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Real-Time Dynamic Carbon Dioxide Administration

A Novel Treatment Strategy for Stabilization of Periodic Breathing With Potential Application to Central Sleep Apnea

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Objectives This study targeted carbon dioxide (CO_2) oscillations seen in oscillatory ventilation with dynamic pre-emptive CO_2 administration.

Background Oscillations in end-tidal CO_2 (et-CO_2) drive the ventilatory oscillations of periodic breathing (PB) and central sleep apnea in heart failure (HF).

Methods Seven healthy volunteers simulated PB, while undergoing dynamic CO_2 administration delivered by an automated algorithm at different concentrations and phases within the PB cycle. The algorithm was then tested in 7 patients with HF and PB.

Results In voluntary PB, the greatest reduction (74%, $p < 0.0001$) in et-CO_2 oscillations was achieved when dynamic CO_2 was delivered at hyperventilation; when delivered at the opposite phase, the amplitude of et-CO_2 oscillations increased (35%, $p = 0.001$). In HF patients, oscillations in et-CO_2 were reduced by 43% and ventilatory oscillations by 68% (both $p < 0.05$). During dynamic CO_2 administration, mean et-CO_2 and ventilation levels remained unchanged. Static CO_2 (2%, constant flow) administration also attenuated spontaneous PB in HF patients ($p = 0.02$) but increased mean et-CO_2 ($p = 0.03$) and ventilation (by 45%, $p = 0.03$).

Conclusions Dynamic CO_2 administration, delivered at an appropriate time during PB, can almost eliminate oscillations in et-CO_2 and ventilation. This dynamic approach might be developed to treat central sleep apnea, as well as minimizing undesirable increases in et-CO_2 and ventilation. (J Am Coll Cardiol 2010;56:1832–7) © 2010 by the American College of Cardiology Foundation

Periodic breathing (PB), Cheyne-Stokes respiration, and central sleep apnea (CSA) are frequently seen (1) oscillatory patterns in heart failure (HF), associated with a worse prognosis (1–3). Although, these ventilatory oscillations are driven by oscillations in CO_2 (4–6), the latter are not specifically targeted by current treatments.

Mathematical modeling (7) suggests that carefully targeting therapy within the PB cycle may fill in the troughs of end-tidal CO_2 (et-CO_2) that produce hypopneas, as well as minimizing any undesirable increase in et-CO_2 that could cause hyperventilation and adrenergic overactivation (8–11).

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We investigated this in 2 ways. First, dynamic CO_2 was administered in voluntary periodic breathing (VPB) (12,13) at different timings and concentrations. Second, dynamic CO_2 was administered to HF patients with spontaneous PB.

Methods

Subjects. Seven healthy subjects free of medications and 7 HF patients with daytime spontaneous PB were enrolled (Table 1). All HF patients were on stable contemporary

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Table 1 Baseline Characteristics of Healthy Subjects and HF Patients

	Healthy Subjects	HF Patients
n	7	7
Men	5	6
Age, yrs	34 ± 13	77 ± 4
BMI, kg/m^2	24.3 ± 0.7	24.1 ± 0.5
Ejection fraction, %	59.0 ± 5.1	18.5 ± 7.4
Heart rate, beats/min	66.1 ± 7.6	74.2 ± 21.3
Cardiac output, l/min	6.5 ± 2.4	4.1 ± 1.2
End-tidal CO_2, kPa	6.0 ± 0.7	4.7 ± 0.4
Oxygen saturation, %	98.4 ± 1.1	93.2 ± 1.3
Ventilation, l/min	7.6 ± 1.5	8.3 ± 1.9
NYHA functional class III/IV		3/1
Etiology		
Ischemic		3
Dilative		2
Valvular		1
Alcoholic		1
Treatment		
Biventricular pacemaker		4
ACE inhibitor/ARBs		7
Beta-blockers		7
Aldosterone antagonists		3
Diuretics		6

Data are expressed as mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; HF = heart failure; NYHA = New York Heart Association.

treatment and free of recent decompensation, ventilatory disorders, and drugs affecting ventilatory drive. Spontaneous PB was defined as an oscillatory pattern in ventilation with a period of ~60 s characterized by phases of hyperventilation and central apnea (cessation of ventilatory effort for ≥10 s) or hypopnea (50% reduction in tidal volume, with ≥4% oxygen saturation) shown during a 30-min outpatient recording (1,14–16). All subjects gave informed consent for the study that was approved by the NHS Research Ethics Committee (05/Q0404/018).

