ORIGINAL ARTICLE

Paradoxical reaction of blood pressure on sleep apnoea patients treated with Positive Airway Pressure

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Abstract
Introduction: Obstructive Sleep Apnoea Syndrome (OSAS) patients may develop hypertension and Positive Airway Pressure (PAP) is an effective treatment in blood pressure (BP) control.
Objectives: Analyse a hypertensive OSAS population with unexpected BP rise after PAP usage and verify correlations between BP rise, either with OSAS severity index or nocturnal ventilatory support compliance.
Methods: Descriptive, retrospective analysis of 30 patients with PAP treated OSA, for one year, on average, and with previous controlled hypertension, who developed a rise in BP, defined as augmentation of > 5 mmHg in systolic (SBP) and/or diastolic BP (DBP), after PAP usage. Co-relational analysis of BP increase, with OSAS severity indexes and therapy compliance, using Pearson coefficient.
Results: Of 508 consecutive patients followed in our Department, treated with nocturnal ventilatory support, 30 evolved with BP rise after initiating treatment (age 58 – 10.8 years; Apnoea-Hypopnoea Index [AHI], 46.1 – 18.68). After PAP usage, mean blood pressure (MBP), Systolic BP (SBP) and Diastolic BP (DBP) variation was 16 15 mmHg, 20 – 25 mmHg and 6 – 19.4 mmHg, respectively. No patient showed significant BMI increase. Epworth Sleepiness Scale (ESS) value decreased 8.9 5.48 points. MBP, SBP and DBP variations were not correlated with P90/P95, residual AHI, leaks or PAP compliance.
Conclusions: No specific characteristics were identified in the group who developed a rise in BP with PAP usage. No correlations were found between rises in BP and OSAS severity indexes or PAP compliance. Neither BMI nor variation in wakefulness status explained the rise in BP. Studies relate polymorphisms of b1-adrenoreceptors with different BP responses to ventilatory support. More studies are needed to clarify the cause of this paradoxical response.

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Reacªo paradoxal da pressªo arterial ao tratamento com pressªo positiva
na via aØrea em doentes com apneia do sono

Resumo

Introduªo: Doentes com sndrome de Apneia Obstrutiva do Sono (SAOS) podem desenvolver hipertensªo arterial (HTA) sendo a pressªo positiva na via aØrea (PAP) um tratamento e caz no controlo da pressªo arterial (PA).

Objectivos: Analisar uma populaªo de doentes com SAOS que desenvolveu aumento inesperado da PA aps o uso de PAP e veri car a existŒncia de correlaıes entre o aumento da PA, quer com os ndices de gravidade da SAOS, quer com a adesªo ao tratamento com suporte ventilatrio nocturno.

MØtodos: AnÆlise retrospectiva e descritiva de 30 doentes com SAOS e hipertensªo previamente controlada, tratados com PAP, em mØdia durante um ano, que desenvolveram um aumento da pressªo arterial, de nida como aumento de 5mmHg na Pressªo Arterial Sistlica (PAS) e/ou Diastlica (PAD), aps instituiªo de terapŒutica PAP.

AnÆlise correlativa do aumento da PA com os ndices de gravidade da SAOS e com a adesªo ao tratamento, utilizando o coe ciente de Pearson.

Resultados: De 508 doentes consecutivos seguidos no nosso Departamento, tratados com suporte ventilatrio nocturno, 30 evoluram com aumento de PA aps o incio do tratamento (idade 58 anos (SD 10.8), ndice de Apneia-Hipopneia (IAH) 46.1 (SD 18.68)).

Aps o uso de PAP, a variaªo da Pressªo Arterial MØdia (PAM), da PAS e da PAD foi, respectivamente, de 16mmHg, 20mmHg e 6 mmHg (SD: 15.0; 25.0; 19,4).

Nenhum doente mostrou aumento signi cativo de ˝ndice de Massa Corporal (IMC). O valor da Escala de SonolŒncia de Epworth (ESE) diminuiu 8,9 pontos (SD 5,48).

As variaıes de PAM, PAS e PAD nªo se relacionaram com P90/P95, IAH residual, fugas ou adesªo a PAP.

Conclusıes: Neste grupo que desenvolveu um aumento da PA com o uso de PAP nªo se identi caram caractersticas espec cas. Nªo foram encontradas correlaıes entre os aumentos da PA, nem com os ndices de gravidade de SAOS nem com a adesªo PAP.

