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Arterial bicarbonate is associated with hypoxic burden and uncontrolled hypertension in obstructive sleep apnea - The ESADA cohort

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ABSTRACT

Objective: Blood bicarbonate concentration plays an important role for obstructive sleep apnea (OSA) patients to maintain acid-base balance. We investigated the association between arterial standard bicarbonate ([$HCO3^-$]) and nocturnal hypoxia as well as comorbid hypertension in OSA.

Methods: A cross-sectional analysis of 3329 patients in the European Sleep Apnea Database (ESADA) was performed. Arterial blood gas analysis and lung function test were performed in conjunction with polysomnographic sleep studies. The 4% oxygen desaturation index (ODI), mean and minimum oxygen saturation (SpO_2), and percentage of time with SpO_2 below 90% (T90%) were used to reflect nocturnal hypoxic burden. Arterial hypertension was defined as a physician diagnosis of hypertension with ongoing antihypertensive medication. Hypertensive patients with SBP/DBP below or above 140/90 mmHg were classified as controlled-, uncontrolled hypertension, respectively.

Results: The [$HCO3^-$] level was normal in most patients (average 24.0 ± 2.5 mmol/L). ODI, T90% increased whereas mean and minimum SpO_2 decreased across [$HCO3^-$] tertiles (ANOVA, $p = 0.030$, <0.001, <0.001, and <0.001, respectively). [$HCO3^-$] was independently associated with ODI, mean SpO_2, minimum SpO_2, and T90% after adjusting for confounders (β value [95%CI]: 1.21 [0.88−1.54], −0.16 [-0.20 to −0.11], −0.51 [-0.64 to −0.37], 1.76 [1.48−2.04], respectively, all $p < 0.001$). 1 mmol/L elevation of [$HCO3^-$] was associated with a 4% increased odds of uncontrolled hypertension (OR: 1.04 [1.01−1.08], $p = 0.013$).

Conclusion: We first demonstrated an independent association between [$HCO3^-$] and nocturnal hypoxic burden as well as uncontrolled hypertension in OSA patients. Bicarbonate levels as an adjunctive measure provide insight into the pathophysiology of hypertension in OSA.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder

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affecting over 1 billion people worldwide [1]. Patients with OSA are, to a variable extent, exposed to intermittent nocturnal hypoxia/reoxygenation in addition to transient increases in CO_2 during sleep [2]. In general, arousal from sleep and a transient augmentation of ventilation during the post apnea/hypopnea phase acts to prevent accumulation of CO_2 and to maintain a steady-state homeostasis of CO_2 [3]. Impaired ventilatory responsiveness at post-event period may cause CO_2 retention and lead to renal bicarbonate elevation during wakefulness which contributes to the development of daytime hypercapnia [4–7]. Serum bicarbonate ≥28 mmol/L was shown to improve the specificity of the STOP-Bang questionnaire for OSA diagnosis in a preoperative patient cohort [8]. We recently demonstrated that daytime arterial standard bicarbonate ([$HCO3^-$]) in patients with diagnosed OSA was increased along with sleep apnea severity [9]. In this cohort, there was also an interesting association between high [$HCO3^-$] and hypertension. Although the exact mechanism of the link was not fully understood, it was speculated that OSA caused blood gas derangements may chronically increase sympathetic activity via the rostral ventrolateral medulla and the locus coeruleus contributing to blood pressure elevation in OSA [10].

CO_2, a waste product during cellular respiration, is rapidly removed from tissue following hydration into a bicarbonate ion. This reaction is catalyzed by the enzyme carbonic anhydrase (CA) and blood bicarbonate is transported to the lungs for dehydration back to CO_2, which is released for exhalation. Further, renal acid-base homeostasis involves an important regulation of hydrogen ions by bicarbonate production and reabsorption in the kidneys, another mechanism regulated by CA [11]. Finally, bicarbonate may neutralize acids like lactic acid and ketones which are generated by other processes such as hypoxemia [12]. Our previous studies on [$HCO3^-$] did not systematically explore a potential relationship between [$HCO3^-$] and nocturnal hypoxia in patients with OSA. The purpose of the current study was therefore to investigate the association between [$HCO3^-$] and various markers of hypoxia conventionally used in sleep studies and to further explore a possible link between [$HCO3^-$] and uncontrolled hypertension in OSA. We hypothesized that, in a large pan European sleep apnea cohort, [$HCO3^-$] would be associated with the severity of nocturnal hypoxia and that a higher [$HCO3^-$] concentration might be a predictor of associated uncontrolled hypertension.

