Independent associations between arterial bicarbonate, apnea severity and hypertension in obstructive sleep apnea

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Abstract

Background: Obstructive sleep apnea is characterized by intermittent hypoxia and hypercapnia. CO2 production, transport and elimination are influenced by the carbonic anhydrase enzyme. We hypothesized that elevated standard bicarbonate, a proxy for increased carbonic anhydrase activity, is associated with apnea severity and higher blood pressure in patients with obstructive sleep apnea.

Methods: A retrospective analysis of a sleep apnea cohort (n = 830) studied by ambulatory polygraphy. Office systolic/diastolic blood pressure, lung function, and arterial blood gases were assessed during daytime.

Results: Arterial standard bicarbonate was increased with apnea severity (mild/moderate/severe 24.1 ± 1.8, 24.4 ± 1.7 and 24.9 ± 2.9 mmol/l, respectively, Kruskal-Wallis test p < 0.001). Standard bicarbonate was independently associated with apnea hypopnea index after adjustment for sex, age, body mass index, smoking, alcohol, hypertension, pO2 and pCO2 (standard bicarbonate quartile 1 vs. quartile 4, β = 1.06, p < 0.001). Log-transformed standard bicarbonate was associated with a diagnosis of hypertension or diastolic blood pressure but not systolic blood pressure adjusting for cofounders (p = 0.007, 0.048 and 0.45, respectively).

Conclusions: There was an independent association between sleep apnea severity and arterial standard bicarbonate. The link between high standard bicarbonate and daytime hypertension suggests that carbonic anhydrase activity may constitute a novel mechanism for blood pressure regulation in sleep apnea.

Keywords: Acid base, Blood pressure, Carbonic anhydrase, Hypercapnia, Obstructive sleep apnea
association between CA activity and blood pressure controlling mechanisms [7, 8]. Hypertensive OSA patients reduced blood pressure in response to pharmacological inhibition of CA [9] and acetazolamide partially prevented blood pressure elevation in OSA patients moving from low- to high altitude [10]. Whether the surrogate for CA activity, \( \text{StHCO}_3 \), is associated with hypertension in OSA patients independent of sleep apnea severity has never been investigated. In the current study, we aimed to address the association between \( \text{StHCO}_3 \) and OSA activity as well as to examine a possible link between \( \text{StHCO}_3 \) and hypertension.

**Methods**

**Study population and protocol**

The study cohort (\( n = 1656 \)) consisted patients successively referred to the Marburg Sleep Disorders Center between 1989–1992 due to clinical symptoms of sleep related breathing disorder [11]. Patients were systematically investigated to study the relationship between OSA, lung function and hypertension. In detail, anthropometric data such as age, sex, body mass index (BMI) were collected. Alcohol consumption, smoking habits along with signs of sleep disorder, such as excessive daytime sleepiness, snoring and insomnia were also recorded. In addition, a medical history including clinical diagnoses and concomitant medication, with particular focus on known and/or treated hypertension, was obtained. Daytime arterial blood samples for determination of blood gases, including \( \text{StHCO}_3 \), were collected. A home sleep study and lung function test using full body plethysmography (Jäger, Würzburg, Germany) were undertaken. All patients gave their written consent for participation in the study according to the contemporary regulations for medical research at the Marburg University, Marburg, Germany in 1989–1992.

**Exclusion criteria for data analysis**

Three hundred ninety six patients were excluded from the analysis due to missing anthropometric data (\( n = 210 \)), blood gas data (\( n = 163 \)), lung function test data (\( n = 20 \)) and sleep data (\( n = 3 \)). Patients with obesity hyperventilation syndrome (\( n = 38 \), defined as BMI > 30 kg/m\(^2\) with a \( \text{pCO}_2 \) > 6 kPa), chronic obstructive pulmonary disease, defined as the ratio of forced expiratory volume in 1 s to forced vital capacity of less than 0.70, were excluded (\( n = 163 \)). In addition, 12 respiratory failure patients with arterial blood gas \( \text{pO}_2 \) ≤ 8.0 kPa and/or \( \text{pCO}_2 \) ≥ 6.5 kPa were excluded. Finally, non-OSA patients with apnea hypopnea index (AHI) <5 n/h were excluded from the analysis (\( n = 217 \)) and a total of 830 patients were included in the data analysis (Fig. 1).

