Control theory prediction of resolved Cheyne–Stokes respiration in heart failure

Scott A. Sands[1,2,3,4], Bradley A. Edwards[3,5,6], Kirk Kee[1,2], Christopher Stuart-Andrews[1], Elizabeth M. Skuza[4], Teanau Roebuck[1], Anthony Turton[7], Garun S. Hamilton[7,8], Matthew T. Naughton[1,2] and Philip J. Berger[4]

Affiliations: [1]General Respiratory and Sleep Medicine, Dept of Allergy Immunology and Respiratory Medicine, The Alfred, Melbourne, Australia. [2]Central Clinical School, Monash University, Melbourne, Australia. [3]Sleep Disordered Breathing Laboratory, Division of Sleep and Circadian Disorders, Depts of Medicine and Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [4]The Ritchie Centre, Hudson Institute of Medical Research, Monash University, Melbourne, Australia. [5]Sleep and Circadian Medicine Laboratory, Dept of Physiology, Monash University, Melbourne, Australia. [6]School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, Australia. [7]Monash Lung and Sleep, Monash Medical Centre, Melbourne, Australia. [8]School of Clinical Sciences, Monash University, Melbourne, Australia.

Correspondence: Scott A. Sands, Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA, 02115, USA. E-mail: sasands@partners.org

ABSTRACT Cheyne–Stokes respiration (CSR) foretells deleterious outcomes in patients with heart failure. Currently, the size of therapeutic intervention is not guided by the patient's underlying pathophysiology. In theory, the intervention needed to resolve CSR, as a control system instability (loop gain >1), can be predicted knowing the baseline loop gain and how much it falls with therapy.

In 12 patients with heart failure, we administered an inspiratory carbon dioxide fraction of 1–3% during CSR (n=95 interventions) as a means to reduce loop gain. We estimated the loop gain on therapy ($LG_{therapy}$), using the baseline loop gain (using hyperpnoea length/cycle length) and its expected reduction (18% per 1% inspired carbon dioxide), and tested the specific hypothesis that $LG_{therapy}$ predicts CSR persistence ($LG_{therapy}$ >1) *versus* resolution ($LG_{therapy}$ <1).

As predicted, when $LG_{therapy}$ >1.0, CSR continued during therapy in 23 out of 25 (92%) trials. A borderline loop gain zone ($0.8<LG_{therapy}<1$) yielded an unpredictable outcome, while $LG_{therapy}$ <0.8 consistently yielded CSR resolution (37 out of 37 trials). A threshold of $LG_{therapy}=0.9$ determined outcome in 76 out of 95 (80%) trials.

We establish proof-of-concept that control theory provides predictive insight into CSR resolution in heart failure. Thus, we now have a means to calculate the size of interventions needed to ameliorate CSR on a patient-by-patient basis.

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Introduction

Cheyne–Stokes respiration (CSR), characterised by a recurrent crescendo–decrescendo pattern of hyperventilation followed by absence of respiratory effort, is common in patients with heart failure and predicts deleterious outcomes [1, 2]. Currently, there is no proven therapy for CSR. Adaptive servo-ventilation, a dynamic mode of bilevel positive airway pressure, was recently found to increase cardiovascular mortality [3]. Remaining treatment options under clinical investigation, including continuous positive airway pressure (CPAP), supplemental oxygen and respiratory stimulants such as acetazolamide and inspired carbon dioxide (CO_2), are effective at resolving CSR in some patients but not others [2, 4–6]. Thus, an individualised approach to managing CSR has been recommended [7, 8].

While CSR resolution with treatment appears unpredictable, our central hypothesis is that prevailing control theory can be used to calculate the dose of a therapy that will restore continuous breathing. According to control theory, CSR resolution will occur when the loop gain of the ventilatory control system is moved sufficiently below the tipping point for instability (loop gain on therapy ($LG_{therapy}$) <1.0) but not otherwise [5, 9, 10] (see methods and online supplementary fig. S1). We propose, that if control instability causes CSR, then estimating the $LG_{therapy}$, based on knowledge of the baseline loop gain and how much a therapy reduces loop gain, will enable the explicit prediction of CSR resolution. The predictive value of this theoretical framework remains untested.

Here we provide proof-of-concept that control theory provides quantitative predictive insight into CSR resolution in patients with heart failure. During CSR, we employed inspired CO_2, a potent dose-dependent respiratory stimulant, to experimentally lower loop gain and acutely stabilise breathing. For each intervention, $LG_{therapy}$ was calculated (see the methods section) and used to test the specific hypothesis that $LG_{therapy}$ predicts persistence ($LG_{therapy}$ >1) *versus* resolution ($LG_{therapy}$ <1) of CSR with each intervention. Accurate prediction is taken as novel evidence to support the applicability of control theory to explain the genesis and resolution of CSR in heart failure.