2. Methods

2.1. Study population

The European Sleep Apnea Database (ESADA) is a large ongoing sleep apnea patient registry including 37 sleep centers from 20 countries [13]. Patients with suspected OSA and aged between 18 and 80 years old are reported to a web-based platform. Information including anthropometrics, lifestyle (e.g. smoking), medical history, concomitant medication (all ongoing medications according to the Anatomical Therapeutic Chemical [ATC] Classification System), blood biochemistry and lung function test are collected [13]. The severity of OSA is assessed according to clinical sleep study routines practiced at each participating center [14]. The ESADA protocol was approved by the local ethical committee at each participating center. Informed consent was collected from all participants.

We used the information extracted from the ESADA database in December 2019. At that point in time a total of 30235 patients with a baseline visit at the sleep center were derived. In order to minimize the methodological variation, only patients with data from an arterial blood gas analysis and a polysomnography (PSG) recording were included in the study (n = 4342). Patients with a diagnosis of alveolar hypoventilation and/or respiratory failure (arterial blood gas $PO_2 \leq 8.0$ kPa and/or $PCO_2 \geq 6.5$ kPa in wakefulness) were excluded (n = 193). In addition, 820 patients were excluded from the analysis, due to missing anthropometric information, missing blood test, or incomplete data from the lung function test. The final cross-sectional analysis included 3329 patients from nine ESADA centers (Fig. 1).

2.2. Definition of hypertension, lung function test and arterial blood gas analysis

Arterial hypertension was defined as patients having a physician-based diagnosis of hypertension and ongoing antihypertensive medication (ATC code C). Hypertensive patients with office systolic/diastolic blood pressure ≥140/90 mmHg were classified as uncontrolled hypertension [15]. Lung function test was performed during daytime at the baseline visit before the sleep study. Arterial blood gas sampling was obtained from the radial artery in the morning/afternoon in a seated/supine position during room air breathing before the sleep study. PaO_2, $PaCO_2$, pH and standard [$HCO3^-$] were calibrated each morning and analyzed according to clinical routines.

2.3. Sleep study

The detailed information of PSG study in the ESADA has been described previously [14]. In short, PSG studies were performed and analyzed according to AASM criteria [16]. Apnea-hypopnea index (AHI) was calculated as the number of apneas/hypopneas events per hour of total sleep time. Oxygen desaturation index (ODI) was defined as the number of oxygen desaturations of ≥4% per hour of sleep. In addition, mean nocturnal oxygen saturation (SpO_2), minimum SpO_2 and the percentage of sleep time with SpO_2 below 90% (T90%) were derived. OSA severity was defined as non-OSA (AHI<5 n/h), mild (5≤AHI<15 n/h), moderate (15≤AHI<30 n/h) and severe (AHI≥30 n/h).

2.4. Statistics

Statistical analysis was performed in SPSS 24.0 (IBM, Armonk, NY, USA). Data are shown as mean (± standard deviation) or percentage. Chi-square tests were used to compare categorical variables. Differences across OSA severity and [$HCO3^-$] tertiles were

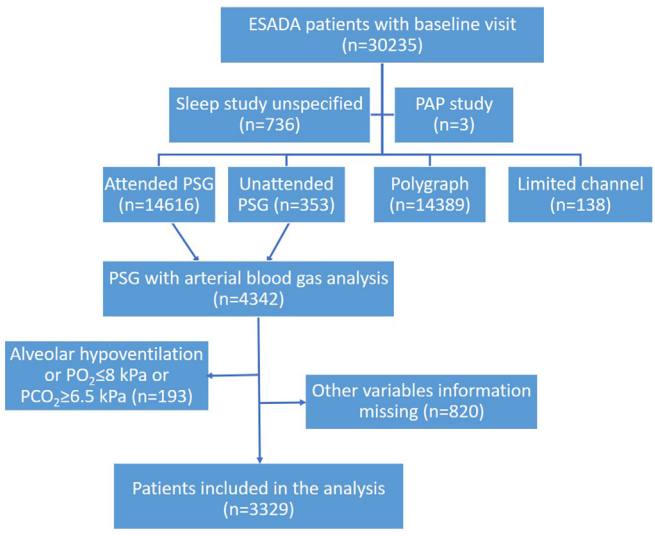

Fig. 1. Study flow chart.

assessed by one-way analysis of variance (ANOVA). Generalized linear models (GLMs) were used to study the associations between [$HCO3^-$] and nocturnal hypoxia markers controlling for anthropometrics, smoking, daytime sleepiness, diuretic medication, study center region, creatinine, lung function and comorbidities. A sensitivity analysis was performed by excluding subjects with diuretics medication. The association between [$HCO3^-$] and arterial hypertension was analyzed using a multivariate generalized binary logistic regression model. An ordinal logistic GLM was conducted to investigate the effect of [$HCO3^-$] by dividing subjects into a normotensive group, a controlled hypertension group (hypertensive patients with office systolic/diastolic blood pressure <140/90 mmHg), and an uncontrolled hypertension group adjusting confounders. Analysis was conducted in complete cases without missing data imputation. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

