Real-time dynamic CO2 administration: a novel treatment strategy for periodic breathing

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Objectives and background: Oscillations in end-tidal carbon dioxide (et-CO2) drive the characteristic ventilatory oscillations of periodic breathing (PB) and Cheyne-Stokes respiration (CSR) in heart failure (HF). Exogenous CO2 administration (constant concentration, constant flow) successfully avoids apnoeas but is associated with significantly increased et-CO2 which may contribute to sympathetic hyperactivity.

We aimed to minimise the quantity of CO2 delivered whilst still stabilising ventilation, by specifically targeting the hyperventilation phase, which drives down CO2 levels. By filling in these troughs in et-CO2 with small doses of CO2, we aimed to establish whether et-CO2 oscillations may be attenuated, stabilizing PB without significantly increasing et-CO2 and ventilation.

Methods: Seven heart failure patients with spontaneous daytime PB (four had apneas, EF 18.5±7.4, cardiac output 4.1±1.2 L/min) underwent dynamic CO2 administration delivered by an automated algorithm that monitors ventilation but not CO2. Starting from a fixed concentration of CO2 in a reservoir and using a custom motorized valve, CO2 was delivered in a sinusoidal profile with the peak concentration (2%) timed to be coincident with peak ventilation for up to half the ventilatory cycle. The coefficient of variation and mean et-CO2 and ventilation, for baseline PB, dynamic therapy and static CO2 administration (2%, constant flow throughout the ventilatory cycle) were assessed.

Overview of the delivery system

![Diagram of the delivery system](image-url)

Representation of the system used to dynamically deliver CO2 to the subject.
Results: Et-CO₂ oscillations were 52% smaller (sd/mean = 0.072±0.03 untreated versus 0.041±0.023 treated CO₂, p<0.01) following dynamic CO₂ administration, without significantly increasing mean et-CO₂ (4.7±0.4 versus 5.0±0.3 kPa, p=0.06). This significant attenuation of end-tidal CO₂ oscillations resulted in dramatic attenuation of the ventilatory oscillations by 68% (sd/mean of ventilation from 0.43±0.19 untreated to 0.13±0.09 treated, p=0.01 but critically there was no increase in mean ventilation with dynamic administration (0.14±0.03 versus 0.16±0.05 L/s, p=0.12). Application of static CO₂ rather than dynamic CO₂ also stabilised breathing (sd/mean of ventilation 0.14±0.06 and sd/mean CO₂ 0.026±0.006). However static CO₂ significantly increased end-tidal CO₂ (5.2±0.3 versus 4.7±0.4 kPa, p=0.03) and ventilation (0.20±0.07 versus 0.14±0.03 L/s, p=0.03). There was a non-significant trend toward reduced oscillations in BP (sd/mean = 0.14±0.11 versus 0.08±0.03, p=0.15 when with dynamic CO₂ administration.

Dynamic CO2 administration in one patient with Cheyne-Stokes respiration

Example of one 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 oscillation in end-tidal CO2, but also the fluctuation in ventilation, without increasing their average values.

Conclusions: This study demonstrates that dynamic CO₂ administration, when given at the right time, almost abolishes the oscillations in end-tidal CO₂ that drive PB. We have demonstrated a simple algorithm that can control delivery in real time, using only a ventilatory signal to guide it. Dynamic CO₂ offers an opportunity to develop therapies for PB, whilst avoiding some pitfalls of static CO₂ therapy.