Methods

Theory

Loop gain is defined as the magnitude of the ventilatory chemoreflex response to a ventilatory disturbance such as apnoea or hypopnoea. When the response is greater than the prior disturbance, *i.e.* loop gain exceeds 1, a small oscillation will grow to yield CSR [9, 10] (online supplementary material). As loop gain rises progressively beyond 1, theoretically, a stronger treatment dose is required to stabilise breathing [5].

Methodological approach

First, we measured a single parameter (m=18) that describes the expected percentage reduction in loop gain for each 1% rise in inspired CO_2. This parameter was measured using the reduction in the difference between alveolar and inspired CO_2 levels (P_{CO_2} (alveolar CO_2 tension (P_{ACO_2}) − inspired CO_2 tension (P_{ICO_2})) with raised inspired CO_2. Theoretically, inspired CO_2 reduces loop gain *via* a proportional fall in $P_{ACO_2}-P_{ICO_2}$ [9–11] and is unlikely to impact the other influencing factors (chemosensitivity, circulatory delay and lung volume; see online supplementary material equation S1). Parameter m was assessed during wakefulness, separately from the CSR interventions, to enable the predictive value of control theory to be tested.

Second, during epochs of CSR in sleep, we measured baseline loop gain and calculated the expected $LG_{therapy}$ for each CO_2 intervention, to predict whether CSR would persist or resolve. For example, if baseline loop gain is 1.4, then 1% CO_2 will reduce loop gain by 18% and should not resolve CSR ($LG_{therapy}$=baseline loop gain×(1 − m×F_{ICO_2})=1.15), whereas 2% CO_2 will reduce loop gain by 36% and should therefore resolve CSR ($LG_{therapy}$=0.896).

Participants

12 male patients with heart failure and CSR (apnoea–hypopnoea index >30 events·h^{-1} and the presence of central events characteristic of CSR) were recruited from The Alfred and Monash Medical Centre (Melbourne, Australia) sleep laboratories (table 1). Patients provided written informed consent and approval was granted by the human research ethics committees of Monash University, Monash Health and The Alfred. Methodological details are provided in the online supplementary material.

Polysomnography

Patients underwent full clinical polysomnography to assess severity of sleep apnoea. Sleep, respiratory events and arousals were scored according to standard criteria (hypopnoeas required ⩾3% desaturation or arousal). Apnoeas were defined as central, rather than obstructive, if there was an absence (⩾90% reduction) of respiratory effort (chest and abdominal excursions). Hypopnoeas were defined as central in

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TABLE 1 Patient characteristics

Demographics	
Age years	67±9
BMI kg·m^{-2}	29±4
Cardiomyopathy	
Aetiology (ischaemic:nonischaemic)	11:1
Systolic function (impaired:preserved)	8:4
Left ventricular ejection fraction	0.42±0.17
New York Heart Association class (1:2:3)	1:5:6
Medications (yes:no)	
Diuretics	9:3
β-blockers	7:5
ACEi/AT2R	11:1
Digoxin	6:6
Class III antiarrhythmic	3:9
Spironolactone	5:7
Diagnostic polysomnography	
Total apnoea–hypopnoea index events·h^{-1}	54±15
Central apnoea index events·h^{-1}	19±15
Central hypopnoea index events·h^{-1}	5±5
Mixed apnoea index events·h^{-1}	19±16
Obstructive apnoea index events·h^{-1}	7±5
Obstructive hypopnoea index events·h^{-1}	4±4
Arousal index events·h^{-1}	36±12
Nadir S_{pO_2} %	81±7
Epworth sleepiness scale	10±4
Ventilatory control[#]	
V'_E[¶] L·min^{-1}	11.2±2.9
P_{ACO_2}[¶] mmHg	30.6±2.6
P_{AO_2}[¶] mmHg	113.2±5.3
Plant gain $\Delta P_{ACO_2}/\Delta V'_E$ mmHg·L^{-1}·min	0.37±0.08
Controller gain $\Delta V'_{drive}/\Delta P_{ACO_2}$ L·min^{-1}·mmHg^{-1}	1.99±0.54
Circulatory delay[+] s	12.5±2.3
Cycle duration s	68±11
Loop gain at baseline[§]	1.25±0.19

Data are presented as n or mean±SD. BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitor; AT2R: angiotensin II receptor antagonist; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; V'_E: ventilation (tidal volume×respiratory rate); P_{ACO_2}: alveolar carbon dioxide tension; P_{AO_2}: alveolar oxygen tension; V'_{drive}: ventilatory drive. [#]: measured during Cheyne–Stokes respiration (baseline periods); [¶]: contrast with normal values for V'_E, P_{ACO_2} and P_{AO_2}, of 7 L·min^{-1}, 40 mmHg and 100 mmHg, respectively [12]; [+]: latency between fluctuations in P_{CO_2} and fluctuations in ventilation; [§]: baseline loop gain values ranged from 1.03–1.70.

the absence of evidence of airflow obstruction (inspiratory flattening/scooping on the flow trace, increased inspiratory time, snoring or thoracoabdominal paradox).