A total of 3329 patients were included in the analysis (73% men, age 52 ± 12 years, body mass index [BMI] 32.9 ± 6.6 kg/m^2, AHI 38 ± 28 n/h). The prevalence of hypertension, cardiac failure, hyperlipidemia, diabetes and chronic obstructive pulmonary disease (COPD) was 38%, 4%, 39%, 22% and 8%, respectively. Compared to ESADA patients excluded from the analysis, the current cohort had slightly higher proportion of male patients, higher BMI, more severe OSA, and higher prevalence of comorbidities (E-supplement, e-table1).

3.2. Sleep apnea, nocturnal hypoxia and [$HCO3^-$]

The mean [$HCO3^-$] was 24.0 ± 2.5 mmol/L in the total population and the [$HCO3^-$] in the severity classes non-OSA, mild, moderate and severe OSA defined by AHI thresholds was 24.1 ± 2.4, 24.0 ± 2.3, 23.9 ± 2.5, 24.1 ± 2.5 mmol/L, respectively (ANOVA, p = 0.41). ODI and T90% increased, whereas mean and minimum SpO_2 decreased across [$HCO3^-$] tertiles (ANOVA, p = 0.030, <0.001, <0.001, and <0.001, respectively, Table 1). In a generalized linear regression model adjusting for sex, age, BMI, waist circumference, smoking, study site, Epworth sleepiness scale score, creatinine, diuretics use, lung function and comorbidities, [$HCO3^-$] was significantly associated with ODI (β = 1.21 n/h, standard error 0.17, 95%CI [0.88 to 1.54], p < 0.001, Table 2). The independent association between [$HCO3^-$] and ODI remained unchanged after excluding subjects medicated with diuretics (n = 3007, β = 1.26 n/h, standard error 0.18, [0.90 to 1.61], p < 0.001). In addition, increased [$HCO3^-$] was associated with a lower mean and minimum SpO_2, and a higher T90% (all p < 0.001, Table 2).

3.3. Hypertension and [$HCO3^-$]

Overall, patients with a hypertension diagnosis had a higher [$HCO3^-$] compared with the normotensive group (24.2 ± 2.7 vs. 23.9 ± 2.4 mmol/L, p = 0.001). The corresponding [$HCO3^-$] between hypertensive vs. normotensives across OSA severities was non-OSA: 24.0 ± 2.6 vs. 24.1 ± 2.4 mmol/L, p = 0.82; mild OSA: 23.8 ± 2.4 vs. 24.0 ± 2.2 mmol/L, p = 0.32; moderate OSA: 24.1 ± 2.7 vs. 23.8 ± 2.4 mmol/L, p = 0.11; severe OSA 24.3 ± 2.7 vs. 23.9 ± 2.4 mmol/L, p < 0.001, respectively. In a generalized binary logistic regression model adjusting for sex, age, BMI, waist circumference, smoking, study site, Epworth sleepiness scale score, cardiac failure, diabetes, hyperlipidemia, COPD, creatinine, diuretics use, forced vital capacity, forced expiratory volume in 1 s and ODI, a 1 mmol/L elevation of [$HCO3^-$] was associated with a 4% increased risk of arterial hypertension (odds ratio: 1.04, 95%CI [1.00–1.08], p = 0.038).

Patients were further classified into normotensive, controlled and uncontrolled hypertension status respectively. The [$HCO3^-$] level was increased in the normotensive, controlled hypertension, and uncontrolled hypertension group in a dose-dependent manner, 23.9 ± 2.4, 24.0 ± 2.6, 24.4 ± 2.7 mmol/L, respectively (ANOVA, p < 0.001, Table 3). The differences between normotensive/hypertensive and normotensive/controlled hypertension/uncontrolled hypertension patients in [$HCO3^-$] were most pronounced in those with an ODI≥10 n/h (Fig. 2a and 2b). In an adjusted ordinal GLM, a 1 mmol/L elevation of [$HCO3^-$] was associated with a 4% increased odds of uncontrolled hypertension (1.04 [1.01–1.08], p = 0.013).

4. Discussion

In this large Pan-European sleep apnea cohort, we demonstrated an independent association between daytime arterial standard [$HCO3^-$] and various hypoxic variables in PSG recordings. Our results suggest that an elevated [$HCO3^-$] concentration, presumably reflecting hypoventilation by impaired breathing during sleep, was associated with the occurrence of comorbid uncontrolled hypertension in patients with OSA. The exact mechanistic nature of this association remains to be further studied as it may represent a novel pathophysiological trait for hypertension development in OSA [17].

