# Prospective targeting and control of end-tidal $CO_2$ and $O_2$ concentrations

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**Current methods of forcing end-tidal $P_{CO_2}$ ($P_{ETCO_2}$) and $P_{O_2}$ ($P_{ETO_2}$) rely on breath-by-breath adjustment of inspired gas concentrations using feedback loop algorithms. Such servo-control mechanisms are complex because they have to anticipate and compensate for the respiratory response to a given inspiratory gas concentration on a breath-by-breath basis. In this paper, we introduce a low gas flow method to prospectively target and control $P_{ETCO_2}$ and $P_{ETO_2}$ independent of each other and of minute ventilation in spontaneously breathing humans. We used the method to change $P_{ETCO_2}$ from control (40 mmHg for $P_{ETCO_2}$ and 100 mmHg for $P_{ETO_2}$) to two target $P_{ETCO_2}$ values (45 and 50 mmHg) at iso-oxia (100 mmHg), $P_{ETO_2}$ to two target values (200 and 300 mmHg) at normocapnia (40 mmHg), and $P_{ETCO_2}$ with $P_{ETO_2}$ simultaneously to the same targets (45 with 200 mmHg and 50 with 300 mmHg). After each targeted value, $P_{ETCO_2}$ and $P_{ETO_2}$ were returned to control values. Each state was maintained for 30 s. The average difference between target and measured values for $P_{ETCO_2}$ was $\pm$ 1 mmHg, and for $P_{ETO_2}$ was $\pm$ 4 mmHg. $P_{ETCO_2}$ varied by $\pm$ 1 mmHg and $P_{ETO_2}$ by $\pm$ 5.6 mmHg (S.D.) over the 30 s stages. This degree of control was obtained despite considerable variability in minute ventilation between subjects ($\pm$ 7.6 l min$^{-1}$). We conclude that targeted end-tidal gas concentrations can be attained in spontaneously breathing subjects using this prospective, feed-forward, low gas flow system.**

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Manipulation of arterial oxygen ($O_2$) and carbon dioxide ($CO_2$) levels has long been used in physiological and clinical studies of, for example, cerebral blood flow and control of breathing (Bradley & Leith, 1978; Ellingsen *et al.* 1987; Laffey & Kavanagh, 1999; Kaanders *et al.* 2002; Ide *et al.* 2003; Floyd *et al.* 2003; Xie *et al.* 2005). In the past, precise independent control of arterial gases in humans has usually been achieved by adjusting inspired gas concentrations on a breath-by-breath basis to attain target end-tidal values (Richardson *et al.* 1966; Weil *et al.* 1970; Moore *et al.* 1984; Ellingsen *et al.* 1987). However, breath-by-breath variations in respiratory frequency and tidal volume ($V_T$) in spontaneously breathing subjects result in an increased variability in end-tidal gas concentrations in a manner that tends to confound closed loop control. For example, a short, small volume breath results in both a lower end-tidal fractional concentration of $CO_2$ ($F_{ETCO_2}$), which would suggest the need for a *higher* inspired fractional concentration of $CO_2$ ($F_{ICO_2}$) for the next breath, as well as a relatively smaller alveolar ventilation ($\dot{V}_A$), which would indicate the need for a *lower* inspired $F_{ICO_2}$ for the next breath. As a result, closed-loop end-tidal forcing requires a very sophisticated prediction–correction scheme. It also requires means to avoid problems inherent in any feedback system, such as signal drift, phase lags and instability, leading to signal oscillations (Smith *et al.* 1978). The introduction of increasingly sophisticated algorithms over the past decade (Robbins *et al.* 1982*a*,*b*; Howard *et al.* 1995; Howson *et al.* 1987), and the use of rapid gas analysers have enabled such end-tidal forcing methods to improve their performance and thus enable a number of sophisticated physiological studies that were not previously feasible (Pandit *et al.* 2003; Poulin *et al.* 1996, 1998, 2002). However, these closed-loop methods still have some drawbacks. They require very high gas flows to meet peak inspiratory flows, and their implementation technology remains bulky, complex and expensive. End-tidal forcing is therefore unsuitable for clinical use and remains restricted to laboratory settings.