Subsequently, patients underwent an overnight research polysomnography with additional physiological measurements, including a sealed full-face mask to facilitate measurement of ventilation and end-tidal CO_2 (NICO; Novametrix, Wallingford, CT, USA). A non-rebreathing valve (Series 2600; Hans Rudolph, Shawnee Mission, KS, USA) enabled switching of inspired gases from air to various concentrations of inspired CO_2 (in 21% oxygen, remainder nitrogen) from a Douglas bag located in an adjacent anteroom. End-tidal gases were used to estimate alveolar levels.

Expected reduction in loop gain with inspired P_{CO_2}

To calculate the effect of inspired CO_2 on $P_{ACO_2}-P_{ICO_2}$ (parameter m), we measured the fall in $P_{ACO_2}-P_{ICO_2}$ with inspired CO_2 prior to sleep (n=8; figure 1). 3% inspired CO_2 was applied for 2 min. The mean value (m=18) was used for all predictions during CSR.

Inspired CO_2 administration during Cheyne–Stokes respiration

During established CSR in non-rapid eye movement (NREM) sleep, inspired gas was switched from room air to 1%, 2% or 3% inspired CO_2 for 10 min repeatedly overnight. Each intervention was classified as resolved or persistent; persistent CSR was defined as ongoing apnoeas/hypopnoeas >25% of the time (equivalent to ~15 events·h^{-1}), allowing time for oscillations to dampen out.

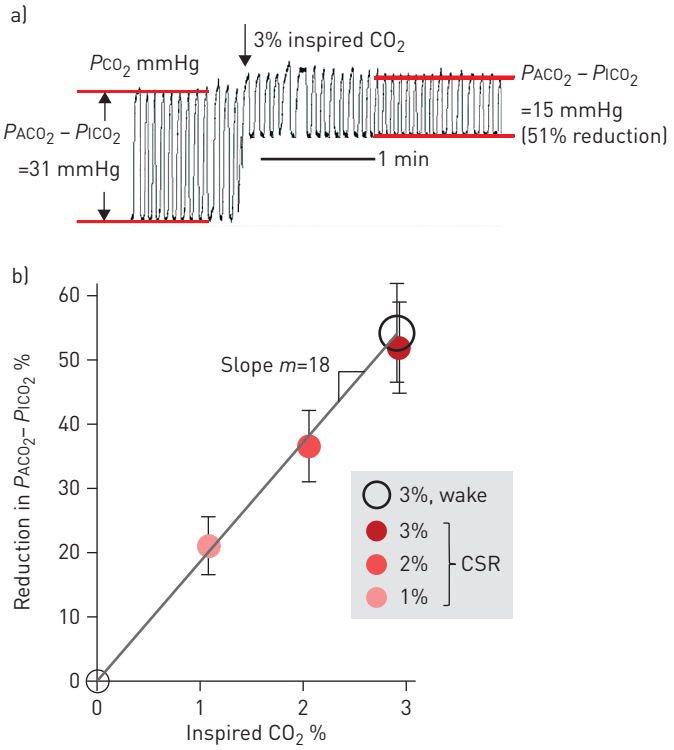

FIGURE 1 Magnitude of reduction in alveolar inspired carbon dioxide tension (P_{CO_2}) gradient (alveolar CO_2 tension (P_{ACO_2}) – inspired CO_2 tension (P_{ICO_2})) with inspired CO_2, the control theory based mechanism by which inspired CO_2 improves ventilatory instability. a) Example trace illustrating the ~50% reduction in $P_{ACO_2} - P_{ICO_2}$ with 3% CO_2 during wakefulness. b) The large open circle illustrates the group data effect of inspired CO_2 on $P_{ACO_2} - P_{ICO_2}$ during wakefulness (y=mx, m=18, n=8). For comparison, closed circles illustrate the effect of inspired CO_2 on $P_{ACO_2} - P_{ICO_2}$ during Cheyne–Stokes respiration (CSR) in sleep (n=12).

