Respiratory Physiology & Neurobiology 249 (2018) 47–53

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

The effect of metabolic alkalosis on the ventilatory response in healthy subjects

E. Oppersma[a,b], J. Doorduin[b,c], J.G. van der Hoeven[b], P.H. Veltink[a], H.W.H. van Hees[d], L.M.A. Heunks[b,e,*]

[a] MIRA – Institute for Biomedical Technology & Technical Medicine, University of Twente, Enschede, The Netherlands
[b] Department of Critical Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
[c] Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands
[d] Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, The Netherlands
[e] Department of Intensive Care Medicine, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Physiology
Neural respiratory drive
Posthypercapnic alkalosis
Pulmonary function test

ABSTRACT

Background: Patients with acute respiratory failure may develop respiratory acidosis. Metabolic compensation by bicarbonate production or retention results in posthypercapnic alkalosis with an increased arterial bicarbonate concentration. The hypothesis of this study was that elevated plasma bicarbonate levels decrease respiratory drive and minute ventilation.

Methods: In an intervention study in 10 healthy subjects the ventilatory response using a hypercapnic ventilatory response (HCVR) test was assessed, before and after administration of high dose sodium bicarbonate. Total dose of sodiumbicarbonate was 1000 ml 8.4% in 3 days.

Results: Plasma bicarbonate increased from 25.2 ± 2.2 to 29.2 ± 1.9 mmol/L. With increasing inspiratory CO_2 pressure during the HCVR test, RR, V_t, Pdi, EAdi and V_E increased. The clinical ratio $\Delta V_E/\Delta P_{et}CO_2$ remained unchanged, but Pdi, EAdi and V_E were significantly lower after bicarbonate administration for similar levels of inspired CO_2.

Conclusion: This study demonstrates that in healthy subjects metabolic alkalosis decreases the neural respiratory drive and minute ventilation, as a response to inspiratory CO_2.

1. Introduction

Respiratory centers in the brainstem control the respiratory drive. Among other factors, activity of these respiratory centers is modulated by pH (Feldman et al., 2013). Patients with acute hypoventilation, will develop arterial carbon dioxide (CO_2) retention, and therefore respiratory acidosis. To maintain homeostasis, metabolic compensation via bicarbonate (HCO_3^-) production or retention develops, which will shift plasma pH towards normal. Controlled mechanical ventilation can restore minute ventilation and normalize the CO_2 surplus. The slow adaptation of bicarbonate remaining in the blood may result in posthypercapnic alkalosis (Banga and Khilnani, 2009). This alkalosis may cause a reduced ventilatory response to hypercapnia in patients with moderate to severe chronic obstructive pulmonary disease (COPD), as demonstrated by a decreased response in minute ventilation (V_E) for a given change in end-tidal carbon dioxide ($P_{et}CO_2$) (Nickol et al., 2009). However, Oren and colleagues showed that chronic metabolic acid-base changes do not alter the hypercapnic ventilatory response (HCVR) in 4 healthy subjects (Oren et al., 1991). Because of the limited number of subjects and several methodological issues in that study, uncertainty remains concerning the effect of bicarbonate retention on the ventilatory response (Oren et al., 1991). Electrical activity of the diaphragm (EAdi) has been used to quantify the respiratory drive (American Thoracic Society/European Respiratory Society, 2002; Jolley et al., 2015) and is therefore a useful tool to study the effect of metabolic alkalosis on respiratory drive to the diaphragm.

In the present study, we hypothesize that increased plasma bicarbonate levels result in a decreased respiratory drive and reduced minute ventilation during a HCVR test. To test this hypothesis, we studied the effect of sodium bicarbonate administration on the HCVR and neural respiratory drive, as assessed by electrical activity of the diaphragm, in healthy subjects. Part of this work has previously been presented at the international conference of the European Respiratory Society (Oppersma et al., 2016).

* Corresponding author at: VU University Medical Center Amsterdam, Department of Intensive Care Medicine, Postbox 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: L.Heunks@VUmc.nl (L.M.A. Heunks).

https://doi.org/10.1016/j.resp.2018.01.002
Received 29 September 2017; Received in revised form 7 December 2017; Accepted 3 January 2018
Available online 04 January 2018

2. Materials and methods

2.1. Subject characteristics

Subjects were eligible when meeting the following inclusion criteria: no relevant past medical history, in particular no neurological, respiratory or cardiac disorders reported, no current use of prescribed drugs, age > 18 years, non-smoking, not pregnant and body weight between 60 and 80 kg. The strict weight criterion was set to achieve corresponding levels of arterial bicarbonate with the same dosage of sodium bicarbonate, for each subject. The study was conducted at the Radboud university medical center and the protocol was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki and its later amendments. All subjects gave their written informed consent.

2.2. Study protocol

In this before-after study design, physiological measurements were performed before and after sodium bicarbonate administration.

Arterial blood was obtained through arterial puncture at baseline for bicarbonate and gas analysis using an i-STAT handheld device with EG7+ cartridges (Abbott Point of Care Inc., Princeton, USA). A multi-electrode esophageal catheter with two balloons (NeuroVent Research Inc, Toronto, Canada) was inserted and positioned, as described previously (Doorduin et al., 2012). The ventilatory response to inhaled CO_2 was assessed by a HCVR test (Nickol et al., 2009; Oren et al., 1991); subjects were seated in upright position with uncast abdomen and wearing a nose clip, breathing through a mouthpiece. First, subjects were breathing ambient air via a one-way valve from a reservoir breathing bag, which was continuously filled with ambient air. Thereafter every 2 min the inspiratory CO_2 pressure ($P_{insp}CO_2$) was increased by 1 kPa, by adding CO_2 to the breathing bag. Subjects were instructed to breathe normally and endure the test as long as possible.

