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 (CO2) oscillations seen in oscillatory ventilation with dynamic pre-emptive CO2 administration.

Background
Oscillations in end-tidal CO2 (et-CO2) 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 CO2 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-CO2 oscillations was achieved when dynamic CO2 was delivered at hyperventilation; when delivered at the opposite phase, the amplitude of et-CO2 oscillations increased (35%, p = 0.001). In HF patients, oscillations in et-CO2 were reduced by 43% and ventilatory oscillations by 68% (both p < 0.05). During dynamic CO2 administration, mean et-CO2 and ventilation levels remained unchanged. Static CO2 (2%, constant flow) administration also attenuated spontaneous PB in HF patients (p = 0.02) but increased mean et-CO2 (p = 0.03) and ventilation (by 45%, p = 0.03).

Conclusions
Dynamic CO2 administration, delivered at an appropriate time during PB, can almost eliminate oscillations in et-CO2 and ventilation. This dynamic approach might be developed to treat central sleep apnea, as well as minimizing undesirable increases in et-CO2 and ventilation. (J Am Coll Cardiol 2010;56:1832–7) © 2010 by the American College of Cardiology Foundation

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We investigated this in 2 ways. First, dynamic CO2 was administered in voluntary periodic breathing (VPB) (12,13) at different timings and concentrations. Second, dynamic CO2 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

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 CO2 (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 CO2 (et-CO2) that produce hypopneas, as well as minimizing any undesirable increase in et-CO2 that could cause hyperventilation and adrenergic overactivation (8–11).
Dynamic CO₂ in Periodic Breathing

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Figure 1

Overview of the System

Representation of the system used to dynamically deliver CO₂ to the subject. The reservoir of CO₂ is maintained at atmospheric pressure, with delivery dependent on the subject’s inspiration.

Table 1

Baseline Characteristics of Healthy Subjects and HF Patients

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>HF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>34 ± 13</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3 ± 0.7</td>
<td>24.1 ± 0.5</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>59.0 ± 5.1</td>
<td>18.5 ± 7.4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.1 ± 7.6</td>
<td>74.2 ± 21.3</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>6.5 ± 2.4</td>
<td>4.1 ± 1.2</td>
</tr>
<tr>
<td>End-tidal CO₂, kPa</td>
<td>6.0 ± 0.7</td>
<td>4.7 ± 0.4</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>98.4 ± 1.1</td>
<td>93.2 ± 1.3</td>
</tr>
<tr>
<td>Ventilation, l/min</td>
<td>7.6 ± 1.5</td>
<td>8.3 ± 1.9</td>
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<tr>
<td>NYHA functional class III/IV</td>
<td>3/1</td>
<td></td>
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<tr>
<td>Etiology</td>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>Dilatative</td>
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</tr>
<tr>
<td>Valvular</td>
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<td></td>
</tr>
<tr>
<td>Alcoholic</td>
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<td></td>
</tr>
<tr>
<td>Treatment</td>
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<tr>
<td>Biventricular pacemaker</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARBs</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

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.

Real-time, with the ventilatory cycle represented as a clock (peak ventilation at 0°, nadir ventilation at 180°).

Dynamically titrated concentrations of CO₂ are delivered according to both magnitude and phase of the current cycle. CO₂ 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.

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 (αVEN) and et-CO₂ (αET-CO₂). The ratio between the alpha values (e.g., αET-CO₂/αVEN) controls for variation in depth of ventilatory oscillations.

CO₂ 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 CO₂ at -40° so that CO₂ would arrive in the alveolar space coincident with peak ventilation.

In VPB, to explore the effect of the phase of CO₂ administration, we performed replicate experiments where CO₂ was delivered at -130°, -85°, 5°, 50°, and 140°. The effect of dose was established by delivering CO₂ at -40° with peak concentration of 1%, 2%, and 4%. In HF patients with spontaneous PB, dynamic CO₂ administration (2% at -40°) and static (2%) CO₂ 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.


t-Test

p < 0.05 was considered significant.


differences between repeated measurements

were analyzed by paired t test

where p < 0.05 was considered significant.