Nem a variaªo do IMC nem do wakefulness status explicaram o aumento da PA.

Estudos tŒm relacionado polimor smos dos adrenoreceptores b_1 com diferentes respostas da PA ao suporte ventilatrio.

Mais estudos sªo necessÆrios am de clari car a causa desta reacªo paradoxal.

Introduction

Obstructive Sleep Apnoea Syndrome (OSAS) has a high prevalence. It affects 24 % of middle-aged men and 9 % of middle-aged women,[1] and is symptomatic in 4-2 %, according to gender.[2] Eighty ve per cent of the clinically signi cant and treatable OSAS has never been diagnosed.[3]

Hypertension is also a great health problem that will affect 29.2 % of the adult population by the year 2025.[4] In 2003, sleep apnoea was recognized as a common and identi able cause of hypertension.[5] About 30 % of patients with hypertension have OSAS and, 50 % of patients with OSAS have hypertension.[3] OSAS may also be a frequent cause of drug resistant hypertension.[6]

In normal sleep, compared to wakefulness, there is a 10-15 % decrease in blood pressure (BP), known as dipping phenomenon, associated with reduction in neural sympathetic traffic (in NREM sleep there is a lower BP, bradycardia and a reduction in cardiac output and systemic vascular resistance).[7]

Mechanisms of the pathophysiology of hypertension in OSAS are: increased sympathetic activity[3] (mostly caused by recurrent nocturnal hypoxia or hypercapnia, sleep fragmentation, or greater falls in pleural pressure due to the increased inspiratory effort[8]); barore ex impairment;[9] endothelial dysfunction;[10] vascular inflammation;[11] and atherosclerotic development.[12]

Several studies have demonstrated that Continuous Positive Airway Pressure (CPAP) is an effective treatment for hypertensive OSAS patients, although some patients are more difficult to control.[3] Recent randomised controlled trials have shown that, compared to controls, CPAP treatment induces BP fall of 3.3 mmHg, with a greater fall of 6.6 mmHg in those on antihypertensive drugs.[13]

However, chronic effects of CPAP treatment are not so clear.[14]

Regarding the effects of antihypertensive drugs on OSAS, it has been reported that, none of the five most commonly used drugs (atenolol, amlodipina, enalapril, losartan and hydrochlorothiazide) showed an effect on overall BP and sleep architecture.[3]

Despite this evidence, we have noticed in our clinical practice that, some of our OSAS patients treated with nocturnal ventilatory support, with previously diagnosed and controlled hypertension, had a paradoxical increase in BP values.

Objectives

The main objective was to analyse general characteristics of an hypertensive OSAS population with BP rise after PAP usage (age; gender; body mass index (BMI); smoking habits, alcohol and caffeine consumption; comorbidities and therapeutics).

The second one was to verify whether there was any correlation between a rise in BP, either with OSAS severity index, or with nocturnal ventilatory support compliance.

Materials and methods

Population

From a universe of 508 patients, diagnosed with OSA, and treated with nocturnal ventilatory support and followed in our Sleep Clinic (Autoadjusting PAP [APAP] or CPAP) for on average one year, we selected 30 patients (28 male and 2 female), who had hypertension which had been diagnosed and controlled and who developed a paradoxical BP reaction to ventilatory treatment, with rising values, measured regularly in each medical appointment in our clinic.

Sleep study

All patients were diagnosed using an overnight cardio-respiratory domicilliary sleep study with a five-channel recording device (Alphascreen; Vyasis, Hoechberg-Germany). This device produces a computerized recording of variations in oronasal airflow (measured by nasal cannula), body position, wrist actimetry, pulse rate, arterial oxygen saturation (measured by nger pulse oximetry), thoracic and abdominal respiratory efforts. In all cases, sleep technicians carried out a manual analysis of the recordings, by counting apnoea (episodes of 20 % of previous air ow with at least 10 seconds of duration) and hypopnoea episodes (episodes showing 20 to 50 % of the previous air ow, with at least 10 seconds of duration joined with a 4 % dip in oxygen saturation), dividing the total number of these episodes by the sleep time in hours, thus obtaining the manual apnoea-hypopnoea index. [15]

Blood pressure

We have defined a rise in BP as an augmentation of 5 mmHg in systolic and/or diastolic BP, measured by manual sphygmomanometer.