After the first part of the measurements, participants were instructed to orally ingest 100 ml of 8.4% sodium bicarbonate solution, thrice daily (7:00 a.m., 2:00 p.m. and 10:00 p.m.) for a total number of 10 doses. This regimen is adopted from previous studies that demonstrated increased plasma bicarbonate (Cohen et al., 2013; Coppoolse et al., 1997; Douroudos et al., 2006; Oren et al., 1991; van de Ven et al., 2002). Within 4 h after the last ingestion initial measurements were repeated. Fig. 1 provides a schematic representation of the study protocol.

2.3. Data acquisition

During the HCVR test, all variables were continuously recorded. EAdi signals were amplified and digitized (Porti 16, 22 bits, 71.5 nV/least significant bit, TMSi; The Netherlands) at a sampling frequency of 2 kHz. CO_2 pressure of the in- and exhaled air was continuously acquired with the NICO cardiopulmonary measurement device (Philips Respironics, The Netherlands). Pressure signals and flow were digitized (Porti 16, 22 bits, 1.4 μV/least significant bit, TMSi; The Netherlands) at a sampling frequency of 2 kHz. Data were stored and buffered on an external drive for offline analysis. Transdiaphragmatic pressure (Pdi) was calculated as Pga – Pes. Tidal volume was obtained by digital integration of the flow signal.

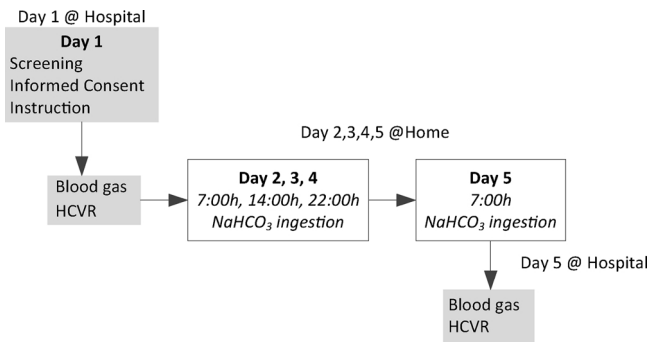

Fig. 1. Schematic description of the protocol.

2.4. Data analysis

Measurement variables were analyzed offline in Matlab R2013a (The Mathworks, Natick, MA).

For every step of $P_{insp}CO_2$ during the HCVR test (both before and after sodium bicarbonate administration), the mean respiratory rate (RR), tidal volume (V_t), minute ventilation (V_E), Pes swings, Pdi, EAdi (as the root mean square of the EAdi signal) and endtidal CO_2 pressure ($P_{et}CO_2$) was calculated during 30 s of stable signal at the end of a period of constant $P_{insp}CO_2$.

The commonly used clinical endpoint of the HCVR test, the ratio between the maximal V_E in respect to its baseline value (ΔV_E) and the maximal $P_{et}CO_2$ in respect to its baseline value ($\Delta P_{et}CO_2$), was calculated (Nickol et al., 2009).

For further analysis only data where all 10 subjects endured the test were analyzed.

Neuromechanical efficiency (NME) is a specific measure for contractile efficiency of the diaphragm; the ability to generate inspiratory pressure for a given neural respiratory effort (NME = Pdi/EAdi) (Doorduin et al., 2017; Doorduin et al., 2012; Liu et al., 2012). Neuroventilatory efficiency (NVE) defines the tidal volume generated for a given neural respiratory effort (NVE = Vt/EAdi) (Liu et al., 2012). Bothe NME and NVE were calculated.

To assess variability in the breathing pattern the coefficient of variation (CV; ratio of standard deviation (SD) to mean) was calculated for EAdi and V_E during 30 s at the start of the HCVR test and 30 s at the last step of $P_{insp}CO_2$ where all 10 subjects endured the test, both before and after sodium bicarbonate administration.

The center frequency of the power spectrum of the EAdi signal (CFdi) was used to assess muscle fiber conduction velocity (Doorduin et al., 2012; Sinderby et al., 2001). The CFdi was calculated during 30 s at the start of the HCVR test and 30 s at the last step of $P_{insp}CO_2$ where all 10 subjects endured the test, both before and after sodium bicarbonate administration.

2.5. Statistics

Statistical analyses were performed with OriginPro 9.1.0 (OriginLab Corporation, Northampton, USA). All values are given in mean ± Standard Error of the Mean (SEM), and $p \leq 0.05$ was considered significant. Descriptive statistics were determined for the subject characteristics. Paired-samples *t*-tests were performed to assess differences between before and after sodium bicarbonate administration for blood gases and breathing parameters, as well as the ratio $\Delta V_E/\Delta P_{et}CO_2$, the maximal achievable $P_{insp}CO_2$, EAdi, CF and CV. The difference between begin and end of the test was also assessed for the CF and CV using a paired-samples *t*-test.

Repeated measures two-way ANOVA was used to analyze within subjects effects of $P_{insp}CO_2$ and bicarbonate and their interaction for all parameters (EAdi, Pes, Pdi, V_E, V_t, RR, neuroventilatory efficiency and neuromechanical efficiency). Tukey post hoc tests were applied when ANOVA showed significant differences between before and after increased bicarbonate levels.

3. Results

3.1. Subject characteristics

Eleven subjects were enrolled in this study, 1 subject withdraw after

Table 1
Subjects' characteristics, blood gas values and baseline breathing in mean of all subjects with standard error of the mean of the paired samples *t*-test. * Significant difference between before and after sodium bicarbonate administration ($p \leq 0.05$).

