0.2% = Parameters (indices) measured and calculated from the application of Negative Expiratory Pressure Technique, either in the seated ($_{se}$) or in the supine($_{su}$) position

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