In OSA patients, repeated upper airway obstructions during sleep lead to intermittent hypoxia and metabolic CO_2 retention. Hyperventilation occurs at post obstruction phase unloading CO_2 to maintain the CO_2 homeostasis in conjunction with cortical arousals. A reduction in magnitude and/or duration of post obstruction ventilation may cause acute hypercapnia followed by shifting in acid-base balance (e.g. respiratory acidosis) [6,18]. Consequently, this leads to the compensatory renal retention of [$HCO3^-$] and excretion of [H^+]. If the excretion of [$HCO3^-$] is slow, the elevation of [$HCO3^-$] may be persistent [4]. On the other hand, elevated [$HCO3^-$] may blunt the change in pH for a given change in PCO_2 resulting in a blunted ventilatory response in OSA – a mechanism claimed to be involved in the development of obesity hypoventilation syndrome [19,20]. Finally, hypoxia is conventionally considered as the major blood-gas derangement in patients with OSA. The production of acids like lactic acid and ketones, generated in tissue during intermittent hypoxemia, may cause increased production of bicarbonate in the kidneys and will therefore influence the associations reported in the current study [21,22]. In fact, [$HCO3^-$] was associated with all considered sleep related hypoxic markers, in particular the T90%, in patients with OSA. Although we may not claim causality in the current cross-sectional analysis, we argue that an elevated [$HCO3^-$] not only represents a risk factor for development of daytime hypercapnia, but may also reflect short term or extended hypercapnia in OSA patients [5,23]. [$HCO3^-$] may therefore be considered as a potential biomarker in OSA, for instance, in two-stage screening strategies [8,24]. Future protocols addressing [$HCO3^-$] concentration in relation to OSA severity, in relation to OSA endotype or in relation to the prevalence of comorbidity in patients with sleep disordered breathing are warranted.

In this study, elevation of [$HCO3^-$] was significantly associated with arterial hypertension, specifically uncontrolled hypertension, after extensively controlling for confounders including ODI. Earlier reports from the ESADA cohort found that the ODI, but not the AHI, was independently associated with prevalent hypertension [25]. Our current observation provides additional evidence on this association and further on a potential mechanism related to the acid-base balance in the pathogenesis of hypertension in OSA [10]. Such

Table 1
Patient characteristics across standard bicarbonate tertiles.

	Total population (n = 3329)	[HCO_3^-] Tertile 1 ≤ 23 mmol/L (n = 1199)	[HCO_3^-] Tertile 2 > 23–25 mmol/L (n = 1224)	[HCO_3^-] Tertile 3 > 25 mmol/L (n = 906)	P value (ANOVA)
Male (%)	73	70	76	74	**0.002**
Age (yrs)	52 (12)	51 (12)	51 (11)	54 (12)	**<0.001**
Body mass index (kg/m^2)	32.9 (6.6)	33.3 (6.5)	32.5 (6.4)	32.9 (6.9)	**0.011**
Waist (cm)	111 (14)	112 (14)	110 (14)	112 (16)	**0.039**
Smoking (%)	29	30	30	26	0.084
European region (%)					
Central	26	13	31	36	**<0.001**
East	8	8	9	8	
South	66	80	59	56	
Epworth sleepiness scale	10 (5)	10 (5)	11 (5)	10 (5)	0.55
Creatinine (μmol/L)	80 (18)	79 (20)	80 (17)	80 (17)	0.69
Diuretic medication (%)	10	9	8	13	**<0.001**
Hypertension (%)	38	36	35	43	**0.001**
Diabetes (%)	22	26	18	21	**<0.001**
Hyperlipidemia (%)	39	34	40	42	**0.001**
Cardiac failure (%)	4	5	3	4.0	0.059
COPD (%)	8	7	8	9	0.21
Total sleep time (min)	351 (75)	350 (67)	354 (78)	347 (81)	0.11
Sleep efficiency (%)	79 (14)	80 (13)	79 (15)	78 (15)	**0.016**
Apnea hypopnea index (n/h)	38 (28)	38 (27)	38 (28)	39 (28)	0.60
Oxygen desaturation index (n/h)	32 (29)	31 (27)	31 (29)	34 (30)	**0.030**
Mean SpO_2 (%)	93 (4)	93 (4)	93 (4)	92 (4)	**<0.001**
Lowest SpO_2 (%)	79 (11)	80 (10)	80 (11)	78 (11)	**<0.001**
Time under SpO_2 90 (%)	15 (23)	11 (19)	14 (23)	20 (28)	**<0.001**
pH	7.44 (0.51)	7.42 (0.03)	7.43 (0.03)	7.46 (0.98)	0.16
PaO_2 (kPa)	11.3 (1.6)	11.7 (1.8)	11.3 (1.5)	10.9 (1.5)	**<0.001**
$PaCO_2$ (kPa)	4.8 (0.6)	4.3 (0.5)	4.9 (0.3)	5.3 (0.4)	**<0.001**
FVC (L)	4.0 (1.2)	3.9 (1.1)	4.1 (1.1)	4.0 (1.3)	**<0.001**
FEV_1 (L)	3.1 (0.9)	3.1 (0.9)	3.2 (0.9)	3.1 (1.0)	**<0.001**