Subject characteristics			mean ± SEM
Subjects: male/female			7/3
Age (y)			22.5 ± 0.7
Body mass index (kg/m^2)			21.9 ± 0.5
	before	after	p-value
Blood gas values			
$HCO3^-$ (mmol/L)	25.2 ± 0.7	29.2 ± 0.6	0.00*
pH	7.41 ± 0.004	7.44 ± 0.005	0.00*
Pco_2 (kPa)	5.3 ± 0.2	5.7 ± 0.1	0.00*
Na^+ (mmol/L)	139 ± 0.4	142 ± 0.5	0.00*
K^+ (mmol/L)	3.9 ± 0.1	3.8 ± 0.1	0.13
Baseline (breathing ambient air)			
V_E (L/min)	9.9 ± 1.6	9.7 ± 1.3	0.78
$P_{et}CO_2$ (kPa)	4.5 ± 0.3	4.6 ± 0.2	0.65
EAdi (μV)	10.0 ± 1.5	6.4 ± 1.0	0.05*
V_t	934.9 ± 105.6	814.6 ± 63.8	0.21
RR	11.3 ± 1.7	12.5 ± 2.1	0.14
Pes (n = 8/10)	−5.6 ± 1.1	−3.2 ± 0.8	0.01*

the first ingestion of sodium bicarbonate due to abdominal discomfort and 7 other subjects experienced minor abdominal discomfort but could complete the study. Subject characteristics and blood gas are presented in Table 1. This table also demonstrates the effects of sodium bicarbonate administration on plasma HCO_3^-, pH, pCO_2, Na^+ and K^+.

3.2. Ventilatory response

Flow, $P_{insp}CO_2$, $P_{et}CO_2$ and EAdi were recorded for every subject during both HCVR tests before and after sodium bicarbonate administration. Means of all parameters were calculated for every step of $P_{insp}CO_2$ as described in the methods section.

3.2.1. HCVR test

A representative response to inspiration of CO_2 during the HCVR test is shown in Fig. 2. The inspiratory CO_2 is represented by the minimum values of the CO_2-curve for each breath, expiratory CO_2 by the maximum values of the curve for each breath. Increasing inspiratory CO_2 results in an increase in ventilation, EAdi and flow, to clear the excess CO_2. An example of V_E as a function of $P_{insp}CO_2$ and $P_{et}CO_2$ for 1 subject during the HCVR test is shown in Fig. 3.

3.2.2. Sodium bicarbonate administration

While breathing ambient air at baseline, EAdi decreased after sodium bicarbonate administration ($p = 0.05$, Table 1). V_E and $P_{et}CO_2$ were not affected by sodium bicarbonate administration.

The commonly used clinical measure for the HCVR ($\Delta V_E/\Delta P_{et}CO_2$) did not change after sodium bicarbonate administration (Table 2). There was no significant difference between before and after sodium bicarbonate administration in maximal achievable $P_{insp}CO_2$, although the paired samples *t*-test shows a trend to increase from 6.7 kPa before to 7.3 kPa at after sodium bicarbonate administration ($p = 0.06$) and accordingly the V_E max did increase (Table 2).

The maximal $P_{insp}CO_2$ level where all subjects still endured the test was 5 kPa, so further analysis was restricted to $P_{insp}CO_2$ from 0 kPa to 5 kPa.

Both the ratio and the separate parameters of the clinical endpoint of the HCVR test (ΔV_E and $\Delta P_{et}CO_2$), as mean for all subjects until a $P_{insp}CO_2$ of 5 kPa, did not change after sodium bicarbonate administration (Table 2).

However, Fig. 4 shows that both EAdi ($p = 0.03$) and V_E ($p = 0.03$) significantly decreased after bicarbonate administration. Tukey post hoc tests showed that the difference between before and after sodium bicarbonate administration was significant within a level of $P_{insp}CO_2$ of 4 and 5 kPa. As a result of elevated levels of $P_{insp}CO_2$, RR ($p = 0.00$), V_t ($p = 0.00$), EAdi ($p = 0.00$) and V_E ($p = 0.00$) all increased (Fig. 4). Pes data was excluded for 2 subjects due to noise in the signal. Pes significantly decreased after bicarbonate administration ($p = 0.01$), according to Tukey's post hoc test within a level of $P_{insp}CO_2$ of 4 and 5 kPa. Due to noise in the Pdi signal, 4 subjects were excluded from further analysis regarding Pdi and NME. Pdi significantly decreased after bicarbonate administration ($p = 0.05$), within a level of $P_{insp}CO_2$ of 4 and 5 kPa according to the Tukey post hoc test. Pdi also increased as a result of elevated levels of $P_{insp}CO_2$ ($p = 0.01$). There was an interaction between $P_{insp}CO_2$ and bicarbonate administration for V_E ($p = 0.04$) and V_t ($p = 0.01$).

NVE was not significantly influenced by increasing inspiratory CO_2 levels, but did increase after sodium bicarbonate administration (Fig. 5). NME showed a significant decrease due to increasing $P_{insp}CO_2$, but only between 2 and 5 kPa. NME was not influenced by sodium bicarbonate administration (Fig. 5).

The coefficient of variation of EAdi and V_E did not change within the tests (begin test versus $P_{insp}CO_2$ of 5 kPa), or between before and after sodium bicarbonate administration (Table 2). This implies that the CV was not influenced by increased bicarbonate levels.

The center frequency of diaphragm did not change within the tests (begin test versus $P_{insp}CO_2$ of 5 kPa) or between before and after sodium bicarbonate administration (Table 2), implying there is no change in muscle fiber conduction velocity due to the increased bicarbonate. This could however be analyzed for respectively 9 and 8 subjects due to noise in the signal.