Resting BP was measured in the sitting position, after 5-min rest, using a manual sphygmomanometer, and an appropriate sized cuff was tted to the non-dominant arm. The rst and last Korotkoff sounds were used to determine systolic and diastolic BP, respectively. We have registered the baseline values and those recorded on subsequent visits to our laboratory.

Treatment

All subjects were under APAP (n = 27) or CPAP (n= 3), the latter titrated manually during an in-lab polysomnography, when APAP were not effective (AHI > 5/h under APAP), for home treatment. All had a minimum of 3 months effective treatment (> 70 % days; > 4 h/night) with nocturnal ventilation, being 12.7 − 7.3 the mean therapy months.

Ventilators in use were REM STAR Auto (Respironics Inc., Murrysville, PA, USA).

The daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS).

Total hours of CPAP usage were checked with software compatible with ventilators registries; mean daily CPAP use was calculated as total hours divided by number of days with CPAP at home.

Ventilation parameters (Maximum Pressure [PMax], Minimum Pressure [PMin] and Pressure at 90 or 95 % of the time [P90/95]) were registered, when on APAP, allowing the clinicians to verify the stability or not of the disease and the pressure required to treat respiratory events.

BP was controlled at baseline, in all enrolled patients, using: angiotensin converting enzyme inhibitors (ACEi) (32.3 %) (n = 10), CCA (29 %) (n= 9), thiazides and ARA-II (19.4 % each) (n= 6), b-blockers (12.9 %) (n = 4) and diuretics (9.7 %) (n = 3).

Six patients were treated with one antihypertensive drug; seven patients with two; three patients with three and two with more than three. Twelve patients were taking antihypertensive medication irregularly but had, nevertheless, blood pressure values within the normal range, at baseline evaluation.

The most frequent anti-hypertensive drugs association was an ACEi with a thiazide, with or without other anti-hypertensive drug.

In none of the cases was anti-hypertensive treatment changed during the reported follow-up.

Data analysis

Statistical software (version 13.0; SPSS; Chicago, IL) was used for data processing and statistical analysis. Continuous variables were expressed as mean − SD and qualitative variables were expressed as percentage.

The relationship between rises in BP, either with OSAS severity index, or with adhesion to nocturnal ventilatory support, was assessed by Pearson correlation.

Results

Each patient was evaluated in several visits to our laboratory (n = 4.6 − 2.1).

The studied population characteristics are depicted in Table 1.

Seven patients presented moderate OSAS (mean AHI, 24.2 − 3.25) and 24 severe OSAS (mean AHI 51.1− 16.57).

All subjects were under CPAP (n = 3) or APAP (n= 27) for home treatment. All had a minimum of 3 months effective treatment with nocturnal ventilation, 12.7 − 7.3 were the mean months of therapy.

Table 1 Studied population characteristics (n = 30) at baseline

Characteristic	Mean	Std. Deviation	Median
Age	57.9	10.8	59.5
BMI	31.9	4.1	31.2
SBP	150.2	17.4	150
DBP	88.6	20.7	87.5
MBP	135.6	16.3	136
ESS	13.1	5.5	12
AHI	46.1	18.7	43.3
DI	41.8	22.5	36.9
Satmin O_2	70.2	13.4	73

AHI: Hypopnoea Apnoea Index; BMI: Body Mass Index; DBP: Diastolic Blood Pressure (mmHg); DI: dessaturation index; EES: Sleepiness Epworth Scale; MBP: Mean Blood Pressure (mmHg); Satmin 0_2: minimum 0_2 saturation (%); SBP: Systolic Blood Pressure (mmHg).

Regarding the habits of the studied population, 40.1 % had caffeine consumption, with an average 1.5 coffee/day (140 mg of caffeine); 46.9 % presented moderate to heavy alcohol consumption; 31.3 % were smokers, with a mean pack/year of 38 and 12.5 % were ex-smokers.

The most frequently found comorbidities were: dislipidemia in 65.6 %, non-insulin dependent diabetes mellitus (NIDDM) in 18.7 %, hyperuricemia in 18.7 % and other cardiovascular pathology in 15.6 %, namely arrhythmias and left ventricular hypertrophy.

Regarding BP values, before ventilatory support, the mean value of SBP, DBP and mean blood pressure (MBP) were 150.2 – 17.35 mmHg; 88.6 – 20.68 mmHg and 135.6 – 16.28 mmHg, respectively.