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; [HCO_3^-] = standard arterial bicarbonate; SpO_2 = oxygen saturation.

Table 2
Fully adjusted multivariate generalized linear models for predictions of markers of hypoxic burden.

	Oxygen desaturation index (n = 3329)		Mean SpO_2 (n = 3324)		Minimum SpO_2 (n = 3316)		SpO_2 under 90% in percentage (n = 3258)	
	β value [95% CI]	P value	β value [95% CI]	P value	β value [95% CI]	P value	β value [95% CI]	P value
[$HCO3^-$] (mmol/L)	1.21 [0.88–1.54]	**<0.001**	-0.16 [-0.20 to −0.11]	**<0.001**	-0.51 [-0.64 to −0.37]	**<0.001**	1.76 [1.48–2.04]	**<0.001**
Men vs. women	9.51 [7.04–11.98]	**<0.001**	-0.95 [-1.30 to −0.60]	**<0.001**	-2.84 [-3.85 to −1.83]	**<0.001**	4.47 [2.34–6.59]	**<0.001**
Age (years)	0.02 [-0.07 − 0.11]	0.69	-0.04 [-0.05 to −0.02]	**<0.001**	-0.05 [-0.09 to −0.02]	**0.005**	0.21 [0.13–0.29]	**<0.001**
Body mass index (kg/m^2)	0.69 [0.43–0.95]	**<0.001**	-0.11 [-0.15 to −0.07]	**<0.001**	-0.29 [-0.40 to −0.18]	**<0.001**	0.50 [0.27–0.72]	**<0.001**
Waist (cm)	0.52 [0.40–0.64]	**<0.001**	-0.05 [-0.07 to −0.03]	**<0.001**	-0.11 [-0.16 to −0.06]	**<0.001**	0.35 [0.24–0.45]	**<0.001**
Smoker vs. non-smoker	2.97 [1.18–4.75]	**0.001**	-0.40 [-0.65 to −0.14]	**0.002**	0.28 [-0.45 − 1.01]	0.45	2.99 [1.47–4.52]	**<0.001**
European region								
East vs. Central	27.78 [24.56–31.00]	**<0.001**	-1.42 [-1.87 to −0.96]	**<0.001**	-7.90 [-9.24 to −6.56]	**<0.001**	7.06 [4.05–10.06]	**<0.001**
South vs. Central	17.94 [15.71–20.17]	**<0.001**	-1.21 [-1.52 to −0.89]	**<0.001**	-3.59 [-4.50 to −2.67]	**<0.001**	7.35 [5.45–9.25]	**<0.001**
Epworth sleepiness scale	0.51 [0.37–0.66]	**<0.001**	-0.07 [-0.09 to −0.05]	**<0.001**	-0.22 [-0.28 to −0.16]	**<0.001**	0.51 [0.38–0.63]	**<0.001**
Hypertension	0.20 [-1.71 − 2.10]	0.84	0.13 [-0.15 − 0.40]	0.37	0.45 [-0.34 − 1.23]	0.26	1.03 [-0.60 − 2.67]	0.22
Cardiac failure	-0.45 [4.70–3.80]	0.84	0.29 [-0.32 − 0.89]	0.35	0.95 [-0.79 − 2.70]	0.29	0.33 [-3.31 − 3.96]	0.86
Diabetes	0.22 [-1.87 − 2.30]	0.84	-0.23 [-0.52 − 0.07]	0.14	-0.45 [-1.30 − 0.41]	0.31	-1.38 [-3.16 − 0.41]	0.13
Hyperlipidemia	2.73 [1.06–4.40]	**0.001**	-0.28 [-0.51 to −0.04]	**0.023**	-0.45 [-1.14 − 0.24]	0.20	3.05 [1.62–4.49]	**<0.001**
COPD	-1.55 [-4.67 − 1.56]	0.33	-0.41 [-0.85 − 0.03]	0.068	1.04 [-0.24 − 2.31]	0.11	12.92 [10.25–15.60]	**<0.001**
Diuretic medication	-4.50 [-7.61 to −1.38]	**0.005**	0.05 [-0.39 − 0.50]	0.82	-0.76 [-2.04 − 0.53]	0.25	-4.18 [-6.87 to −1.48]	**0.002**
Creatinine (μmol/L)	0.001 [-0.046 − 0.048]	0.96	-0.001 [-0.008 − 0.005]	0.69	-0.003 [-0.023 − 0.016]	0.75	0.020 [-0.021 − 0.060]	0.34
pH	-0.45 [-1.97 − 1.06]	0.56	0.01 [-0.20 − 0.23]	0.92	0.07 [-0.55 − 0.69]	0.83	-0.83 [-2.11 − 0.46]	0.21
FVC (L)	-4.06 [-6.39 to −1.73]	**0.001**	0.27 [-0.06 − 0.61]	0.11	1.45 [0.49–2.41]	**0.003**	-3.69 [-5.69 to −1.68]	**<0.001**
FEV_1 (L)	3.24 [0.36–6.11]	**0.027**	-0.13 [-0.54 − 0.28]	0.52	-0.85 [-2.03 − 0.33]	0.16	4.06 [1.59–6.54]	**0.001**