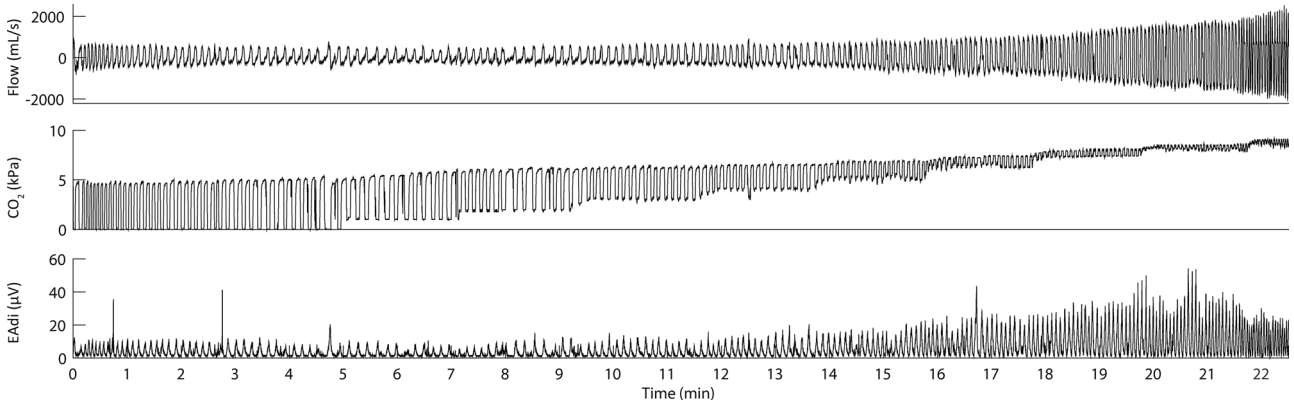

Fig. 2. Flow, CO_2 and EAdi tracings during a HCVR test. Inspiratory CO_2 is given by the minimum values of the curve for each breath, expiratory CO_2 by the maximum values of the curve for each breath.

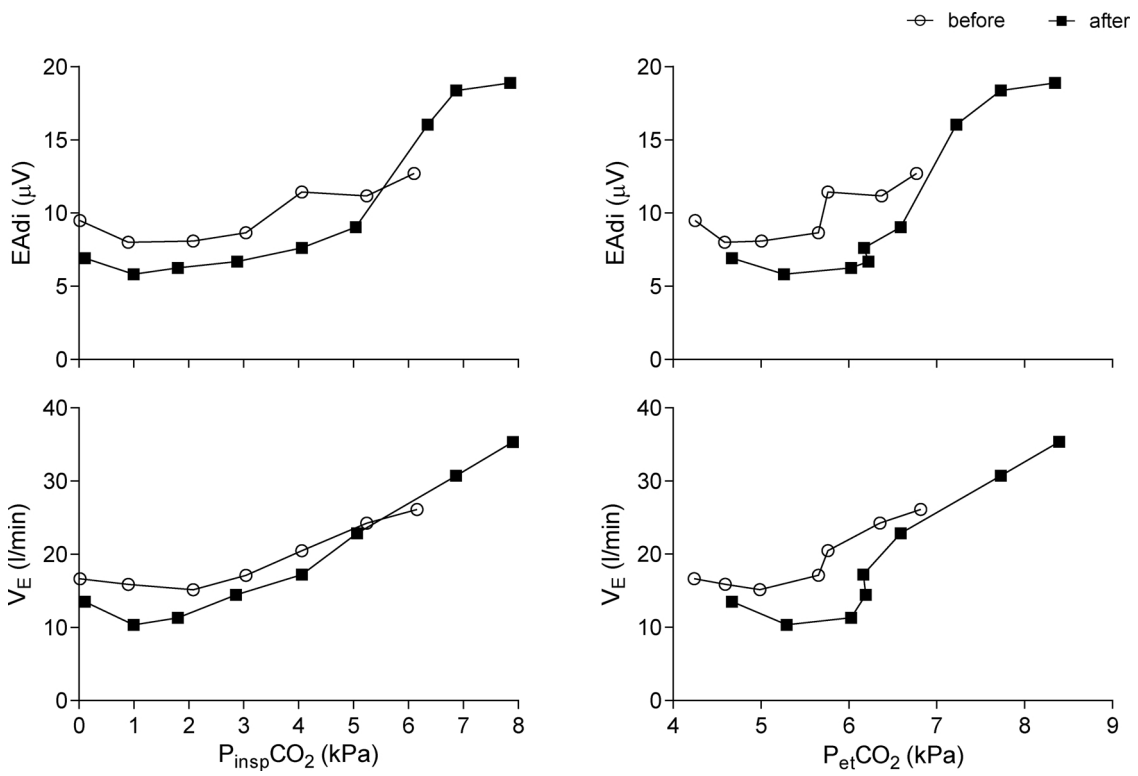

Fig. 3. EAdi and minute ventilation (V_E) as function of inspiratory CO_2 pressure ($P_{insp}CO_2$) and endtidal CO_2 pressure ($P_{et}CO_2$) for one subject during the HCVR test before and after sodiumbicarbonate administration.

Table 2
Results of the HCVR test in mean of all subjects with standard error of the mean of the paired samples *t*-test. * Significant difference between before to after sodium bicarbonate administration ($p \leq 0.05$).

	before	after	p-value
HCVR test			
$\Delta V_E/\Delta P_{et}CO_2$ L/min/kPa	8.2 ± 1.7	7.9 ± 1.2	0.70
max $P_{insp}CO_2$ (kPa)	6.7 ± 0.3	7.3 ± 0.2	0.06
max V_E (L/min)	30.9 ± 2.1	35.9 ± 2.6	0.04*
$P_{insp}CO_2$ 0–5 kPa			
ΔV_E (L/min)	9.5 ± 2.0	7.7 ± 1.4	0.28
$\Delta P_{et}CO_2$ (kPa)	1.9 ± 0.2	2.0 ± 0.1	0.54
$\Delta V_E/\Delta P_{et}CO_2$ L/min/kPa	6.3 ± 1.6	4.3 ± 0.9	0.14
Center Frequency			
CF start test (Hz)	95.9 ± 2.4	97.0 ± 5.8	0.29
CF at $P_{insp}CO_2$ 5 kPa (Hz)	100.8 ± 5.4	82.7 ± 11.0	0.86
Coefficient of variation			
CV EAdi start test	0.31 ± 0.08	0.14 ± 0.04	0.08
CV EAdi at $P_{insp}CO_2$ 5 kPa	0.20 ± 0.04	0.19 ± 0.03	0.81
CV V_E start test	0.18 ± 0.11	0.26 ± 0.13	0.69
CV V_E at $P_{insp}CO_2$ 5 kPa	0.13 ± 0.03	0.12 ± 0.05	0.79