**Blood pressure, blood gas and blood sample assessment**

Systolic (SBP) and diastolic (DBP) blood pressures were obtained with the patient in a sitting position after a minimum of 10 minutes rest, between 9.00 and 11.00 a.m., using the World Health Organization standard protocol [12]. Heart rate defined as beats per minute was determined in the sitting position by pulse wave palpation. Blood samples were obtained at the morning following an overnight fast. A blood gas analysis (samples obtained at noon) was performed using a RADIOMETER*-gas analyzer (Radiometer, Copenhagen, Denmark).

**Definition of hypertension**

Hypertension was defined as patients with a previous positive history of diagnosed hypertension and/or on ongoing hypertensive medication. Normotension was defined as patients with no previous hypertensive medical history and no ongoing anti-hypertensive treatment.

**Sleep study**

All patients underwent unattended home monitoring of nocturnal breathing on two consecutive nights using the MESAM 4 polygraphy device (MAP®, Munich, Germany). The polygraphy system was applied in the afternoon for a recording span between 6.00 p.m. and 8.00 a.m. Time to bed, lights out, final awakening, longer periods of sleep interruption and estimated sleep time were assessed using a patient diary. The first night was an adaptation night and the AHI value used for calculation in this study was obtained from the second night. Only when the recording was technically insufficient (<10% of recordings) or the subjective sleep time was <5 hours (<1% of recordings), then AHI was obtained from the first night.

The MESAM 4 device records oxygen saturation using finger pulse oximetry, snoring using an electret-miniature microphone placed over the larynx, beat to beat heart rate analysis using ECG, and body position using a circular sensor taped just below the sternum. It is a validated sleep diagnostic instrument for clinical and epidemiological studies [13, 14]. In the current study, apnea hypopnea events were determined visually using the previously described methods of MESAM 4 evaluation [15]. In detail, events were first scored with a concomitant oxygen desaturation of ≥ 4% from baseline. Subsequently, the scorers edited this information by checking the heart rate (significant drop and reduced variability when going to bed, abrupt increase and plateau after final awakening), movement artefacts, and body position signal (e.g. change from upright to supine position). Estimated sleep time was determined based on the information from the sleep diary (time going to bed, lights out, final awakening, lights on, longer periods of sleep interruption). Finally, AHI was calculated as the number of apnea/hypopnea events per hour of edited recording time. OSA severity was defined as...
mild \( (5 \leq \text{AHI} < 15 \text{ n/h}) \), moderate \( (15 \leq \text{AHI} < 30 \text{ n/h}) \) and severe \( (\text{AHI} \geq 30 \text{ n/h}) \).

**Statistics**

Statistical analysis was conducted using IBM SPSS 20 (SPSS Inc, Chicago, USA). Kolmogorov-Smirnov test was used to determine the distribution of the data. Spearman correlation was used to study the association between arterial \( \text{StHCO}_3^- \) and AHI, SBP and DBP. Fisher exact test was used to compare category variables. Depending on data distribution, differences across apnea severity groups and \( \text{StHCO}_3^- \) quartiles were assessed by one-way analysis of variance (ANOVA) or Kruskal-Wallis test. Multivariate generalized linear models were used to address the independent association between \( \text{StHCO}_3^- \), apnea severity and hypertension. \( \text{StHCO}_3^- \) was log-transformed in order to enable parametric statistics. Data are presented as mean ± SD. A \( p \)-value < 0.05 was considered statistically significant.

**Results**

**Study population and blood gas characteristics**

In total 830 patients were included in the study (93.3% men, age 51 ± 10 years, BMI 30 ± 5 kg/m², AHI 32 ± 24 n/h). Hypertension was prevalent in 53.3% of the patients and increased with OSA severity class. Patient characteristics in different OSA severity classes are shown in Table 1. There was a small but significant change in arterial blood gases in higher AHI severity classes. Mean \( \text{pO}_2 \) decreased with approximately 0.5 kPa from mild to severe OSA patients \( (p < 0.001) \). Mean \( \text{pCO}_2 \) increased slightly in patients with severe OSA \( (p = 0.046) \). The pH and lung function values did not change along with severity class of OSA.