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; [$HCO3^-$] = standard bicarbonate; SpO_2 = oxygen saturation.

mechanisms may include modification of peripheral vascular control by mechanisms related to direct vascular effects, central chemosensory- or altered autonomic vascular control [26,27]. Our results are also in keeping with a recent study in an OSA cohort demonstrating that CA enzyme activity was increased in patients with hypertension compared to normotensive controls [28]. Additionally, there are several studies demonstrating that acetazolamide (a CA enzyme inhibitor) not only modifies breathing, but also attenuates the elevation of blood pressure associated with an ascent to high altitude [29,30]. Given the link between [$HCO3^-$] and

Table 3
Patient characteristics in normotensive, controlled hypertension, and uncontrolled hypertension groups (n = 3240).

	Normotensive (n = 2035)	Controlled hypertension (n = 629)	Uncontrolled hypertension (n = 576)	P value (ANOVA)
Male (%)	76.9	65.8	71.2	**<0.001**
Age (yrs)	48.3 (11.3)	57.9 (9.9)	58.2 (10.4)	**<0.001**
Body mass index (kg/m^2)	31.8 (6.4)	34.7 (6.8)	34.8 (6.0)	**<0.001**
Waist (cm)	109 (14)	115 (14)	116 (13)	**<0.001**
Smoking (%)	32.5	24.0	21.9	**<0.001**
Epworth sleepiness scale	10.4 (5.4)	10.5 (5.3)	10.8 (5.5)	0.24
Systolic blood pressure (mmHg)	130 (16)	123 (9)	149 (12)	**<0.001**
Diastolic blood pressure (mmHg)	78 (11)	72 (9)	84 (11)	**<0.001**
Creatinine (μmol/L)	79 (16)	81 (21)	82 (20)	**<0.001**
Cardiac failure (%)	2.4	6.8	7.5	**<0.001**
Diabetes (%)	11.8	38.6	36.6	**<0.001**
Hyperlipidemia (%)	30.9	48.5	53.8	**<0.001**
COPD (%)	5.5	12.2	12.2	**<0.001**
Total sleep time (min)	358 (69)	336 (79)	342 (90)	**<0.001**
Sleep efficiency (%)	80.9 (13.4)	75.5 (15.1)	75.6 (15.7)	**<0.001**
Apnea hypopnea index (n/h)	35.7 (27.8)	39.7 (26.5)	44.9 (26.5)	**<0.001**
Oxygen desaturation index (n/h)	28.5 (28.8)	35.6 (27.8)	40.6 (28.9)	**<0.001**
Mean SpO_2 (%)	93.1 (3.7)	92.0 (3.7)	91.7 (3.7)	**<0.001**
Lowest SpO_2 (%)	80.5 (10.4)	78.0 (10.2)	76.3 (11.4)	**<0.001**
Time under SpO_2 90 (%)	11.3 (20.7)	19.8 (26.6)	21.2 (26.1)	**<0.001**
pH	7.43 (0.03)	7.43 (0.03)	7.48 (1.23)	0.081
PaO_2 (kPa)	11.6 (1.6)	11.0 (1.6)	10.8 (1.6)	**<0.001**
$PaCO_2$ (kPa)	4.8 (0.6)	4.7 (0.6)	4.9 (0.6)	**<0.001**
[$HCO3^-$] (mmol/L)	23.9 (2.4)	24.0 (2.6)	24.4 (2.7)	**<0.001**
FVC (L)	4.3 (1.1)	3.5 (1.1)	3.6 (1.1)	**<0.001**
FEV_1 (L)	3.4 (0.9)	2.7 (0.8)	2.8 (0.9)	**<0.001**
FEV_1/FVC ratio (%)	79.0 (7.7)	78.4 (7.5)	78.3 (7.9)	0.074

Mean (SD); COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; [$HCO3^-$] = standard arterial bicarbonate; SpO_2 = oxygen saturation.