Baseline loop gain during Cheyne–Stokes respiration

To determine the baseline loop gain we measured the median duty ratio (ventilatory length/cycle length; figure 2) using the respiratory excursion signals in the 5 min preceding each CO_2 intervention [5]. Loop gain was calculated from the duty ratio using a simple equation $LG_{baseline}=2\pi$ / (2π(duty ratio) − sin2π (duty ratio)) [5] (online supplementary material).

Confirming the stabilising mechanism of inspired CO_2

In secondary analysis, we confirmed that inspired CO_2 acts to reduce loop gain *via* a reduction in $P_{ACO_2}-P_{ICO_2}$ rather than other factors (chemosensitivity or circulatory delay). Lowering $P_{ACO_2}-P_{ICO_2}$ theoretically reduces the magnitude of P_{ACO_2} swings relative to swings in ventilation (plant gain). Accordingly, we measured plant gain, chemosensitivity and circulatory delay in the 5 min before and after the onset of each intervention. Plant gain was measured by fitting a single-compartment gas exchange model [9] that transforms ventilatory fluctuations into a continuous P_{ACO_2} signal (best-fit to end-tidal P_{CO_2}). Similarly, chemosensitivity and circulation delay were calculated using a delayed single-compartment model that converts P_{ACO_2} into a ventilation signal (best-fit to ventilation data while ventilation >0). The continuous model P_{ACO_2} enabled assessment of changes to the mean $P_{ACO_2} - P_{ICO_2}$ during CSR.

Statistics

Differences in baseline loop gain between interventions leading to persistent *versus* resolved CSR were assessed using t-tests. Logistic regression assessed whether loop gain predicted responses to CO_2 stimulation after accounting for potential effects of individual subjects. Repeated measures ANOVA assessed differences in multiple variables with intervention (including $P_{ACO_2}-P_{ICO_2}$). $p<0.05$ was considered statistically significant.

Results

The study group exhibited severe, predominantly central sleep apnoea with substantial hyperventilation and hypocapnia (table 1).

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Expected reduction in loop gain with inspired P_{CO_2}

During wakefulness, 3% inspired CO_2 produced a mean±SEM 54±3% reduction in $P_{ACO_2}-P_{ICO_2}$ (figure 1), equivalent to an 18% reduction in loop gain per percentage increase in inspired CO_2 (m=18).

Predicting persistent versus *resolved Cheyne–Stokes respiration*

Figure 2 illustrates an example effect of inspired CO_2 on CSR (during NREM stage 1 sleep). Based on the baseline loop gain of 1.4, 1% CO_2 was expected to yield persistent CSR ($LG_{therapy}$ >1), whereas 2% CO_2 was expected to yield resolved CSR ($LG_{therapy}$ <1), as observed experimentally.

In total, a mean±SD 8±6 interventions were delivered during CSR per patient (95 in total). Group data demonstrated that baseline loop gain was higher prior to epochs of persistent CSR than epochs of resolved CSR with 1% and 2% CO_2; 3% CO_2 resolved CSR in all cases (figure 3a). The predicted loop gain post-intervention, $LG_{therapy}$, was markedly greater in persistent *versus* resolved CSR (figure 3b). A loop gain ($LG_{therapy}$) threshold of 0.9 correctly predicted successful/failed interventions in 76 (80±4%) out of 95 interventions. Of the 37 interventions in which $LG_{therapy}$ was <0.8, CSR was resolved on all 37 occasions. When $LG_{therapy}$ was >1.0, CSR persisted on 23 out of 25 occasions. Accounting for individual patients using logistic regression did not alter these findings (online supplementary material).

Confirming the stabilising mechanism of inspired CO_2

During CSR, inspired CO_2 had a small impact on mean P_{ACO_2} (figure 4a) consistent with a marked rise in mean ventilation (figure 4b) (by ~18% per 1% rise in inspired CO_2), such that $P_{ACO_2} - P_{ICO_2}$ fell by 18% per 1% rise in inspired CO_2 (confirming m=18; figure 4c). The magnitude of reduction in plant gain matched the magnitude of reduction in $P_{ACO_2} - P_{ICO_2}$ (figure 4d, e), as proposed. The example trace in figure 2 illustrates that with 1% and 2% inspired CO_2, plant gain was reduced by 20% and 37% from baseline (note smaller oscillations in P_{ACO_2} per swings in ventilation). We found no effect of inspired CO_2 on chemosensitivity (p=0.4, repeated-measures ANOVA; figure 4f) or circulatory delay (p=0.7; figure 4g).