4. Discussion

This is the first study to evaluate neural respiratory drive and resulting minute ventilation in healthy subjects with compensated metabolic alkalosis. Neural drive is represented by the electrical activity of the diaphragm (Beck et al., 2001). The main finding of this study is that an increased arterial bicarbonate level causes a decrease in the mean EAdi and minute ventilation of all subjects during a hypercapnic ventilatory response test at normal plasma pH levels.

4.1. Effect of elevated plasma bicarbonate on respiratory drive

We hypothesized that elevated plasma bicarbonate levels increase the buffer capacity for CO_2 resulting in decreased sensitivity of the respiratory centers to increased inhaled CO_2 during the HCVR test; so-called reduced chemosensitivity of breathing (Heinemann and Goldring, 1974; Rialp et al., 2014).

We found that when breathing ambient air, elevated plasma bicarbonate did not affect the HCVR test ($\Delta V_E/\Delta P_{et}CO_2$), V_E or $P_{et}CO_2$. However, baseline EAdi was lower after bicarbonate administration. In addition, further analysis of the ventilatory response to elevated $P_{insp}CO_2$ demonstrated different patterns before and after sodium bicarbonate administration. The respiratory centers respond differently to inhaled CO_2 when arterial bicarbonate levels are increased. This is probably as a result of the enhanced buffer capacity; more arterial bicarbonate supplies more capacity to buffer CO_2 before the respiratory centers sense an increased arterial CO_2.

First, the respiratory drive, represented by the electrical activity of the diaphragm (American Thoracic Society/European Respiratory Society, 2002; Jolley et al., 2015), is decreased with increasing arterial bicarbonate levels, resulting in a decreased V_E. This is different from the findings of Oren in 1991; that study showed no difference in minute ventilation related to $P_{et}CO_2$ between pre and post sodium bicarbonate administration (arterial bicarbonate from 25.5 ± 0.6 to 30.6 ± 1.7 mEq/l in 3 days) (Oren et al., 1991). Also van de Ven et al. found no difference in ventilatory response in normocapnic and hypercapnic COPD patients under varying acid-base conditions (van de Ven et al., 2002). An explanation for this difference with the study of van de Ven could be that in the current study healthy subjects are measured, whereas van de Ven included COPD patients, with a possibility of changed respiratory mechanics influencing the hypercapnic ventilatory response. Our study adds measurement of EAdi, reflecting motor output of the central nervous system to the diaphragm muscle (American Thoracic Society/European Respiratory Society, 2002), which causes contraction of the diaphragm. EAdi is thereby a more specific and sensitive reflective of neural respiratory drive than V_E, which could also be influenced by mechanical properties of the respiratory system (Jolley et al., 2015). Herrera and Kazemi studied the