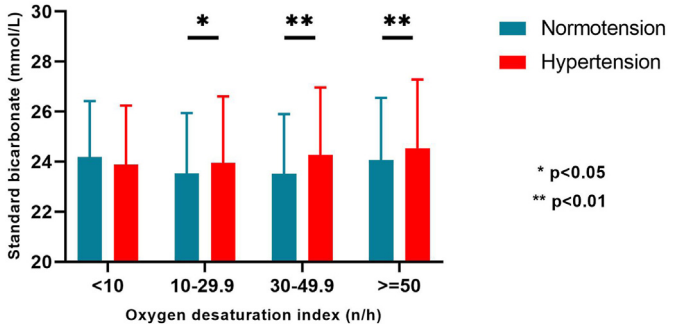

Fig. 2a. Standard bicarbonate and hypertension status stratified by 4% oxygen desaturation index class (student t-test). Bar represents mean and standard deviation.

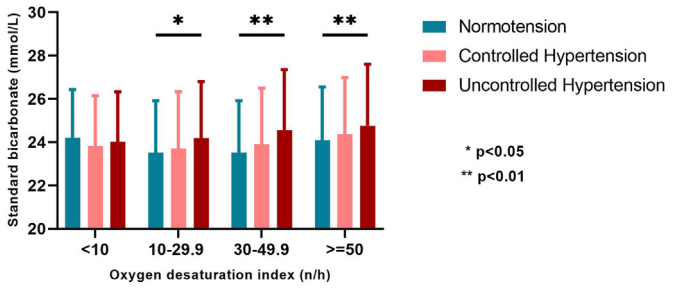

Fig. 2b. Standard bicarbonate, controlled/uncontrolled hypertension by 4% oxygen desaturation index class (ANOVA test). Bar represents mean and standard deviation.

CA activity, it is possible that the current association reflects the potential role of CA in OSA related hypertension. Finally, an elevated [$HCO3^-$] without hypercapnia has been suggested as an early marker of obesity related hypoventilation [31–33]. Although we excluded patients with manifest daytime hypercapnia from our analysis, two third of patients were obese in the current cohort. It is therefore possible that elevated [$HCO3^-$] in our study may have mirrored comorbid obese condition as well as an associated increased cardiovascular risk (e.g. preclinical obesity hypoventilation syndrome) [34].

There is a need to identify companion biomarkers of OSA that contribute to phenotyping patients and guide their personalized management [35]. Understanding disease traits and clinical/physiological phenotypes could improve the personalized diagnostics as well as the initiation of a tailored therapy for OSA patients [36]. As a pivotal factor in the acid-base balance, [$HCO3^-$] is easily monitored but has yet not been systematically studied in OSA. Indeed [$HCO3^-$] is sensitive to various influences (e.g. renal function), and is therefore not well suited as a stand-alone biomarker for OSA diagnostics. Nevertheless, once the OSA diagnosis is established, [$HCO3^-$] may be used as a physiological trait to sub-classify patients (e.g. diminished ventilatory responsiveness) or even as a marker for pharmacological treatment response (drug with CA inhibitory properties) [37–39]. For this purpose, venous bicarbonate which closely mirrors [$HCO3^-$] in the arterial blood gas analysis is less invasive and easy to assess in the clinic [40].

The current study has several strengths and limitations. This is the largest clinical cohort study addressing the link between [$HCO3^-$], nocturnal hypoxia and uncontrolled hypertension in OSA patients without daytime hypercapnia. To our knowledge, one study reported an association between nocturnal percentage of SpO_2 under 90% and increased [$HCO3^-$] in chronic kidney disease patients [41]. Only patients that underwent PSG were included in the study and a considerable number of confounding factors were adjusted in the analysis. The extent of hypoxemia from PSG findings was not used as a selection criterion. [$HCO3^-$] was used as a linear rather than a categorical variable in our analysis in order to reflect the physiologic change of [$HCO3^-$] in patients [42]. Another strength of the study includes a strict hypertension definition

which was based on the combination of medical history and antihypertensive medications [25]. It is considered as a limitation that 24-h blood pressure recordings were not obtained and this may have led to underdiagnosis of masked nocturnal hypertension [15]. Arterial blood gas analysis and lung function tests were scheduled in either the morning or the afternoon depending on local routines at ESADA centers. Information regarding significant renal impairment was not available. The use of diuretics, a drug class which may have prominent effects on the [$HCO3^-$] concentration, was adjusted in the analysis. Indeed, other medications may also have influenced the acid-base balance and [$HCO3^-$] concentrations [43]. Finally, renal [$HCO3^-$] excretion rate and CA enzyme activity were not assessed [4,44]. Whether additional mechanisms contribute to elevation of [$HCO3^-$] in OSA needs to be investigated in future studies.