**The association between \( \text{StHCO}_3^- \) and sleep apnea**

Arterial \( \text{StHCO}_3^- \) was significantly correlated with \( \text{pCO}_2 \) (Spearman correlation \( r = 0.75, p < 0.001 \), Additional file 1: Figure S1). \( \text{StHCO}_3^- \) increased across OSA severity classes although the mean absolute magnitude of change was moderate (Kruskal-Wallis test, \( p < 0.001 \), Table 1). The association between OSA severity and \( \text{StHCO}_3^- \) was observed in hypertensive OSA patients but not in normotensive OSA patients (Fig. 2). \( \text{StHCO}_3^- \) was positively correlated with AHI (Spearman correlation \( r = 0.16, p < 0.001 \), Additional file 1: Figure S2). Mean AHI increased from 27 ± 21 n/h (\( \text{StHCO}_3^- \) quartile 1) to 39 ± 26 n/h (\( \text{StHCO}_3^- \) quartile 4) in the whole population \( (p < 0.001, \text{Table 2}) \). A similar but
A nonsignificant trend was found in OSA patients without a hypertension diagnosis ($n = 388$, $p = 0.094$, Additional file 1: Table S1). In a generalized linear model controlling for sex, age, BMI, smoking, alcohol consumption, $pO_2$, $pCO_2$ and hypertension status, $\text{StHCO}_3^-$ was independently associated with AHI ($Q1$ vs. $Q4$ $\beta = 10.6$, $p < 0.001$, Table 3).

**Association between $\text{StHCO}_3^-$, hypertension and office blood pressure**

$\text{StHCO}_3^-$ was higher in hypertensive ($n = 442$) compared with normotensive ($n = 388$) patients (24.9 ± 2.7 vs. 24.1 ± 1.9 mmol/l, $p < 0.001$). The percentage of patients with a clinical hypertension diagnosis is 46.8, 49.8, 54.3 and 62.7% respectively across $\text{StHCO}_3^-$ quartiles (Q1 to Q4).

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**Table 1 Patient characteristics across sleep apnea severity**

|                  | Mild $n = 272$ | Moderate $n = 211$ | Severe $n = 347$ | $P$ value (ANOVA) |
|------------------|----------------|-------------------|-----------------|------------------|
| Male sex (%)     | 89 (31%)       | 95 (45%)          | 96 (27%)        | 0.001*           |
| Age (yrs)        | 50 (11)        | 51 (9)            | 52 (9)          | 0.10             |
| Body mass index (kg/m$^2$) | 28 (4)       | 29 (4)            | 32 (6)          | <0.001           |
| Smoking (%)      | 28             | 29                | 28              | 0.98*            |
| Systolic BP (mmHg) | 141 (18)    | 145 (21)          | 152 (22)        | <0.001           |
| Diastolic BP (mmHg) | 91 (12)     | 94 (12)           | 97 (13)         | <0.001           |
| Heart rate (bpm) | 71 (11)        | 71 (10)           | 77 (11)         | <0.001           |
| Hypertension (%) | 40.4 (15.7)    | 51.7 (27.8)       | 64.3 (24.3)     | <0.001*          |
| Apnea hypopnea index (n/h) | 9 (3)       | 22 (4)            | 55 (18)         | <0.001           |
| FEV1/FVC (%)     | 82 (6)         | 81 (5)            | 81 (6)          | 0.33             |
| pH               | 7.41 (0.02)    | 7.42 (0.02)       | 7.42 (0.03)     | 0.075            |
| $pO_2$ (kPa)     | 10.8 (1.0)     | 10.7 (1.0)        | 10.3 (1.0)      | <0.001           |
| $pCO_2$ (kPa)    | 5.06 (0.40)    | 5.07 (0.36)       | 5.13 (0.39)     | 0.046            |
| $\text{StHCO}_3^-$ (mmol/l) | 24.1 (1.8)  | 24.4 (1.7)        | 24.9 (2.9)      | <0.001*           |