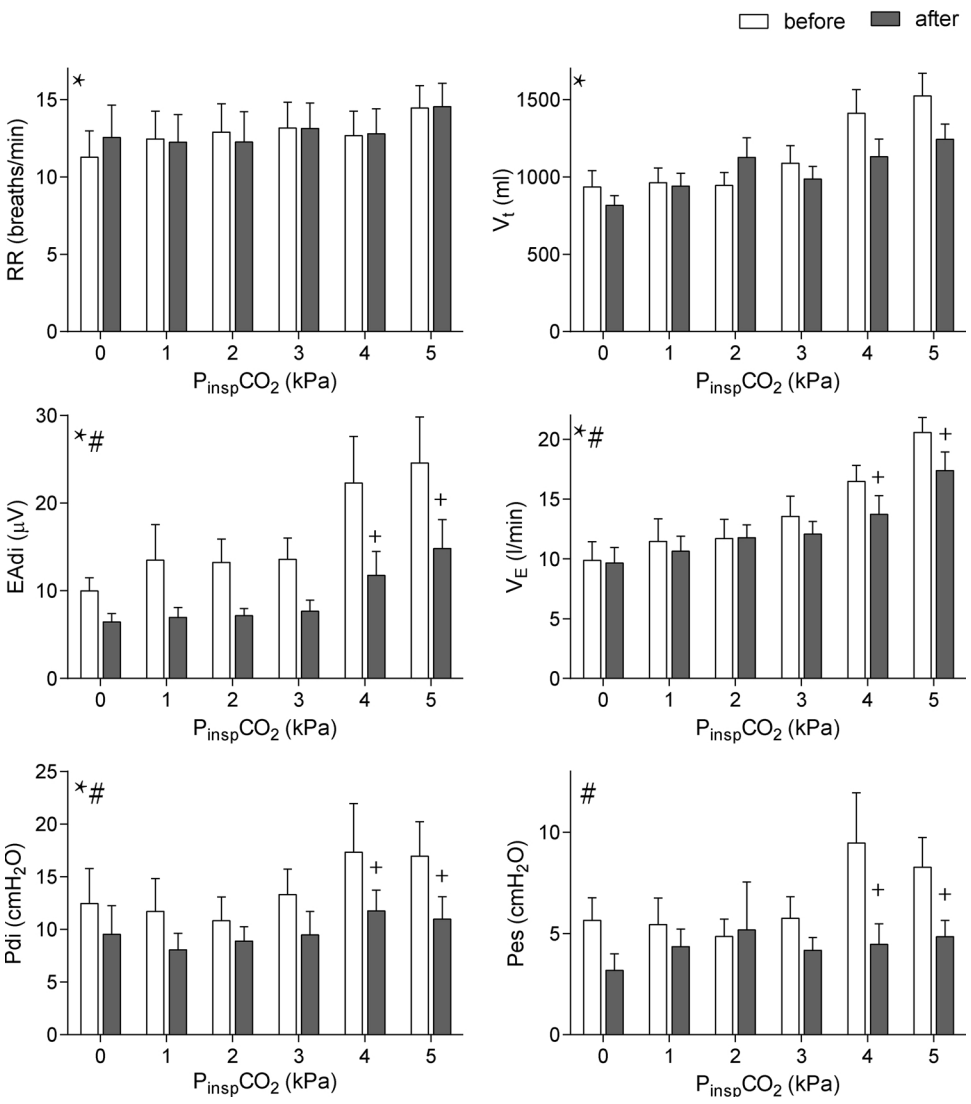

Fig. 4. Mean and SEM for RR, V_t, V_E, EAdi, Pdi and Pes before and after sodium bicarbonate administration for all subjects, as function of $P_{insp}CO_2$. *Significant increase with increasing $P_{insp}CO_2$ with ANOVA. # significant decrease from before to after sodium bicarbonate administration with ANOVA. +Tukey's post hoc difference between before and after sodium bicarbonate administration. Note: Pes is analyzed for 8 subjects and Pdi is analyzed for 6 subjects.

phrenic nerve output in dogs, as an index of neural output from the respiratory centers in the brain, and found that its response to hypoxia is significantly decreased when bicarbonate levels in the cerebrospinal fluid are increased (Herrera and Kazemi, 1982). Although minute ventilation is not measured in these anesthetized dogs, this adheres to the findings of the current study.

Second, NVE appears to increase after sodium bicarbonate administration. This is due to EAdi decreasing more than V_E: less diaphragm electrical activity is needed to generate the same tidal volumes. The most likely explanation is a change in respiratory pump function, by recruitment of accessory muscles additional to the diaphragm.

Lastly, the maximal achievable V_E after sodium bicarbonate administration was higher than before. Although the maximal achievable $P_{insp}CO_2$ was not significantly increased, the p-value of 0.06 shows a trend towards longer endurance of the test after sodium bicarbonate administration. Longer endurance implies subjects also reach a higher minute ventilation.

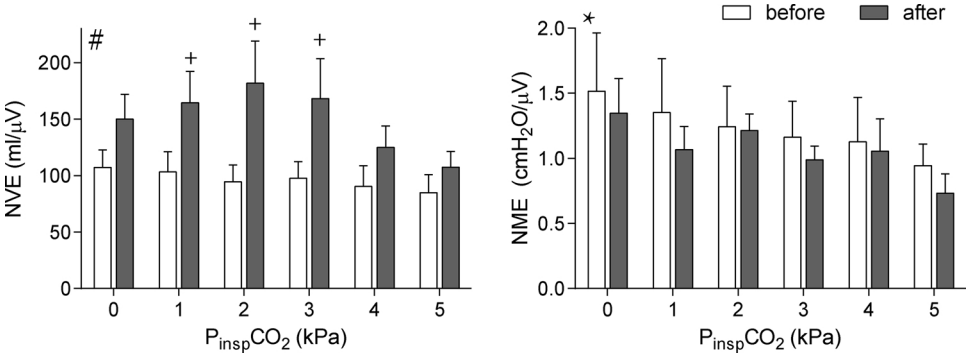

Fig. 5. Mean and SEM for NVE and NME before and after sodium bicarbonate administration for all subjects, as function of $P_{insp}CO_2$. *Significant increase with increasing $P_{insp}CO_2$ with ANOVA. # Significant decrease from before to after sodium bicarbonate administration with ANOVA. +Tukey's post hoc difference between before and after sodium bicarbonate administration. Note: NME is analyzed for 6 subjects.

4.2. Coefficient of variation

Variability of ventilation has been shown to improve oxygenation in animals and also in humans such high variability might be beneficial (Arold et al., 2002; Schmidt et al., 2010; Suki et al., 1998). For example, Schmidt et al. showed that in patients who were mechanically ventilated in a partially supported mode, reducing the load increased variability of breathing. So the more unloading of the respiratory muscles is achieved by the ventilator, the higher the variability of breathing, by improved neuromechanical coupling (Schmidt et al., 2010). However, effects of increased inspiratory CO_2 levels on variability of electrical activity of the diaphragm and ventilation are variable. Busha et al. found that increased inspired CO_2 in rats resulted in a decrease of the CV of peak EAdi but also an increased breath-to-breath variability, indicating a difference in short- and long-term correlations in the variability of breathing (BuSha and Stella, 2002), whereas Fiamma et al. found that hypercapnia decreased the breath-to-breath variability of ventilation (Fiamma et al., 2007). It is proposed by Nattie (BuSha and Stella, 2002; Nattie, 1999, 2000) that there are multiple sites of chemoreception throughout the brain stem where different chemosensors may be more or less active during different levels of CO_2. With increasing inspired CO_2, a greater number of inputs drives the respiratory centers resulting in more dynamic behaviour of the output (Nattie, 1999, 2000). However, because in the current study bicarbonate levels are increased, we hypothesize that the inspired CO_2 will be buffered and the behaviour of the respiratory center will not change. We indeed found no effect of sodiumbicarbonate on the coefficient of variation which confirms our hypothesis that CV is not changed by an increased plasma bicarbonate level during the HCVR test.