Discussion

Our study demonstrates that the magnitude of the stabilising intervention (reduction in loop gain) necessary to convert CSR into continuous breathing in patients with heart failure is mathematically predictable using control theory. Using inspired CO_2 to lower loop gain, we found that a more potent and quantifiable dose is required to achieve stable breathing for cases with a higher baseline loop gain. Through

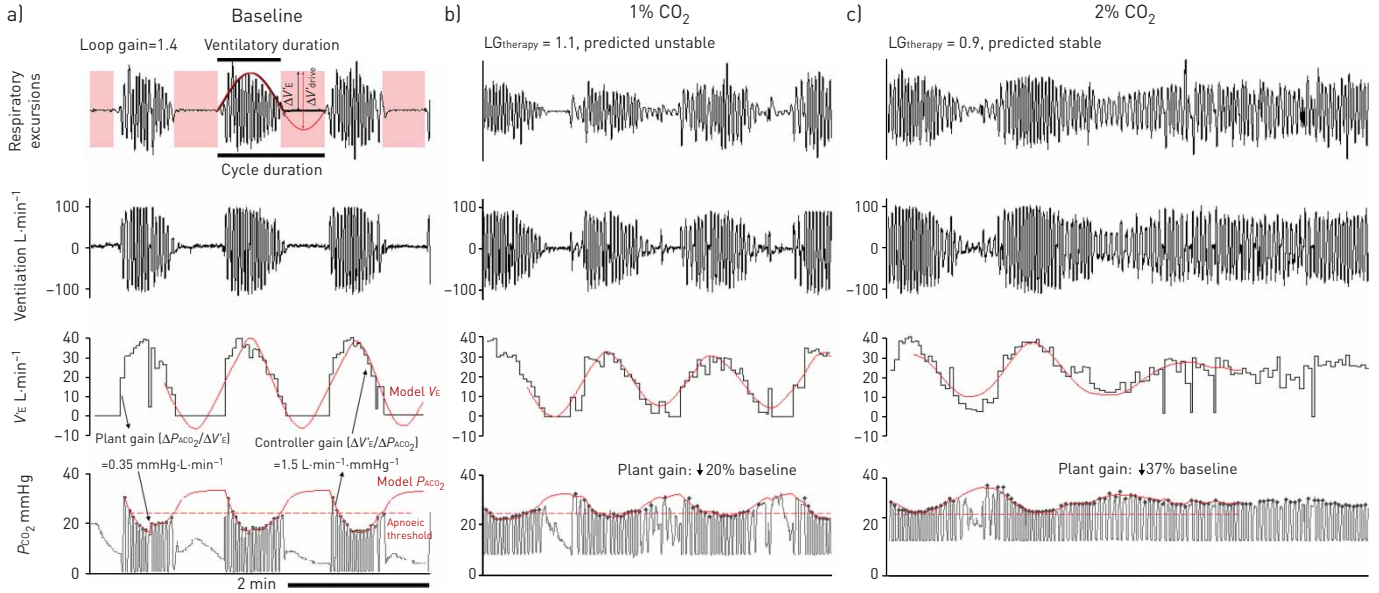

FIGURE 2 Example trace illustrates that loop gain predicts the dose of inspired carbon dioxide (CO_2) required to resolve Cheyne–Stokes respiration (CSR). a) Baseline measurements. Loop gain (LG) at baseline was 1.4, as revealed by the duty ratio of the CSR pattern (ventilatory duration/cycle duration); the superimposed sinusoid illustrates that the swings in ventilatory drive ($\Delta V'_{drive}$) are 1.4 times larger than the swings in ventilation ($\Delta V'_E$). b) 1% inspired CO_2 yields persistent CSR, as predicted based on the expected reduction in loop gain (18%). c) Administration of 2% CO_2 yields resolved CSR, as predicted based on the expected reduction in loop gain (36%). Shaded regions in (a) denote central apnoeas. The respiratory excursions signal is the sum of thoracic and abdominal signals. Red lines denote best-fit model traces for alveolar CO_2 tension (P_{ACO_2}) and ventilation used to calculate plant gain, chemosensitivity and delay. The P_{ACO_2} threshold that yields apnoea (24 mmHg) is also shown. See text for additional details. P_{CO_2}: carbon dioxide tension.