As a result, many clinical (Vesely *et al.* 2001; Mikulis *et al.* 2005; Venkataraman *et al.* 2005; Xie *et al.* 2005) and field (Sato *et al.* 1992) studies have relied on

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**Table 1. List of abbreviations**

| Abbreviation | Definition |
|---|---|
| $\dot{V}_A$ | Alveolar ventilation |
| $\dot{V}_{CO_2}$ | Metabolic $CO_2$ production |
| $\dot{V}_{O_2}$ | Metabolic $O_2$ consumption |
| $\dot{V}_{G_1}$ | Flow of Gas 1 |
| $\dot{V}_E$ | Minute ventilation |
| $F_{ACO_2}$ | Alveolar fractional concentration of $CO_2$ |
| $F_{AO_2}$ | Alveolar fractional concentration of $O_2$ |
| $F_{ETCO_2}$ | End-tidal fractional concentration of $CO_2$ |
| $F_{ETO_2}$ | End-tidal fractional concentration of $O_2$ |
| $F_{G_1CO_2}$ | Fractional concentration of $CO_2$ in $\dot{V}_{G_1}$ |
| $F_{G_1O_2}$ | Fractional concentration of $O_2$ in $\dot{V}_{G_1}$ |
| $F_{ICO_2}$ | Inspired fractional concentration of $CO_2$ |
| $G_1$ | Gas 1, entering SGD circuit on inspiratory side |
| $G_2$ | Gas 2, entering SGD circuit after depletion of Gas 1, previously exhaled gas |
| $P_{ETCO_2}$ | End-tidal $P_{CO_2}$ |
| $P_{ETO_2}$ | End-tidal $P_{O_2}$ |
| SGD | Sequential gas delivery |
| $VD_{AN}$ | Anatomical dead space |
| $V_{G_1}$ | Volume of Gas 1 |
| $V_T$ | Tidal volume |

simple breathing circuits that enable maintenance of isocapnia and iso-oxia independent of changes in ventilation and ventilatory pattern. The main advantage of such circuits over the end-tidal forcing technique is that they are self-regulating and do not require sophisticated feedback protocols. The major limitations of such circuits, however, are their inability to precisely target desired end-tidal $CO_2$ and $O_2$ concentrations and to control them independently.

Our aim was to extend the capability of these self-regulating systems to allow prospective targetting and control of end-tidal $P_{CO_2}$ and $P_{O_2}$ ($P_{ETCO_2}$ and $P_{ETO_2}$) independently of each other in spontaneously breathing subjects. Our goal was to simplify the method sufficiently to make it suitable for application in such clinical settings as MRI suites, ophthalmology clinics and vascular ultrasound labs. We illustrate the suitability of our method for clinical testing laboratories by using it to produce rapid cyclic step-changes in both $P_{ETCO_2}$ and $P_{ETO_2}$ with short duration steady states – a feature critical in MRI imaging where inherent drift in the baseline MRI signal requires multiple comparative measurements to be made between two steady-states in order to improve statistical matching of the MR signal to end-tidal gas concentrations (Vesely *et al.* 2001). It is important to point out that the purpose of this study was not to provide a rigorous validation of the 'clamping' properties of the sequential gas delivery (SGD) circuit, which has already been done (Banzett *et al.* 2000; Somogyi *et al.* 2005), but rather to illustrate two new concepts, namely the ability to precisely target $P_{ETCO_2}$ and $P_{ETO_2}$ and control them independently.

## Methods

### Rationale

See Table 1 for a list of the abbreviations used in the following description. In a steady state, $F_{ETCO_2}$ reflects the alveolar fractional concentration of $CO_2$ ($F_{ACO_2}$), which is determined by the metabolic $CO_2$ production ($\dot{V}_{CO_2}$) and $\dot{V}_A$, according to the equation:

$$F_{ACO_2} = \dot{V}_{CO_2} / \dot{V}_A + F_{ICO_2} \quad (1)$$

Gas exchange occurs as gases diffuse down their partial pressure gradients, and the partial pressure of a gas in the alveoli is a function of its concentration and the ambient barometric pressure according to the equation:

$$P_{gas} = F_{gas} \times (P_{bar} - 47) \quad (2)$$

where $P_{gas}$ is the partial pressure of a gas in mmHg, $F_{gas}$ is its fractional concentration, $P_{bar}$ is ambient barometric pressure in mmHg, and 47 is the partial pressure of water vapour at body temperature in mmHg.

In this paper we will refer to both partial pressures and fractional concentrations, as the former is often more familiar to the reader and the latter is required for mass balance calculations.

