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

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).

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
Table 1  Baseline Characteristics of Healthy Subjects and HF Patients

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>HF Patients</th>
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<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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<td>NYHA functional class III/IV</td>
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<table>
<thead>
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<th>Etiology</th>
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<tr>
<td>Ischemic</td>
<td>3</td>
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<tr>
<td>Dilative</td>
<td>2</td>
</tr>
<tr>
<td>Valvular</td>
<td>1</td>
</tr>
<tr>
<td>Alcoholic</td>
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<th>Treatment</th>
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<tbody>
<tr>
<td>Biventricular pacemaker</td>
<td>4</td>
</tr>
<tr>
<td>ACE inhibitor/ARBs</td>
<td>7</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6</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.

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.
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 $-40^\circ$ (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 $-40^\circ$. In the extreme (180° away from $-40^\circ$, 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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Absolute Amplitude of Oscillation</th>
<th>Relative Amplitude of Oscillation Compared With That in Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation, l/min</td>
<td>9.6 ± 2.4</td>
<td>4.2 ± 1.8</td>
<td>0.42 ± 0.15</td>
</tr>
<tr>
<td>End-tidal CO$_2$, kPa</td>
<td>5.08 ± 0.73</td>
<td>0.45 ± 0.21</td>
<td>0.09 ± 0.04</td>
</tr>
<tr>
<td>End-tidal O$_2$, kPa</td>
<td>16.14 ± 1.36</td>
<td>0.94 ± 0.45</td>
<td>0.06 ± 0.03</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72.26 ± 7.41</td>
<td>1.83 ± 1.30</td>
<td>0.03 ± 0.02</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>88.91 ± 22.93</td>
<td>3.44 ± 1.79</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.59 ± 1.72</td>
<td>0.32 ± 0.15</td>
<td>0.06 ± 0.03</td>
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</tbody>
</table>

VPB = voluntary periodic breathing.

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**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.
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 (S_pO₂) 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 S_pO₂: 93.6 ± 1.7 vs. 89.4 ± 1.7, p = 0.01).
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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REFERENCES


Key Words: carbon dioxide • periodic breathing • treatment.