Measurements. Subjects underwent baseline recordings recumbent, breathing through a pneumotachograph (Hans Rudolph Inc., Shawnee, Kansas) attached to a Multicap (Datex Instrumentarium, Helsinki, Finland) measuring gas concentrations. They were monitored via electrocardiogram (Hewlett-Packard, Palo Alto, California), beat-by-beat blood pressure and cardiac output (Finometer, Finapres Medical Systems, Amsterdam, Netherlands).

Data acquisition. Data were sampled at 1,000 Hz simultaneously from all devices using an analog-to-digital card (DAQCard 6062E, National Instruments, Austin, Texas) with LabView (version 7.0, National Instruments) and analyzed offline (17–19).

CO_2 administration system. Using a motorized valve (Fig. 1), the system delivers CO_2 in any configuration of timing and dose. Custom software (Matlab, Natick, Massachusetts) (17–19) analyzes ventilation and computes the magnitude and the phase of ventilatory oscillations in real-time, with the ventilatory cycle represented as a clock (peak ventilation at 0°, nadir ventilation at 180°).

Dynamically titrated concentrations of CO_2 are delivered according to both magnitude and phase of the current cycle. CO_2 concentration is varied smoothly, from 0, before peak administration, rising to a brief peak level, and then declining to 0 again, in a sinusoidal shape.

Abbreviations and Acronyms

CSA = central sleep apnea
et-CO_2 = end-tidal carbon dioxide
HF = heart failure
PB = periodic breathing
VPB = voluntary periodic breathing

VPB in healthy volunteers. Voluntary PB was achieved using computer program guidance (20). We defined the relative amplitude of oscillation (α) as the ratio between amplitude and mean, for ventilation (α_{VEN}) and et-CO_2 ($\alpha_{ET\text{-}CO2}$). The ratio between the alpha values (e.g., $\alpha_{ET\text{-}CO2}/\alpha_{VEN}$) controls for variation in depth of ventilatory oscillations.

CO_2 administration protocol. The average delay between starting the motor and gas reaching the alveolar space was ~7s corresponding to an angle of 40° (7/60 ≈ 40/360). We delivered CO_2 at −40° so that CO_2 would arrive in the alveolar space coincident with peak ventilation.

In VPB, to explore the effect of the phase of CO_2 administration, we performed replicate experiments where CO_2 was delivered at −130°, −85°, 5°, 50°, and 140°. The effect of dose was established by delivering CO_2 at −40° with peak concentration of 1%, 2%, and 4%). In HF patients with spontaneous PB, dynamic CO_2 administration (2% at −40°) and static (2%) CO_2 administration were each compared to baseline.

Statistical analysis. Values are presented as mean ± SD for continuous data and percentages for categorical data. Differences between repeated measurements were analyzed by paired *t* test where $p < 0.05$ was considered significant,

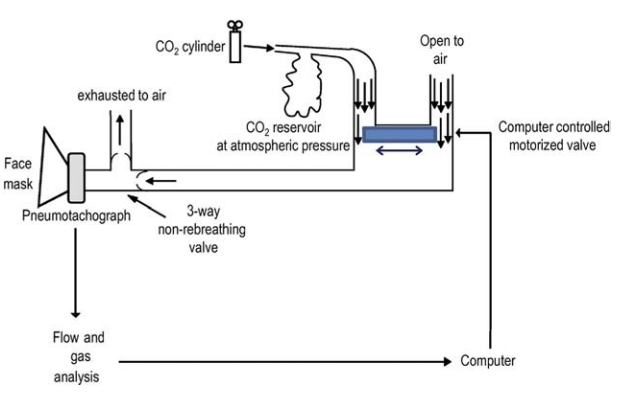

Figure 1 Overview of the System

Representation of the system used to dynamically deliver CO_2 to the subject. The reservoir of CO_2 is maintained at atmospheric pressure, with delivery dependent on the subject's inspiration.