### Sequential gas delivery

In a steady state, $\dot{V}_{CO_2}$ for any subject is constant. To control $F_{ACO_2}$ and $\dot{V}_A$ we adjust the composition and flow of gas entering an SGD circuit (Somogyi *et al.* 2005) (Fig. 1). We refer to the gas entering the SGD on the inspiratory side as Gas 1, symbolized as $G_1$ (and its volume and flow into the SGD circuit as $V_{G_1}$ and $\dot{V}_{G_1}$, respectively). Gas 2 ($G_2$) refers to the gas entering the lung during inspiration following the exhaustion of $G_1$ in the inspiratory reservoir. In the case of the SGD circuit in Fig. 1, $G_2$ is previously exhaled gas that is rebreathed from the expiratory reservoir via the bypass conduit.

In the following arguments we will derive a series of five rules, using classical physiological principles, that apply to SGD circuits, and which permit prospective determination of end-tidal partial pressures of $O_2$ ($P_{ETO_2}$) and $CO_2$ ($P_{ETCO_2}$) in spontaneously breathing subjects. Although derivation of these rules and the accompanying examples may seem a little pedantic to experienced respiratory physiologists, we feel that this approach will allow the reader to better understand the underlying theory.

### Relationship of $\dot{V}_{G_1}$ to alveolar ventilation ($\dot{V}_A$)

Suppose that a subject is breathing spontaneously on a SGD circuit and $\dot{V}_{G_1}$ into the circuit is gradually reduced until the inspiratory reservoir collapses on average at the end of each inspiration. $\dot{V}_{G_1}$ at this point will be equal

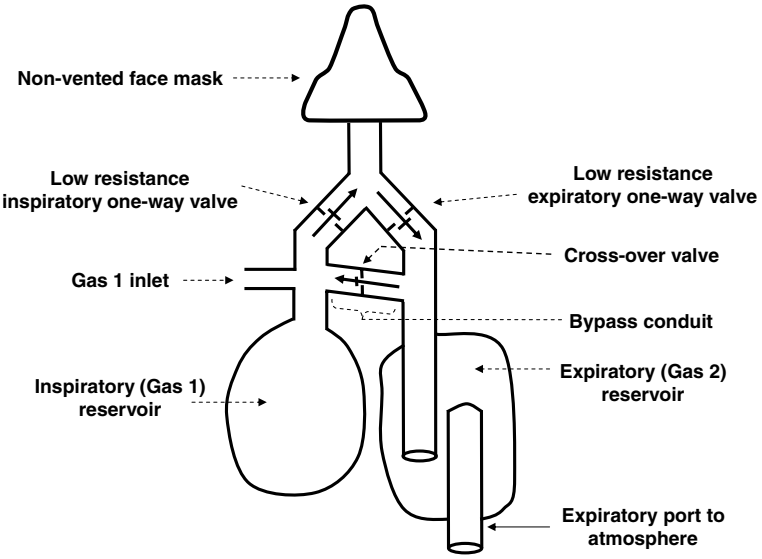


**Figure 1. Schematic of the modified sequential gas delivery circuit**
The manifold attached to the non-vented mask is separated into inspiratory and expiratory limbs using one-way low resistance valves. The two limbs are connected via a bypass limb with a one-way cross-over valve that has an opening pressure greater than that of the other two valves. During exhalation, all of the exhaled gas is directed through the expiratory limb into the atmosphere, with the last portion of the exhaled breath trapped in the expiratory reservoir. At the same time, Gas 1 ($G_1$) collects in the inspiratory reservoir. At the beginning of inhalation, $G_1$ is drawn from the Gas 1 inlet and the inspiratory reservoir. If minute ventilation exceeds the flow of $G_1$ during inhalation, $G_1$ in the reservoir is depleted and the reservoir collapses. The negative pressure in the inspiratory limb causes the cross-over valve to open and the balance of the breath is then made up of Gas 2 from the expiratory reservoir.