4.3. Center frequency

Administration of sodiumbicarbonate changes the electrolyte status, and could thereby influence the membrane potentiation of the diaphragm. CFdi is a measure for muscle fiber conduction velocity, which is known to decrease during loaded breathing (Doorduin et al., 2012) and fatigue, attributed to many factors including a decreased extracellular sodium concentration which inhibits force development (Fortune and Lowery, 2009; Overgaard et al., 1997). In this study CFdi remains constant, although the administration of sodium bicarbonate resulted in a significant increased plasma sodium concentration, indicating no effect on diaphragm fiber conductivity probability of fatigue of the diaphragm.

4.4. Methodological issues

Arterial bicarbonate levels can be safely increased in healthy subjects as shown in this study. Sodium bicarbonate administration resulted in a relevant increase in bicarbonate levels exceeding standard laboratory reference values (HCO_3^- 22–28 mmol/L), whereas pH remained within reference value limits (pH 7.35–7.45). The response of the respiratory drive to an increased arterial bicarbonate level was evaluated by administering a fixed dose to all subjects. Although only subjects with a weight of 60–80 kg were included, this results in a varying dose for each subject within these margins and thereby a varying arterial bicarbonate level. This resulted in a dosage of 0.3–0.4 g/kg/day (during 3 days), where i.e. Oren administered 0.7 g/kg/day (during 3 days) and Douroudos administered 0.3–0.5 g/kg/day (during 5 days) (Douroudos et al., 2006; Oren et al., 1991). Resulting arterial bicarbonate levels were all comparably high (29.2 mmol/L, 30.6 mmol/L and 29.8–32.3 mmol/L respectively) and also pH was comparable and did not explain the difference in minute ventilation between the studies (7.44, 7.47 and 7.45–7.47). The HCVR test is used to assess the response of the respiratory centers to increased inspiratory CO_2 concentrations and provides a measure of the chemosensitivity of the brain. The chemosensitivity influences regulation of V_E and the response of various physiological and pathophysiological states to V_E (Oren et al., 1991). There are various protocols to test the hypercapnic ventilatory response, all aiming at measuring the increase in V_E by increasing $P_{insp}CO_2$ (American Thoracic Society/European Respiratory Society, 2002; Nickol et al., 2009; Oren et al., 1991). This study used an adapted version of these protocols, and succeeded in changing V_E and $P_{et}CO_2$ as a result of increased $P_{insp}CO_2$. Baseline tidal volumes were high, probably due to a high instrumental dead space. We found that after sodium bicarbonate administration, the maximal achievable V_E and $P_{insp}CO_2$ were significantly higher, which could also be due to the familiarization of the subjects to the experimental protocol, without a placebo control group in this setup. However, subjects were unaware of the results of the previous test, of the duration of the HCVR test and of the current $P_{insp}CO_2$. Next to that, we showed that EAdi decreased with elevated levels of arterial bicarbonate. We have however no data of the electrical activity of other (accessory) respiratory muscles to analyze their behaviour during this state and in particular the interaction between the diaphragm and other muscles, which could possibly explain the behaviour of the diaphragm and the decrease in EAdi.

4.5. Clinical implications

The results of the current study may be relevant for the approach of patients difficult to wean from mechanical ventilation and of patients with COPD. Metabolic alkalosis is common in these patients (Banga and Khilnani, 2009) and our data indicate that this may affect breathing pattern, in particular respiratory drive during loaded breathing. Although in our study the healthy subjects were able to maintain adequate ventilation at baseline, ventilation during the HCVR test did decrease after administration of sodium bicarbonate. Patients with COPD could have mechanical difficulties and be unable to maintain adequate ventilation. These patients that suffer from (an exacerbation of) COPD or other causes of acute respiratory failure mostly require (non-invasive) mechanical ventilation to recover adequate minute ventilation, which restores the hypercapnia and thus pH to normal levels. Bicarbonate on the other hand is found to remain elevated in patients with posthypercapnic alkalosis (Banga and Khilnani, 2009). It is suggested that excreting bicarbonate could correct metabolic alkalosis and, subsequently, increase minute ventilation and improve oxygenation, facilitating weaning from mechanical ventilation in patients with COPD or other pulmonary diseases (Heming et al., 2012). Recently, Faisy et al. showed in a randomized trial that the use of acetazolamide did not result in a significant reduction in the duration of mechanical ventilation compared to placebo (Faisy et al., 2016). However, serum bicarbonate levels were decreased after acetazolamide administration and there was a clinically substantial decrease (median 16 h) in duration of mechanical ventilation (Faisy et al., 2016). This supports the findings of the current study that increased arterial bicarbonate levels suppress ventilation and excreting bicarbonate in patients with metabolic alkalosis could stimulate the respiratory centers.

5. Conclusions

In conclusion, the present study in healthy subjects demonstrates that an increased arterial bicarbonate level decreased the respiratory drive to the diaphragm and consequently decreased minute ventilation.

References

American Thoracic Society/European Respiratory Society, 2002. ATS/ERS statement on respiratory muscle testing. Am. J. Respir. Crit. Care Med. 166, 518–624.
Arold, S.P., Mora, R., Lutchen, K.R., Ingenito, E.P., Suki, B., 2002. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. Am. J. Respir. Crit. Care Med. 165, 366–371.
Banga, A., Khilnani, G.C., 2009. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. COPD 6, 437–440.
Beck, J., Gottfried, S.B., Navalesi, P., Skrobik, Y., Comtois, N., Rossini, M., Sinderby, C.,