Nocturnal ventilatory support data is presented in Table 2.

The leaks were at an elevated but acceptable level (30.6 – 16.99 L/min).

The mean value registered for the residual apnoea /hypopnoea index (AHI) was 4.6 – 2.51.

We found a 6 % (30 patients in 508) prevalence of paradoxical BP response to PAP.

BP variation values are showed in Table 3.

Patients treated with b-blockers (in monotherapy or combined) had, on average, the lowest increase either in SBP (18 mmHg) or in MBP (14 mmHg) when compared with patients under other anti-hypertensive drugs. On the contrary those treated with diuretics (in monotherapy or combined) had the highest increase in SBP (51 mmHg), DBP (19 mmHg) and MBP (32 mmHg). However, between groups, there was no statistic signi cance found for this means.

In relation to anti-hypertensive drugs used in the studied patients, BP was controlled prior to nocturnal ventilatory support (in monotherapy or combined) with: angiotensin converting enzyme inhibitors (ACEi) (30 %) (n = 9), CCA (26.7 %) (n = 8), thiazides and ARA-II (20 % each) (n= 6), b-blockers (13.3 %) (n = 4) and diuretics (10 %) (n = 3). Seven patients were treated with two antihypertensive drug; three patients with three and two patients with more than three.

The most frequent association was an ACEi with a thiazide, with or without another anti-hypertensive drug.

MBP, SBP and DBP variations were not correlated with OSAS severity indexes (AHI) or with nocturnal ventilatory support ef cacy (considering residual AHI, P90 or P95, leaks) and compliance (considering % use days, hours/night). (Pearsons correlation coef cients are showed on Table 4).

Discussion

The global features of our hypertensive OSAS population differed to that found in a recent metanalysis, [13] our population was older (mean age 57.9 vs 51.3), with more severe OSAS (mean AHI 46.1 vs 36.2) and with higher BP values (SBP 150.2 vs 130.9 and DP 88.6 vs 80.1).

Nowadays, the prevalence of hypertension is gender similar [16] and prevalence of OSA is 3.2 men for each woman.[17] We found in the studied population a greater predominance of male gender (93.5 %), much higher than expected.

The comorbidities found were those expected in these kinds of patients. [18]

Regarding the baseline BP values, and considering those found in a metanalysis (that included five studies with clinical BP evaluation, using the same manually inflated cuff as we did), [14] mean SBP and mean DBP were 130.9 and 80.1 mmHg, respectively, similar to those found in a 24 h ambulatory BP monitoring (24h ABPM) analysis. [13] Judging by these results, the lack of a 24h-ABPM may not be a signi cant limitation in the present study.

Table 2 PAP compliance (n = 30)

PAP variables	Minimum	Maximum	Mean	Std. Deviation	Median
Pmax APAP	8	20	15.69	2.468	16
Pmin APAP	4	8	4.34	1.035	4
P90/95	6.2	16.5	10.55	2.511	10.1
PAP % Daily use	70	100	92.43	18.362	99.6
PAP hours/night use	4	9	6.58	1.134	6.5
DESS	0	23	8.89	5.479	8.5

DEES: Sleepiness Epworth Scale variation pre- and post- treatment; PAP: Positive Airway Pressure; Pmax APAP: Maximum Pressure in Autoadjusting Positive Airway Pressure (cmH_2O); PminAPAP: Minimum Pressure in Autoadjusting Positive Airway Pressure (cmH_2O); P90/95: Pressure at 90 or 95 % of the time (cmH_2O).

Table 3   Blood pressure variations with PAP usage (n = 30)

BP	Mean	Std. Deviation
SBP2	170.25	23.122
DBP2	94.69	8.939
MBP2	151.44	10.548
DSBP	20.03	25.024
DDBP	6.06	19.396
DMBP	15.87	14.999

BP: Blood Pressure; DBP2: Diastolic Blood Pressure after Positive Airway Pressure usage (mmHg);DDBP: Diastolic Blood Pressure variation after Positive Airway Pressure usage (mmHg); DMBP: Mean Blood Pressure variation after Positive Airway Pressure (mmHg); DSBP: Systolic Blood Pressure variation after Positive Airway Pressure usage (mmHg); MBP2: mean Blood Pressure after Positive Airway Pressure usage (mmHg); SBP2: Systolic Blood Pressure after Positive Airway Pressure usage (mmHg).