Table 2 Effect of VPB in Healthy Volunteers on Ventilatory and Hemodynamic Parameters

	Voluntary Periodic Breathing			
	Mean ± SD	Absolute Amplitude of Oscillation	Relative Amplitude of Oscillation	Relative Amplitude of Oscillation Compared With That in Ventilation
Ventilation, l/min	9.6 ± 2.4	4.2 ± 1.8	0.42 ± 0.15	1 (reference)
End-tidal CO_2, kPa	5.08 ± 0.73	0.45 ± 0.21	0.09 ± 0.04	0.20 ± 0.03
End-tidal O_2, kPa	16.14 ± 1.36	0.94 ± 0.45	0.06 ± 0.03	0.13 ± 0.05
Heart rate, beats/min	72.26 ± 7.41	1.83 ± 1.30	0.03 ± 0.02	0.08 ± 0.07
Mean arterial pressure, mm Hg	88.91 ± 22.93	3.44 ± 1.79	0.04 ± 0.01	0.10 ± 0.05
Cardiac output, l/min	5.59 ± 1.72	0.32 ± 0.15	0.06 ± 0.03	0.16 ± 0.09

VPB = voluntary periodic breathing.

or by analysis of variance with Bonferroni post hoc correction in cases of multiple comparisons with VPB where 6 different times of administration were tested and $p < 0.003$ was considered significant, and likewise for 3 different doses (1%, 2%, and 4%), $p < 0.008$.

Results

Subject characteristics. Seven healthy subjects were enrolled (Table 1), each of them able to consistently perform VPB (Table 2). Seven HF patients with spontaneous PB (Table 1) were recruited, of whom 4 had apneas and 3 only hypopneas.

Impact of timing and peak dose of dynamic CO_2 administration in VPB. The greatest reduction in size of et-CO_2 oscillations occurred when CO_2 was delivered at −40° (Fig. 2), which is a 74% reduction below baseline (0.05 ± 0.02 kPa vs. 0.20 ± 0.03 kPa, $p < 0.0001$).

The other phases of CO_2 delivery were less effective in attenuating et-CO_2 oscillations. Efficiency declined progressively as the treatment angle was moved from −40°. In the extreme (180° away from −40°, approximately trough ventilation), oscillations were 35% larger than at baseline (0.27 ± 0.05 kPa vs. 0.20 ± 0.03 kPa, $p = 0.001$) (Fig. 2).

Dynamic CO_2 with peak concentration of 2% was more effective than 1% in attenuating et-CO_2 oscillations (0.05 ± 0.02 vs. 0.13 ± 0.03, $p < 0.001$). However, a peak concentration higher than 2% did not further reduce et-CO_2 oscillations (0.05 ± 0.01 vs. 0.05 ± 0.02, $p = 0.47$) (Fig. 3).

Dynamic CO_2 administration in HF patients with spontaneous PB. When CO_2 was delivered coincident with peak ventilation, et-CO_2 oscillations were reduced by 43% (SD ÷ mean: 0.07 ± 0.03 untreated vs. 0.04 ± 0.02 treated