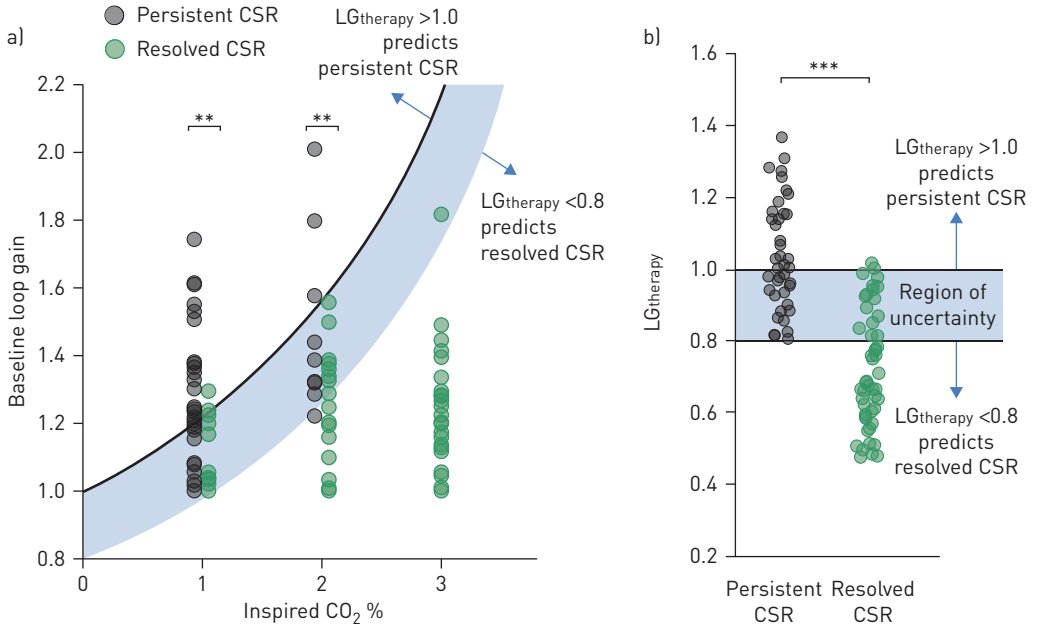

FIGURE 3 Group data demonstrate that loop gain predicts the resolution of Cheyne–Stokes respiration (CSR) with inspired carbon dioxide (CO_2). a) Loop gain at baseline, calculated using the duty ratio of CSR, is lower prior to epochs of resolved CSR than epochs of persistent CSR with 1% and 2% CO_2. 3% CO_2 resolved CSR in all cases. The expected loop gain on therapy ($LG_{therapy}$) is calculated from the baseline loop gain and the expected reduction in plant gain (18% reduction in alveolar CO_2 tension (P_{ACO_2}) – inspired CO_2 tension (P_{ICO_2}) per % inspired CO_2): $LG_{therapy}$ >1 predicts persistent CSR (solid line), and $LG_{therapy}$ <0.8 predicts resolved CSR. b) $LG_{therapy}$ is greater in persistent *versus* resolved CSR. **: p<0.01; ***: p<0.001 using t-tests.

such a demonstration, our study provides novel evidence that control theory explains the genesis and resolution of CSR in heart failure. Employing this quantitative approach to CSR treatment may ultimately enable provision of therapies with appropriate scope to ameliorate CSR on an individualised basis.

Predicting persistent versus *resolved Cheyne–Stokes respiration*

Our study demonstrates that a more severe ventilatory instability (higher baseline loop gain) requires a greater, yet predictable therapeutic dose to reduce loop gain sufficiently to resolve CSR. Consistent with this finding, we previously reported that loop gain is higher in heart failure patients whose CSR persists on