*Fisher exact test; †Kruskal-Wallis test; BP = blood pressure; bpm = beat per minute; FEV1/FVC = forced expiratory volume at 1 second interval/forced vital capacity; $pO_2$ = arterial partial pressure of oxygen; $pCO_2$ = arterial partial pressure of carbon dioxide; $\text{StHCO}_3^-$ = arterial standard bicarbonate

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**Fig. 2** Arterial standard bicarbonate concentrations by sleep apnea severity class
Both OSA severity and higher StHCO3 were associated with increased prevalence of hypertension in this population (Fig. 3). In a generalized linear model controlling for sex, age, BMI, smoking, alcohol consumption, pO2, pCO2 and apnea severity, LogStHCO3 was independently associated with a clinical diagnosis of hypertension (β = 8.0, SE 3.0, 95% CI [2.1 – 13.8], p = 0.007, Table 4).

An additional analysis was performed to study the relationship between StHCO3 and office blood pressure. StHCO3 was modestly correlated with SBP and DBP (Spearman correlation, r = 0.10 and 0.12, p = 0.003 and <0.001, respectively). In generalized linear models with SBP and DBP, respectively, as dependent variables, a positive independent association was found between LogStHCO3 and DBP (β = 27.6, SE 14.0, 95% CI [0.2–55.0], p = 0.048) but not with SBP (β = 17.1, SE 22.3, 95% CI [-26.7–60.9], p = 0.45) after adjustment for sex, age, BMI, smoking, alcohol usage, pO2, pCO2 and apnea severity (Additional file 1: Table S2 and S3).

Table 2 Patient characteristics across StHCO3 quartiles (n = 830)

|                | Q1 [17.5–23.2] mmol/l | Q2 [23.3–24.5] mmol/l | Q3 [24.6–25.7] mmol/l | Q4 [25.8–46.1] mmol/l | P value (ANOVA) |
|----------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Male sex (%)   | 92                    | 92                    | 97                    | 93                    | 0.081*          |
| Age (yrs)      | 51 (10)               | 51 (9)                | 49 (9)                | 52 (10)               | 0.058           |
| Body mass index (kg/m²) | 29 (5)                | 30 (5)                | 30 (5)                | 31 (5)                | 0.071           |
| Smoking (%)    | 26                    | 30                    | 33                    | 25                    | 0.27*           |
| Systolic BP (mmHg) | 144 (19)              | 144 (21)              | 147 (22)              | 150 (22)              | 0.006           |
| Diastolic BP (mmHg) | 92 (11)               | 93 (13)               | 95 (13)               | 96 (13)               | 0.005           |
| Heart rate (bpm) | 73 (11)               | 72 (11)               | 73 (11)               | 75 (12)               | 0.065           |
| Hypertension (%) | 46.8                  | 49.8                  | 54.3                  | 62.7                  | 0.007*          |
| Apnea hypopnea index (r/h) | 27 (21)               | 31 (22)               | 30 (24)               | 39 (26)               | <0.001          |
| FEV1/FVC (%)   | 82 (6)                | 81 (6)                | 82 (6)                | 82 (6)                | 0.90            |
| pH             | 7.41 (0.03)           | 7.41 (0.02)           | 7.42 (0.02)           | 7.43 (0.02)           | <0.001          |
| pO2 (kPa)      | 10.9 (1.1)            | 10.6 (0.9)            | 10.6 (1.0)            | 10.2 (1.0)            | <0.001          |
| pCO2 (kPa)     | 4.67 (0.30)           | 5.03 (0.24)           | 5.26 (0.24)           | 5.43 (0.25)           | <0.001          |
| StHCO3 (mmol/l) | 22.0 (1.1)            | 23.9 (0.4)            | 25.2 (0.3)            | 27.2 (2.6)            | -               |