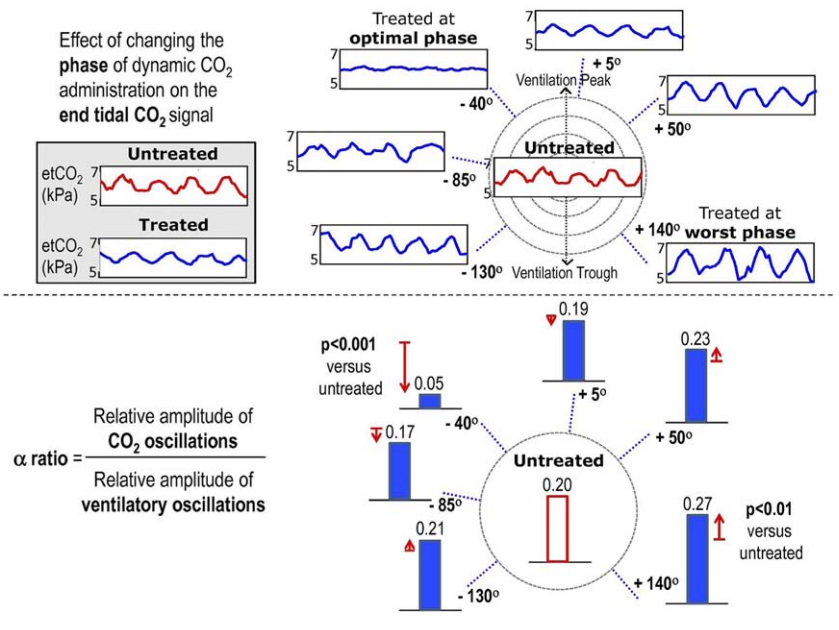

Figure 2 Phase of CO_2 Administration in VPB

Effect of changing the phase of dynamic CO_2 on end-tidal CO_2 in 1 volunteer **(top)** and on the $\alpha_{CO2}/\alpha_{VEN}$ ratio in all volunteers **(bottom)**.
VPB = voluntary periodic breathing.

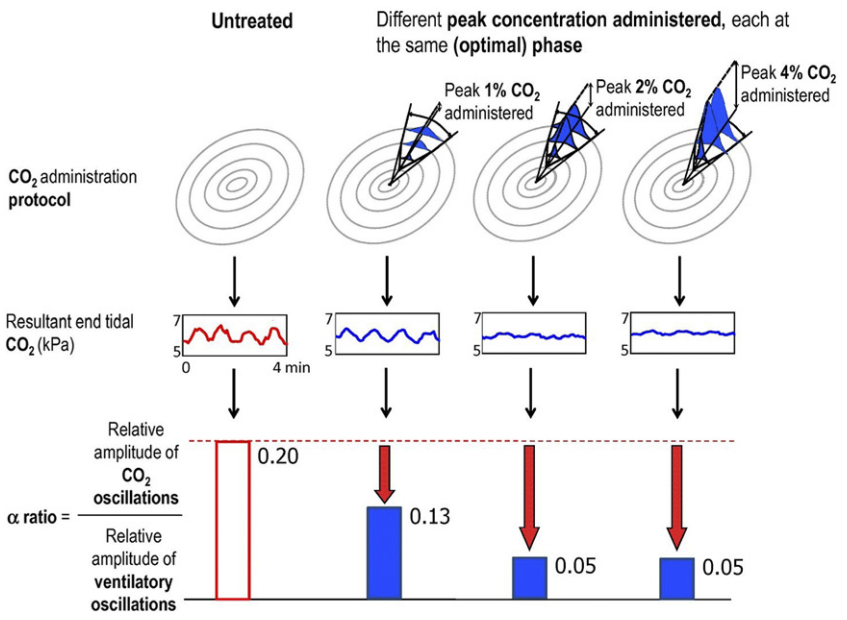

Figure 3 **Peak Dose of CO_2 Administration in VPB**

Effect of changing the peak dose of dynamic CO_2 on end-tidal CO_2 in 1 volunteer **(top)** and on the $\alpha_{CO2}/\alpha_{VEN}$ ratio in all volunteers **(bottom)**. VPB = voluntary periodic breathing.