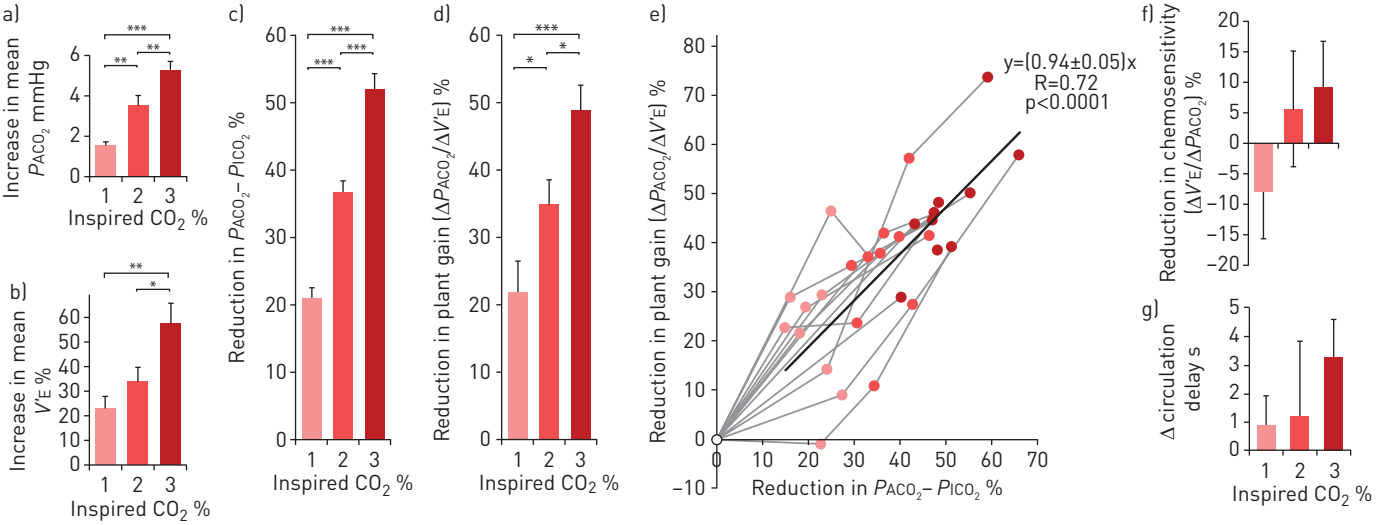

FIGURE 4 Confirming the stabilising mechanism of inspired carbon dioxide (CO_2). Effects of inspired CO_2 stimulation on (a) mean alveolar CO_2 tension (P_{ACO_2}); (b) mean ventilation (V'_E); (c) the alveolar–inspired CO_2 tension (P_{CO_2}) gradient (P_{ACO_2} – P_{ICO_2}); and (d) plant gain for CO_2 ($\Delta P_{ACO_2}/\Delta V'_E$). e) Inspired CO_2 lowered plant gain in direct proportion to the reduction in P_{ACO_2} – P_{ICO_2}. Neither controller gain (f) nor circulatory delay (g) was significantly lowered by inspired P_{CO_2}. *: p<0.05; **: p<0.01; ***: p<0.001 ANOVA with *post hoc* comparisons.

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a CPAP titration *versus* those with resolved CSR [5]. Furthermore, a higher loop gain on CPAP, in patients without heart failure, predicts CSR persistence with continued CPAP treatment over time [13].

Control theory as general framework for CSR pathogenesis and treatment

Our work provides quantitative evidence supporting the concept that CSR manifests due to unstable chemoreflex feedback control of ventilation [5, 9, 10, 14–16]. We show here that control theory explains the pattern of CSR changes with an increasing P_{ICO_2}. Based on control theory, inspired CO_2 has its primary impact *via* reducing $P_{ACO_2} - P_{ICO_2}$ and thus plant gain: the fundamental reason for CSR resolution is that ventilatory swings are now markedly less effective at altering P_{ACO_2}. A role for reducing plant gain with inspired P_{CO_2} has been suggested previously, based on theoretical principles [11, 17], but the powerful size of this effect had not been proven experimentally in human patients. In an ovine model of periodic breathing we previously illustrated that reduction of the alveolar inspired gradient lowered loop gain in direct proportion [5]. Similarly, by direct measurement in patients with heart failure, we show for the first time that lowering $P_{ACO_2} - P_{ICO_2}$ lowers plant gain in direct proportion, and CSR abates when a sufficient dose is administered relative to baseline loop gain.

The three other main variables that determine loop gain (online supplementary equation S1) are unlikely to be affected by inspired CO_2 stimulation. Lung gas volume is unlikely to be affected, although a small increase may accompany increased ventilation; however, any substantial increase in lung gas volume should have been manifest as a more-than-unity relationship between the reduction in plant gain *versus* $P_{ACO_2} - P_{ICO_2}$ (figure 4e). We did not observe a physiologically-relevant reduction in chemosensitivity (figure 4f) (although there was a nonsignificant 5% fall with 2% CO_2 and a <10% fall with 3% CO_2). In addition, circulatory delay (figure 4g) did not fall, suggesting no overt stabilising effect *via* increased cardiac output. Hence, it is the change in plant gain, *via* $P_{ACO_2} - P_{ICO_2}$ alone, that has the capacity to explain how inspired CO_2 has such potency for reducing loop gain and improving ventilatory control system stability. This insight provides a unified mechanism by which respiratory stimulants such as acetazolamide and theophylline, *via* increased ventilation and lowered P_{ACO_2}, act to lower loop gain and improve CSR [12, 18, 19].

As an alternative explanation for CSR, investigators have hypothesised that CSR manifests as a result of the eupnoeic arterial P_{CO_2} lying close to the P_{CO_2} threshold for apnoea [18, 20–33]. In principle, a closer proximity to the apnoeic threshold must increase the likelihood of an apnoea occurring consequent to a spontaneous fall in P_{CO_2} or rise in ventilation. However, this established concept has been extrapolated to explain the genesis of CSR [18, 20–33]. Likewise, CSR suppression *via* inspired CO_2, pharmacological agents, CPAP and supplemental oxygen has been attributed to these treatments promoting reduced proximity to the apnoeic threshold [18, 23–25, 27, 29, 33]. The main weakness of this theory as a stand-alone mechanism of CSR is that it relies upon an external source of cyclic ventilatory perturbations (*e.g.* due to sleep–wake transitions) to drive P_{CO_2} above and below the apnoeic threshold [32]. In contrast, control theory explains the source of ventilatory oscillations and their progressive decay and ultimate disappearance with inspired CO_2 (see online supplementary data figs S2–S4 for additional analysis). Thus, control theory provides a more complete framework for CSR pathogenesis and its resolution with intervention.