*Fisher exact test; BP blood pressure, bpm beat per minute, FEV1/FVC forced expiratory volume at 1 second interval/forced vital capacity, pO2 arterial partial pressure of oxygen, pCO2 arterial partial pressure of carbon dioxide, StHCO3 arterial standard bicarbonate

(p = 0.007, Table 2). LogStHCO3 and DBP (β = 27.6, SE 14.0, 95% CI [0.2–55.0], p = 0.048) but not with SBP (β = 17.1, SE 22.3, 95% CI [-26.7–60.9], p = 0.45) after adjustment for sex, age, BMI, smoking, alcohol usage, pO2, pCO2 and apnea severity (Additional file 1: Table S2 and S3).

Table 3 Generalized linear model investigating the association between apnea hypopnea index and arterial bicarbonate quartiles controlled for confounding factors

|                | Beta value | Standard error | 95% confidence interval | P-value |
|----------------|------------|----------------|-------------------------|---------|
| Male sex       | 8.28       | 3.03           | 2.35 – 14.21            | 0.006   |
| Age (years)    | 0.12       | 0.08           | -0.05 – 0.28            | n.s.    |
| Body mass index (kg/m²) | 1.45       | 0.16           | 1.14 – 1.76             | <0.001  |
| Smoking        | 4.37       | 1.71           | 1.03 – 7.72             | 0.01    |
| Alcohol        | 2.00       | 1.58           | -1.11 – 5.10            | n.s.    |
| Hypertension   | 4.89       | 1.54           | 1.86 – 7.92             | 0.002   |
| pO2 (kPa)      | -0.36      | 0.10           | -0.57 – -0.16           | 0.001   |
| pCO2 (kPa)     | -0.52      | 0.38           | -1.27 – 0.23            | n.s.    |
| StHCO3 Q2 vs. Q1 | 4.76       | 2.29           | 0.27 – 9.25             | 0.038   |
| StHCO3 Q3 vs. Q1 | 4.34       | 2.67           | -0.90 – 9.57            | n.s.    |
| StHCO3 Q4 vs. Q1 | 10.63      | 3.00           | 4.76 – 16.51            | <0.001  |

Discussion

In this large cross sectional study of a predominantly male clinical sleep apnea cohort, we established an independent association between wake arterial StHCO3 concentration and the intensity of sleep apnea. In addition, there was an independent association between StHCO3 and hypertension as well as daytime office DBP. Our data suggest that mechanisms related to acid-base balance may link to the expression of OSA and its
cardiovascular sequelae. Given the strong inter-correlation between StHCO$_3^-$ and CA activity we speculate that CA activity is involved in blood pressure regulation in OSA patients.

Elevated StHCO$_3^-$ concentration has been used as a marker for hypercapnia in patients with respiratory disorders such as obesity-hypoventilation syndrome (OHS) and pre-clinical OHS [16, 17]. The association between StHCO$_3^-$ and OSA is less well studied. In this study we excluded patients with chronic obstructive pulmonary disease and OHS based on information of a gold-standard evaluation of respiratory function and a blood gas analysis. Our data unequivocally demonstrated a dose dependent association between OSA and daytime arterial StHCO$_3^-$ concentration in this group of patients without a chronic respiratory disorder. Although the magnitude of the StHCO$_3^-$ elevation across the spectrum of OSA severity may be considered as rather limited, the association was statistically significant and remained after extensive control of important confounders. To our knowledge this is the first study to demonstrate this association in a well characterized clinical OSA cohort.

The exact mechanism behind this finding in OSA remains unknown. Severe OSA may lead to mild nocturnal hypercapnia. The long term effect of OSA on PCO$_2$ (i.e. StHCO$_3^-$) is determined by the net change of CO$_2$ over each cycle of apnea/hyperventilation and asymmetry in how the rise and fall of CO$_2$ affects the kidney. It is

![Fig. 3 Prevalence of hypertension by sleep apnea severity and arterial standard bicarbonate quartile](image)