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differences between repeated measurements

were analyzed by paired t test

where p < 0.05 was considered significant.
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 CO₂ administration in VPB.** The greatest reduction in size of et-CO₂ oscillations occurred when CO₂ 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 CO₂ delivery were less effective in attenuating et-CO₂ 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 CO₂ with peak concentration of 2% was more effective than 1% in attenuating et-CO₂ 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-CO₂ oscillations (0.05 ± 0.01 vs. 0.05 ± 0.02, \( p = 0.47 \)) (Fig. 3).

**Dynamic CO₂ administration in HF patients with spontaneous PB.** When CO₂ was delivered coincident with peak ventilation, et-CO₂ oscillations were reduced by 43% (SD = mean: 0.07 ± 0.03 untreated vs. 0.04 ± 0.02 treated

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of VPB in Healthy Volunteers on Ventilatory and Hemodynamic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voluntary Periodic Breathing</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>Ventilation, l/min</td>
<td>9.6 ± 2.4</td>
</tr>
<tr>
<td>End-tidal CO₂, kPa</td>
<td>5.08 ± 0.73</td>
</tr>
<tr>
<td>End-tidal O₂, kPa</td>
<td>16.14 ± 1.36</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72.26 ± 7.41</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>88.91 ± 22.93</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.59 ± 1.72</td>
</tr>
</tbody>
</table>

VPB = voluntary periodic breathing.

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**Figure 2** Phase of CO₂ Administration in VPB

Effect of changing the phase of dynamic CO₂ on end-tidal CO₂ in 1 volunteer (top) and on the \( \alpha_{CO₂}/\alpha_{VEN} \) ratio in all volunteers (bottom). VPB = voluntary periodic breathing.
CO₂, p < 0.01) (Figs. 4 and 5). This significant attenuation of et-CO₂ 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-CO₂ (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 (SₚO₂) was higher following dynamic CO₂ administration (95.0 ± 2.4% treated vs. 93.2 ± 1.3% untreated, p = 0.02). Moreover, the magnitude of desaturation was reduced (minimum SₚO₂: 93.6 ± 1.7 vs. 89.4 ± 1.7, p = 0.01).

**Figure 3** Peak Dose of CO₂ Administration in VPB

Effect of changing the peak dose of dynamic CO₂ on end-tidal CO₂ in 1 volunteer (top) and on the α<sub>CO₂/ven</sub> ratio in all volunteers (bottom). VPB = voluntary periodic breathing.

**Figure 4** Dynamic CO₂ 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 CO₂. The delivery of 2% CO₂ (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 CO₂, but also the fluctuations in ventilation, without increasing their average values. HF = heart failure; PB = periodic breathing.
Static CO₂ administration in HF patients with spontaneous PB. Static CO₂ also stabilized breathing (SD ± mean: of ventilation, 0.14 ± 0.06, and of CO₂, 0.03 ± 0.01). However, static CO₂ significantly increased et-CO₂ (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 CO₂ 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 CO₂ 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 CO₂ oscillations that drive PB using dynamically timed CO₂ administration. However, timing is critical, the most efficacious administration being coincident with peak ventilation.

Because CO₂ is only delivered for a small part of the PB cycle, the total quantity of CO₂ delivered is markedly reduced, thus minimizing unwanted consequences of increased et-CO₂, such as increased mean ventilation and sympathetic overactivation (8–11).

Periodic breathing and CO₂. 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 CO₂ is efficacious in abolishing CSA (8,9), by increasing eupneic CO₂ when wakefulness drive is lost (25), but creates undesirable elevations in mean ventilation and sympathetic activity (8–11). With dynamic CO₂, the average dose of CO₂ delivered is lower (0.5%), compared with static CO₂ (2%), but achieves a 67% and 43% reduction in et-CO₂ oscillations in VPB and spontaneous PB, respectively.

There is a nonsignificant trend toward higher et-CO₂ 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. CO₂ administration may not only increase the eupneic CO₂, but may beneficially lower pulmonary capillary wedge pressure via vasodilation (26).

The minimization of dose was achieved using the following strategy:

1. CO₂ 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 CO₂ 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 CO₂ administration, when given at the right time, almost abolishes the oscillations in et-CO₂ that drive PB. This administration is found to be most effective when CO₂ arrives in the alveoli coincident with hyperventilation. Our results with dynamic CO₂ 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 CO₂ administration.

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