Critical loop gain threshold for stability

We expected *a priori* that lowering loop gain below 1 would be sufficient to stabilise breathing. However, we observed that a loop gain threshold of 0.9 provided an improved predictive value compared with 1.0, and targeting a more conservative loop gain threshold (0.8) consistently resolved CSR (37 out of 37 cases). We propose the following explanation for the region of uncertainty ($0.8 < LG_{therapy} < 1.0$, figure 3): While stable systems (loop gain <1) may not yield self-sustained oscillations, they can still profoundly augment disturbances to ventilation (*e.g.* random hypopnoeas) that perturb the feedback loop, akin to the concept of a resonance [34–39]. For example, if loop gain is 0.9, then an external perturbation will be amplified 10-fold (1/(1−loop gain)) to yield ventilatory oscillations at the frequency of CSR [34–39]. In addition, we consider that the simplifying assumption of a roughly linear loop gain underlying CSR may not hold precisely for all cases (*e.g.* those without a typical crescendo–decrescendo pattern); novel approaches to incorporate nonlinear responses may improve the predictive value of the current approach.

Clinical implications

Despite optimal medical therapy for heart failure, the prevalence of CSR remains high [1]. Since the scope of each treatment on loop gain varies widely, understanding how therapies act to lower loop gain, and by what magnitude, provides the knowledge base necessary for personalised clinical management. Respiratory stimulants, which raise ventilation and lower $P_{ACO_2}-P_{ICO_2}$, remain of major interest to clinical investigators [18, 23, 40, 41]. Acetazolamide and theophylline also appear promising at resolving CSR [18, 19, 40, 42]; quantitatively, a high dose of acetazolamide reduces P_{ACO_2}, and thus $P_{ACO_2} - P_{ICO_2}$, by ~20% [12], and should prove effective in patients with a loop gain <1.1. CPAP of 10 cmH_2O increases lung volume by ~20–30%,

a level consistent with it preventing CSR in patients with loop gain <1.2 [5]. Supplemental oxygen lowers loop gain by ~40% in patients without heart failure (at an inspired level of 40%) and therefore could be effective in those with loop gain as high as 1.5 [43]. For cases with higher loop gain, inspired CO_2 or equivalent levels of dead space can effectively resolve CSR, although levels >2% can have adverse effects on sleep [23–25].

It is clear from our work that treatments of insufficient power to resolve CSR can nevertheless reduce loop gain. It follows that a combination of therapies could be used to lower loop gain, an approach that would allow avoidance of undesirable side-effects associated with each individual therapy, such as excessive positive airway pressure effects on cardiac preload and afterload, adverse renal effects of acetazolamide or sleep-related side-effects of CO_2. The combined impact of multiple therapies on loop gain may be interpreted according to the interactive effects of each factor on loop gain (online supplementary equation S1). For example, combining 10 cmH_2O CPAP (~25% reduction in loop gain), 500 mg of acetazolamide (10% reduction in loop gain) and 150 mL dead space (~1% CO_2; 18% reduction in loop gain) may be sufficient to resolve CSR with loop gain up to 1.6, which exceeds the loop gain of almost all patients with CSR [5]. More aggressive cardiac therapies (diuretics and cardiac resynchronisation therapy) may also lower loop gain enough to enable CPAP or acetazolamide to become effective. Our work demonstrates the feasibility of a quantitative approach to CSR interventions, although long-term effects of any contemplated therapies warrant further clinical investigation.

Conclusions

CSR treatment is notoriously challenging, and the current empirical approach to therapy ignores patient pathophysiology: therapies are tried, not knowing whether they will work, or why they fail. We provide proof-of-concept supporting the utility of control theory for predicting and explaining CSR resolution using CO_2 stimulation. We show that application of a therapeutic dose that leaves loop gain >1 is futile, yet readily predicted and that halving loop gain is universally stabilising. We envisage that employing control theory principles may ultimately enable clinicians to select therapies whose stabilising potency best matches an individual's underlying instability. Such an approach holds promise for restoring continuity of respiration and sleep for those whose conditions currently appear intractable.

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