CO_2, $p < 0.01$) (Figs. 4 and 5). This significant attenuation of et-CO_2 oscillations resulted in attenuation of ventilatory oscillations by 68% (SD ÷ mean: from 0.43 ± 0.19 untreated to 0.14 ± 0.09 treated, $p = 0.01$) and not at the cost of significantly increased et-CO_2 (4.7 ± 0.4 kPa vs. 5.0 ± 0.3 kPa, $p = 0.06$). Nor was mean ventilation significantly increased (8.26 ± 1.85 l/min vs. 9.41 ± 2.71 l/min, $p = 0.12$). Mean oxygen saturation (S_pO_2) was higher following dynamic CO_2 administration (95.0 ± 2.4% treated vs. 93.2 ± 1.3% untreated, $p = 0.02$). Moreover, the magnitude of desaturation was reduced (minimum S_pO_2: 93.6 ± 1.7 vs. 89.4 ± 1.7, $p = 0.01$).

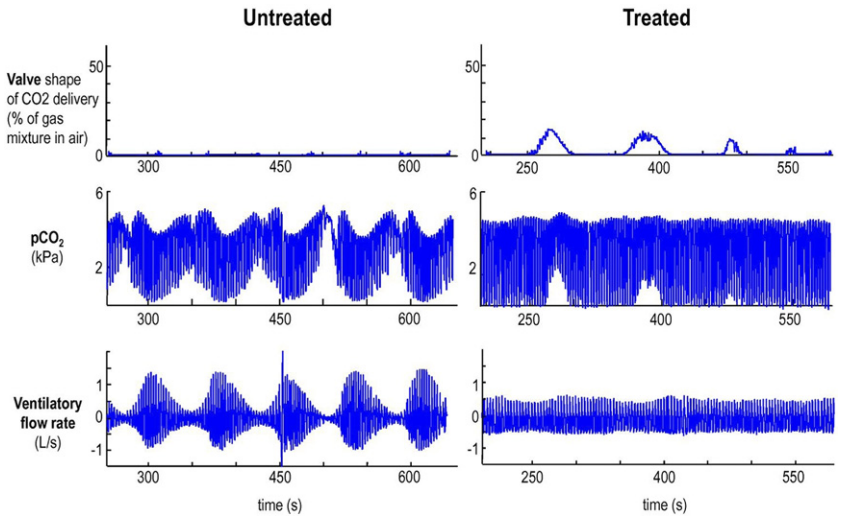

Figure 4 **Dynamic CO_2 Administration in an Example Patient With HF and Spontaneous PB**

Example of 1 patient with heart failure and daytime Cheyne-Stokes respiration efficaciously treated with dynamic CO_2. The delivery of 2% CO_2 (peak dose) at 0° with an angle width of delivery ranging from –90° to +140° was able to abolish not only the oscillations in end-tidal CO_2, but also the fluctuations in ventilation, without increasing their average values. HF = heart failure; PB = periodic breathing.

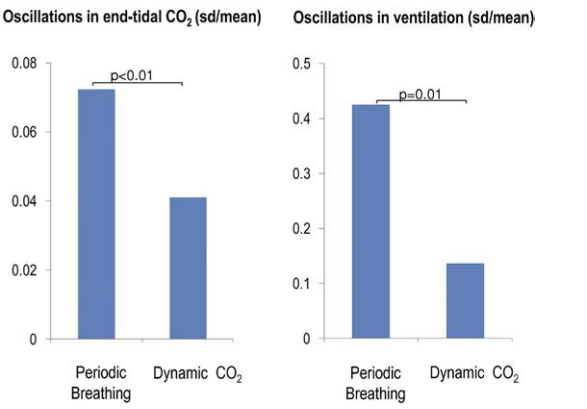

Figure 5 **Effect of Dynamic CO_2 on Spontaneous PB of HF**

Dynamic CO_2 administration was able to attenuate oscillations in end-tidal CO_2 and ventilation in 7 heart failure patients with daytime periodic breathing. Abbreviations as in Figure 4.