Table 4   Pearson correlation coeﬃcient of MBP, SBP and DBP variations (after PAP usage) with residual AHI, P90 or P95, leaks, % use days, hours/night (n = 30)

Analysed variables	DMBP	DSBP	DDBP
AHI			
Pearson Correlation	.354	.054	.058
Sig. (2-tailed)	.05	.772	.759
Residual AHI			
Pearson Correlation	.158	.217	.035
Sig. (2-tailed)	.575	.438	.901
P90/P95			
Pearson Correlation	.033	.061	.362
Sig. (2-tailed)	.868	.757	.059
Leaks			
Pearson Correlation	.008	.257	.18
Sig. (2-tailed)	.979	.375	.537
% use days			
Pearson Correlation	.051	.186	.124
Sig. (2-tailed)	.786	.316	.506
Hours/night			
Pearson Correlation	.175	.065	.253
Sig. (2-tailed)	.346	.73	.169

AHI: Hypopnoea/Apnoea index; DDBP: Diastolic Blood Pressure variation after Positive Airway Pressure usage (mmHg); DMBP: Mean Blood Pressure variation after Positive Airway Pressure (mmHg); DSBP: Systolic Blood Pressure variation after Positive Airway Pressure usage (mmHg); P90/95: Pressure at 90 or 95 % of the time (cmH$_2$O).

The authors could not ﬁnd a correlation between the OSAS severity indexes and the BP values but, on SBP and DBP, the values were not far from statistical signiﬁcance. So, we can speculate that if the sample had been bigger the correlation could have existed.

Compliance to therapy was very good, with a mean daily use superior to that found to be cardiovascular protective [10,19,20] and a concordant improvement in subjective daytime sleepiness (ESS decreased 8.9 points). Also the treatment was effective as residual AHI was under 5/h.

We can state that the increases in BP observed in this population cannot be explained by under treatment, bad compliance or changes in anti-hypertensive drugs as they did not occur.

The data obtained for the ﬁnal BP values showed a greater increase in SBP than DBP. We already knew that long-term CPAP treatment was more likely to re-establish the normal circadian dipping pattern of patients rather than inﬂuence the DBP change.[9]

Also, the lowest increase of BP was on patients treated with b-blockers. So, we may hypothesize that, in our group, there is a paradoxical response of the adrenergic sympathetic system to PAP. Also, the existing polymorphisms in the b1-adrenoceptor gene described by others [21] may be involved. Although in the Cardiovascular Health Study no effect of the Arg16Gly and Gln27Glu polymorphisms on BP was shown, the R389R polymorphism may have a functional role in the treatment response of OSAS patients. [20] Nevertheless, in Borgels study, the DBP of OSAS patients treated with CPAP for 6 months were reduced signiﬁcantly only in Gly389 carriers. [22]

These results are not yet explained. Further studies are needed in this direction and our ﬁndings, despite the small sample size, of this paradoxical effect on BP, on PAP OSAS treated patients, may be of great value, revealing a need for a more profound search and investigation.

We would like to comment on limitations of this study: 24 BPM would probably be a more accurate method than manual punctual BP measurement but we used a number of determinations (n = 4.6), on different days, for a mean of 12.7 months of follow up to establish the paradoxical BP response to PAP, so the effects of a single measurement are diluted.

Also, we did not perform a polysomnography study with PAP usage in order to exclude the existence of arousals that could maintain activation of the sympathetic system during the night, apart from PAP therapy. However, we can speculate about the effectiveness of the PAP treatment with these patients, as they show a low residual AHI and a good clinical response shown by the improvement in ESS.

Conclusions

In our speciﬁc population there was a high prevalence of paradoxical BP response to PAP in male gender.

No other speciﬁc characteristics were identiﬁed in this sub-group of patients with OSAS and hypertension and no correlation was established between BP variations, OSAS severity indexes or treatment compliance.

Patients under b-blockers showed a smaller increase in BP values when compared to the others.

Some studies relate genetic polymorphisms of b1-adrenoreceptors R389G with different responses to anti-hypertensive treatment in patients with OSAS and ventilatory support.

More studies are needed to clarify the cause of the paradoxical response of BP in these patients.

Conflict of interest

Authors declare that they dont have any conflict of interest.

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