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

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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).

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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.

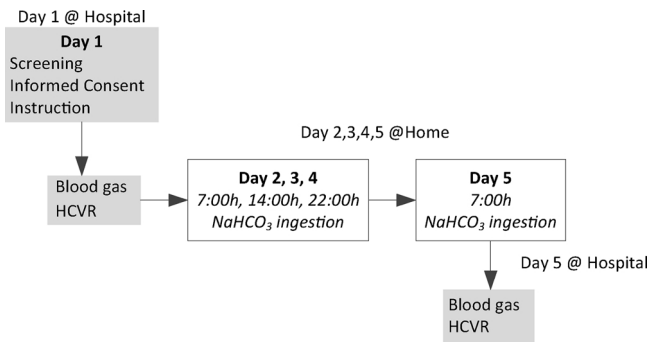

Fig. 1. Schematic description of the protocol.

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