Static CO_2 administration in HF patients with spontaneous PB. Static CO_2 also stabilized breathing (SD ÷ mean: of ventilation, 0.14 ± 0.06, and of CO_2, 0.03 ± 0.01). However, static CO_2 significantly increased et-CO_2 (5.2 ± 0.3 kPa vs. 4.7 ± 0.0 kPa, p = 0.03) and ventilation (12.00 ± 4.08 l/min vs. 8.26 ± 1.85 l/min, p = 0.03).

Hemodynamic consequences of dynamic CO_2 in HF patients with spontaneous PB. There was no hemodynamic evidence of increased sympathetic hyperstimulation in the HF patients with no change in heart rate (75.3 ± 23.5 beats/min treated vs. 74.2 ± 21.3 beats/min untreated, p = 0.32) or mean arterial pressure (61.3 ± 8.9 mm Hg vs. 58.9 ± 10.0 mm Hg, p = 0.11).

In no patient did dynamic CO_2 increase ectopy, a marker of sympathetic activity (21). There were fewer ectopics in Patients #3 and #4 (from 37 to 14, and from 18 to 0 per 10-min recording, respectively).

Discussion

This study demonstrates the possibility of attenuating CO_2 oscillations that drive PB using dynamically timed CO_2 administration. However, timing is critical, the most efficacious administration being coincident with peak ventilation.

Because CO_2 is only delivered for a small part of the PB cycle, the total quantity of CO_2 delivered is markedly reduced, thus minimizing unwanted consequences of increased et-CO_2, such as increased mean ventilation and sympathetic overactivation (8–11).

Periodic breathing and CO_2. Frequently in HF, with either preserved or reduced systolic function (1,22), the chemoreflex is enhanced and delayed (6,23). In CSA, there may be sleep disruption, fatigue, adrenergic overactivation (24), and increased mortality (2). Delivery of static CO_2 is efficacious in abolishing CSA (8,9), by increasing eupneic CO_2 when wakefulness drive is lost (25), but creates undesirable elevations in mean ventilation and sympathetic activity (8–11). With dynamic CO_2, the average dose of CO_2 delivered is lower (0.5%), compared with static CO_2 (2%), but achieves a 67% and 43% reduction in et-CO_2 oscillations in VPB and spontaneous PB, respectively. There is a nonsignificant trend toward higher et-CO_2 in the treatment group, but the numerical size is much smaller than that seen with static administration. Moreover, this may be of less significance given the positive effects on oxygen saturation. CO_2 administration may not only increase the eupneic CO_2, but may beneficially lower pulmonary capillary wedge pressure via vasodilation (26).

The minimization of dose was achieved using the following strategy:

1. CO_2 was only delivered for a portion of the PB cycle.
2. Delivery was gradually built up within each cycle.
3. Peak delivery was dependent on magnitude of ventilatory oscillations.

Because breathing may only be periodic for a portion of sleep time, this algorithm would deliver CO_2 only during oscillations. The algorithm was successful in both groups despite spontaneous PB being more variable from cycle to cycle than VPB, which has experimentally enforced regularity (27).

Clinical implications. This might be developed for CSA if facemasks (which are often rejected in clinical practice) (28) were replaced with nasal cannulas and the pneumotachograph by an alternative ventilation sensor.

Study limitations. Larger studies that go beyond this proof-of-concept to evaluate sleep architecture are needed to examine the effect of this administration on CSA in HF patients and to assess whether CSA is converted to obstructive sleep apnea (29).

Conclusions

This study demonstrates that dynamic CO_2 administration, when given at the right time, almost abolishes the oscillations in et-CO_2 that drive PB. This administration is found to be most effective when CO_2 arrives in the alveoli coincident with hyperventilation. Our results with dynamic CO_2 intervention support the concept of apneas and hypopneas arising from pathological hypocapnia and may offer an opportunity to develop therapies for PB and CSA that might avoid some of the pitfalls of static CO_2 administration.

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Key Words: carbon dioxide ■ periodic breathing ■ treatment.