Table 4 Generalized linear model investigating the association between hypertension status and log-transformed arterial bicarbonate controlled for confounding factors

|                      | Beta value | Standard error | 95% confidence interval | P-value |
|----------------------|------------|----------------|-------------------------|---------|
| Male sex             | 0.33       | 0.31           | –0.28 – 0.94            | n.s.    |
| Age (years)          | 0.019      | 0.009          | 0.002 – 0.036           | 0.025   |
| Body mass index (kg/m$^2$) | 0.09 | 0.02 | 0.06 – 0.13 | <0.001 |
| Smoking              | –0.35      | 0.17           | –0.69 – –0.02           | 0.039   |
| Alcohol              | 0.16       | 0.16           | –0.15 – 0.47            | n.s.    |
| Moderate vs. mild OSA| 0.33       | 0.19           | –0.05 – 0.70            | 0.088   |
| Severe vs. mild OSA  | 0.52       | 0.18           | 0.16 – 0.88             | 0.004   |
| PO$_2$ (kPa)         | –0.01      | 0.01           | –0.04 – 0.01            | n.s.    |
| PCO$_2$ (kPa)        | –0.02      | 0.04           | –0.09 – 0.05            | n.s.    |
| LogStHCO$_3^-$       | 7.96       | 2.97           | 2.15 – 13.77            | 0.007   |
likely that changes of CA activity can modulate the transition of obstructive apnea/ventilation cycle and influence the increase in 
StHCO\textsubscript{3}\textsuperscript{-} [18–20]. We therefore propose that transient hypercapnic episodes during sleep in patients with more severe OSA lead to increased renal reabsorption of StHCO\textsubscript{3}\textsuperscript{-} and/or that a chronic increase of StHCO\textsubscript{3}\textsuperscript{-} production [18] is induced by high or possibly even up-regulated CA activity.

StHCO\textsubscript{3}\textsuperscript{-} concentration is known to be influenced by CA enzyme activity. One major function of this enzyme includes the catalysis of the interconversion of bicarbonate and protons into CO\textsubscript{2} and water for subsequent removal of CO\textsubscript{2} via the respiratory apparatus [2]. In OSA, repetitive changes in pCO\textsubscript{2} may induce CA enzyme activity and increase arterial StHCO\textsubscript{3}\textsuperscript{-} concentration. Alternatively, anaerobic metabolism and respiratory acidosis following intermittent hypoxia may induce an increased activity of enzymes and transporters involved in cellular pH regulation and erythrocyte acid-base handling [21]. In this manner both hypercapnia and hypoxia may contribute to increased CA activity in patients with OSA. Along these lines it is worth mentioning that CA enzyme inhibition has been shown to reduce StHCO\textsubscript{3}\textsuperscript{-} concentration in patients with sleep disordered breathing [9, 22, 23] and that we previously have demonstrated an association between CA activity and the severity of OSA [3].

A particularly interesting finding in the current study was the strong association between StHCO\textsubscript{3}\textsuperscript{-} and hypertension status or diastolic blood pressure. It may be argued that this association could be explained by the well-established link between OSA and hypertension [5]. However, our data suggest that StHCO\textsubscript{3}\textsuperscript{-} was linked to hypertension independently of the AHI. Only few studies have addressed the possible association between StHCO\textsubscript{3}\textsuperscript{-} and hypertension. In a population based study of middle-aged non-obese females, lower plasma StHCO\textsubscript{3}\textsuperscript{-} was associated with an elevated incidence of hypertension [24]. A small experimental study of oral sodium bicarbonate induced approximately 5 mmHg reduction of systolic blood pressure [25] whereas other studies did not [26, 27]. However, these studies did not address subjects with the acute blood gas changes that characterize the OSA condition. In fact, our data suggest that the association between hypertension and StHCO\textsubscript{3}\textsuperscript{-} is mainly confined to subjects with severe OSA. As previously stated several different mechanisms, including increased renal re-absorption of StHCO\textsubscript{3}\textsuperscript{-} extended CO\textsubscript{2} loading and/or increased CA activity, could all have increased of StHCO\textsubscript{3}\textsuperscript{-} in OSA [3, 18, 28]. In fact, a positive association between whole blood CA activity and blood pressure has been reported [3]. In addition, CA inhibition by zonisamide in OSA patients reduced both the AHI and the systolic blood pressure [9]. The CA inhibitor acetazolamide and hydrochlorothiazide induced vasodilation by an activation of calcium activated potassium channels [7, 29] or via a modulation of nitric oxide metabolism activity [30]. It cannot be excluded that the increase of StHCO\textsubscript{3}\textsuperscript{-} in our study might have resulted from the effect of hypertension on renal StHCO\textsubscript{3}\textsuperscript{-} reabsorption. However, this is less likely the explanation considering that StHCO\textsubscript{3}\textsuperscript{-} was elevated only in the severe OSA group with hypertension. We therefore propose that increased CA activity in OSA may provide a novel intermediary mechanism for hypertension development in OSA.