2001. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am. J. Respir. Crit. Care Med. 164, 419–424.
BuSha, B.F., Stella, M.H., 2002. State and chemical drive modulate respiratory variability. J. Appl. Physiol. (1985) 93, 685–696.
Cohen, B., Laish, I., Brosh-Nissimov, T., Hoffman, A., Katz, L.H., Braunstein, R., Sagi, R., Michael, G., 2013. Efficacy of urine alkalinization by oral administration of sodium bicarbonate: a prospective open-label trial. Am. J. Emerg. Med. 31, 1703–1706.
Coppoolse, R., Barstow, T.J., Stringer, W.W., Carithers, E., Casaburi, R., 1997. Effect of acute bicarbonate administration on exercise responses of COPD patients. Med. Sci. Sports Exerc. 29, 725–732.
Doorduin, J., Sinderby, C.A., Beck, J., Stegeman, D.F., van Hees, H.W., van der Hoeven, J.G., Heunks, L.M., 2012. The calcium sensitizer levosimendan improves human diaphragm function. Am. J. Respir. Crit. Care Med. 185, 90–95.
Doorduin, J., Nollet, J.L., Roesthuis, L.H., van Hees, H.W., Brochard, L.J., Sinderby, C.A., van der Hoeven, J.G., Heunks, L.M., 2017. Partial neuromuscular blockade during partial ventilatory support in sedated patients with high tidal volumes. Am. J. Respir. Crit. Care Med. 195, 1033–1042.
Douroudos, I.I., Fatouros, I.G., Gourgoulis, V., Jamurtas, A.Z., Tsitsios, T., Hatzinikolaou, A., Margonis, K., Mavromatidis, K., Taxildaris, K., 2006. Dose-related effects of prolonged NaHCO3 ingestion during high-intensity exercise. Med. Sci. Sports Exerc. 38, 1746–1753.
Faisy, C., Meziani, F., Planquette, B., Clavel, M., Gacouin, A., Bornstain, C., Schneider, F., Duguet, A., Gibot, S., Lerolle, N., Ricard, J.D., Sanchez, O., Djibre, M., Ricome, J.L., Rabbat, A., Heming, N., Urien, S., Esvan, M., Katsahian, S., Investigators, D., 2016. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: a randomized clinical trial. JAMA 315, 480–488.
Feldman, J.L., Del Negro, C.A., Gray, P.A., 2013. Understanding the rhythm of breathing: so near, yet so far. Annu. Rev. Physiol. 75, 423–452.
Fiamma, M.N., Straus, C., Thibault, S., Wysocki, M., Baconnier, P., Similowski, T., 2007. Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R1985–1993.
Fortune, E., Lowery, M.M., 2009. Effect of extracellular potassium accumulation on muscle fiber conduction velocity: a simulation study. Ann. Biomed. Eng. 37, 2105–2117.
Heinemann, H.O., Goldring, R.M., 1974. Bicarbonate and the regulation of ventilation. Am. J. Med. 57, 361–370.
Heming, N., Urien, S., Faisy, C., 2012. Acetazolamide: a second wind for a respiratory stimulant in the intensive care unit? Crit. Care 16, 318.
Herrera, L., Kazemi, H., 1982. Modification of phrenic nerve output to hypoxia after two hours of hypercapnia and increased cerebrospinal fluid [HCO3-]. Am. Rev. Respir. Dis. 126, 70–774.
Jolley, C.J., Luo, Y.M., Steier, J., Rafferty, G.F., Polkey, M.I., Moxham, J., 2015. Neural respiratory drive and breathlessness in COPD. Eur. Respir. J. 45, 355–364.
Liu, L., Liu, H., Yang, Y., Huang, Y., Liu, S., Beck, J., Slutsky, A.S., Sinderby, C., Qiu, H., 2012. Neuroventilatory efficiency and extubation readiness in critically ill patients. Crit. Care 16, R143.
Nattie, E., 1999. CO2: brainstem chemoreceptors and breathing. Prog. Neurobiol. 59, 299–331.
Nattie, E., 2000. Multiple sites for central chemoreception: their roles in response sensitivity and in sleep and wakefulness. Respir. Physiol. 122, 223–235.
Nickol, A.H., Dunroy, H., Polkey, M.I., Simonds, A., Cordingley, J., Corfield, D.R., Morrell, M.J., 2009. A quick and easy method of measuring the hypercapnic ventilatory response in patients with COPD. Respir. Med. 103, 258–267.
Oppersma, E., Doorduin, J., van der Hoeven, J., Veltink, P., Heunks, L., 2016. Influence of Bicarbonate on Ventilatory Drive in Healthy Subjects [Abstract]. European Respiratory Society, London, UK.
Oren, A., Whipp, B.J., Wasserman, K., 1991. Effects of chronic acid-base changes on the rebreathing hypercapnic ventilatory response in man. Respir. Int. Rev. Thorac. Dis. 58, 181–185.
Overgaard, K., Nielsen, O.B., Clausen, T., 1997. Effects of reduced electrochemical Na + gradient on contractility in skeletal muscle: role of the Na + -K + pump. Pflugers Arch.: Eur. J. Physiol. 434, 457–465.
Rialp, G., Raurich, J.M., Llompart-Pou, J.A., Ayestaran, I., Ibanez, J., 2014. Respiratory CO2 response depends on plasma bicarbonate concentration in mechanically ventilated patients. Med. Intensiva 38, 203–210.
Schmidt, M., Demoule, A., Cracco, C., Gharbi, A., Fiamma, M.N., Straus, C., Duguet, A., Gottfried, S.B., Similowski, T., 2010. Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. Anesthesiology 112, 670–681.
Sinderby, C., Spahija, J., Beck, J., 2001. Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity. Am. J. Respir. Crit. Care Med. 163, 905–910.
Suki, B., Alencar, A.M., Sujeer, M.K., Lutchen, K.R., Collins, J.J., Andrade Jr., J.S., Ingenito, E.P., Zapperi, S., Stanley, H.E., 1998. Life-support system benefits from noise. Nature 393, 127–128.
van de Ven, M.J., Colier, W.N., van der Sluijs, M.C., Oeseburg, B., Vis, P., Folgering, H., 2002. Effects of acetazolamide and furosemide on ventilation and cerebral blood volume in normocapnic and hypercapnic patients with COPD. Chest 121, 383–392.