5. Conclusion

We demonstrated that [$HCO3^-$] concentration was associated with nocturnal hypoxia and an increased risk of comorbid uncontrolled hypertension in eucapnic OSA patients. A higher bicarbonate via reduction of ventilatory responsiveness aggravates nocturnal hypoxia, may lead to persistent elevated blood pressure in hypertensive patients with sleep apnea. We propose that elevated bicarbonate may characterize a specific subgroup of OSA patients with a modified chemosensory function and altered hemodynamic control that may be specifically targeted [45]. Studies addressing blood bicarbonate level as an endotypic biomarker in OSA are warranted.

CRediT authorship contribution statement

Ding Zou: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Ludger Grote:** Conceptualization, Investigation, Resources, Data curation, Writing – original draft. **Ozen K. Basoglu:** Investigation, Resources, Data curation, Writing – review & editing. **Johan Verbraecken:** Investigation, Resources, Data curation, Writing – review & editing. **Sophia Schiza:** Investigation, Resources, Data curation, Writing – review & editing. **Pawel Sliwinski:** Investigation, Resources, Data curation, Writing – review & editing. **Paschalis Steiropoulos:** Investigation, Resources, Data curation, Writing – review & editing. **Carolina Lombardi:** Investigation, Resources, Data curation, Writing – review & editing. **Holger Hein:** Investigation, Resources, Data curation, Writing – review & editing. **Jean-Louis Pépin:** Investigation, Resources, Data curation, Writing – review & editing. **Gianfranco Parati:** Investigation, Resources, Data curation, Writing – review & editing. **Walter T. McNicholas:** Investigation, Resources, Data curation, Writing – review & editing. **Jan Hedner:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft, Supervision, Funding acquisition. **P. Steiropoulos:** Investigation, Resources. **J. Verbraecken:** Investigation, Resources. **E. Petiet:** Investigation, Resources. **Georgia Trakada:** Investigation, Resources. **I. Fietze:** Investigation, Resources. **T. Penzel:** Investigation, Resources. **Ondrej Ludka:** Investigation, Resources. **I. Bouloukaki:** Investigation, Resources. **S. Schiza:** Investigation, Resources. **W.T. McNicholas:** Investigation, Resources. **S. Ryan:** Investigation, Resources. **R.L. Riha:** Investigation, Resources. **J.A. Kvamme:** Investigation, Resources. **L. Grote:** Investigation, Resources. **J. Hedner:** Investigation, Resources. **D. Zou:** Investigation, Resources. **Dirk Pevernagie:** Investigation, Resources. **S. Bailly:** Investigation, Resources. **J.L. Pépin:** Investigation, Resources. **R. Tamisier:** Investigation, Resources. **H. Hein:** Investigation, Resources. **O.K. Basoglu:** Investigation, Resources. **M.S. Tasbakan:** Investigation, Resources. **J. Buskova:** Investigation, Resources. **P. Joppa:** Investigation, Resources. **R. Staats:** Investigation, Resources. **Dries Testelmans:** Investigation, Resources. **Haralampos Gouveris:** Investigation, Resources. **K. Ludwig:** Investigation, Resources. **C. Lombardi:** Investigation, Resources. **G. Parati:** Investigation, Resources. **M.R. Bonsignore:** Investigation, Resources. **Francesco Fanfulla:** Investigation, Resources. **M. Drummond:** Investigation, Resources. **M. van Zeller:** Investigation, Resources. **W. Randerath:** Investigation, Resources. **Marcel Treml:** Investigation, Resources. **Z. Dogas:** Investigation, Resources. **R. Pecotic:** Investigation, Resources. **A. Pataka:** Investigation, Resources. **S. Mihaicuta:** Investigation, Resources. **U. Anttalainen:** Investigation, Resources. **T. Saaresranta:** Investigation, Resources. **P. Sliwinski:** Investigation, Resources.

Declaration of competing interest

DZ, OKB, JV, SS, P. Sliwinski, P. Steiropoulos, CL, HH, JLP, GP, and WTM declare no competing interests related the current work. LG reports grants from Bayer, Philips Respironics Foundation, ResMed Foundation for the ESADA network during the conduct of the study. JH reports grants from ResMed, Respironics, European Respiratory Society and Bayer, during the conduct of the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.11.041.

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