Our study has both strengths and limitations. First, this large predominantly male clinical OSA cohort applied a rigorous and unique control of important confounders of StHCO\textsubscript{3}\textsuperscript{-} like arterial blood gas samples and pulmonary function tests. Second, blood pressure and hypertension status were carefully assessed during daytime as part of the study protocol. Sleep disordered breathing was assessed with a contemporary polygraphy recording device on two consecutive nights in order to exclude inaccuracy of the AHI value due to a first night effect [31]. Weaknesses include a lack of quantitative data on overnight hypoxic events like oxygen desaturation in the multivariate analyses. However, nocturnal hypoxic exposure was captured as 4% oxygen desaturation events that were used for computation of AHI. Another weakness in this study is the lack of detailed information on the type of antihypertensive medication. It cannot be excluded that prescribed antihypertensive medication, e.g. diuretics such as hydrochlorothiazide, might have influenced the association between StHCO\textsubscript{3}\textsuperscript{-} and blood pressure although the influence of thiazides on StHCO\textsubscript{3}\textsuperscript{-} is likely to be very limited [32]. Information on CA was not available in this retrospective study. Finally, the cross sectional design of our study does not allow conclusions about the causality of the demonstrated associations.

Conclusions
It is concluded that StHCO\textsubscript{3}\textsuperscript{-} concentration was independently associated with AHI, a hypertension diagnosis and office diastolic blood pressure in OSA patients. The potential causal relationship(s) behind these associations remain unclear. Higher StHCO\textsubscript{3}\textsuperscript{-} was linked to more intense OSA indicating that high or upregulated CA activity is associated with OSA. In addition, StHCO\textsubscript{3}\textsuperscript{-} was associated with hypertension independent of sleep apnea suggesting a novel CA–related mechanism for blood pressure regulation in hypertensive OSA patients.

Additional file
Additional file 1: Table S1. Normotensive patient characteristics across StHCO\textsubscript{3}\textsuperscript{-} quartiles (n = 388). Table S2. Association between LogStHCO\textsubscript{3}\textsuperscript{-} and systolic blood pressure in a generalized linear model. Table S3. Association between LogStHCO\textsubscript{3}\textsuperscript{-} and diastolic blood pressure in a generalized linear model. Figure S1. Relationship between pCO\textsubscript{2} and stHCO\textsubscript{3}\textsuperscript{-} (Spearman correlation). Figure S2. Relationship between apnea hypopnea index and stHCO\textsubscript{3}\textsuperscript{-} (Spearman correlation). (DOCX 107 kb)
Abbreviations
AHI: Apnea hypopnea index; ANOVA: One-way analysis of variance; BMI: Body mass index; CA: Carbonic anhydrase; CO2: Carbon dioxide; DBP: Diastolic blood pressure; OHS: Obesity-hypoventilation syndrome; OSA: Obstructive sleep apnea; SBP: Systolic blood pressure; SHCO3: Bicarbonate

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors’ contributions
DZ, DE and JH contributed to conception and design, analysis and interpretation of data, and the writing of the manuscript. LG contributed to conception and design, acquisition and interpretation of data, and critical review the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
All patients gave their written consent for participation in the study according to the contemporary regulations for medical research (1989–1992) at the Marburg University, Marburg, Germany.

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