to subject's minute ventilation ($\dot{V}_E$) (Fig. 2, stage A). If $\dot{V}_{G_1}$ is then reduced further, the cross-over valve will open and the balance of inspiration will be composed of $G_2$. However, with small reductions in $\dot{V}_{G_1}$ below the subject's $\dot{V}_E$, $F_{ETCO_2}$ does not rise despite rebreathing of the exhaled gas (Somogyi *et al.* 2005) (see stylized capnograph tracing in Fig. 2, stage B). This apparent contradiction can be explained by referring to a simple lung model consisting of anatomical dead space ($VD_{AN}$) in series with alveolar space. Since $G_2$ is only inspired after all of $G_1$ has entered the lung, $G_2$ is initially distributed exclusively to $VD_{AN}$ and therefore has a negligible effect on alveolar gas exchange. In fact, $F_{ETCO_2}$ remains constant until $\dot{V}_{G_1}$ is reduced sufficiently below $\dot{V}_E$ to diminish the fresh gas delivered to the alveoli, i.e. until $\dot{V}_A$ is decreased. In this circumstance, the reduction of $G_1$ is compensated by an increase in $G_2$ (Fig. 2, stage D). Thus, the $\dot{V}_{G_1}$ at which $F_{ETCO_2}$ starts to increase corresponds to the subject's $\dot{V}_A$ ($\dot{V}_E - VD_{AN}$) as illustrated in Fig. 2, stage C. At such a $\dot{V}_{G_1}$, all of $VD_{AN}$ is filled with $G_2$ (Fig. 2, stage C) and any further reduction in $\dot{V}_{G_1}$ effectively reduces $\dot{V}_A$, causing a corresponding increase in $F_{ETCO_2}$ (Fig. 2, stage D). We conclude that the following rule applies to the SGD circuit:

Rule 1: *Whenever $\dot{V}_{G_1}$ is less than or equal to $\dot{V}_A$ (or $\dot{V}_A$ is greater than or equal to $\dot{V}_{G_1}$), then $\dot{V}_{G_1}$ determines $\dot{V}_A$.*

## Concept of 'neutral gas'

When $\dot{V}_{G_1}$ is less than or equal to $\dot{V}_A$, $VD_{AN}$ is filled with previously expired gas, so that the gas in the expired gas reservoir will have a composition that differs from that of a subject breathing room air with a $\dot{V}_{G_1}$ greater than $\dot{V}_A$. Instead of being filled with a 'mixed expired gas' consisting of a combination of alveolar gas and $G_1$ from $VD_{AN}$ it is filled only with *mixed alveolar* gas, because the gas in $VD_{AN}$ is previously expired gas. Mixed alveolar gas is, by definition, fairly well equilibrated with pulmonary capillary blood (West, 1990) and reflects average arterial blood gas partial pressures as long as there are negligible effects from alveolar dead space ventilation and shunt. Therefore mixed alveolar gas re-entering the alveolar space from $VD_{AN}$ during inspiration, increases lung volume but does not affect the $F_{ACO_2}$ and alveolar fractional

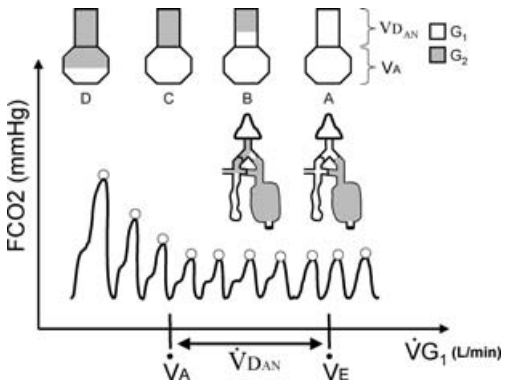


**Figure 2. Changes in end-tidal partial pressure of $CO_2$ ($P_{ETCO_2}$, ○) in response to progressive decrease in the flow of Gas 1 ($\dot{V}_{G_1}$)**
Also shown in the figure is the stylized raw capnograph tracing (continuous line). At the top of the figure, the observed results are explained with a lung model consisting of anatomical dead space ($VD_{AN}$) in series with alveolar volume ($V_A$). If $\dot{V}_{G_1}$ exceeds minute ventilation ($\dot{V}_E$), then the lung is only filled with Gas 1 ($G_1$). When, on average, the inspiratory reservoir of the SGD circuit collapses at the end of each inspiration, $\dot{V}_{G_1}$ equals $\dot{V}_E$ (stage A). If $\dot{V}_{G_1}$ is less than $\dot{V}_E$, Gas 2 ($G_2$) starts to enter the lungs via a bypass conduit of the SGD circuit. This is confirmed by a characteristic rebreathing 'shoulder' at the end of the inspiratory portion of the raw $CO_2$ tracing. $G_2$ remains trapped in $VD_{AN}$ (stage B), however, and therefore has no effect on $P_{ETCO_2}$. $P_{ETCO_2}$ only starts to increase when $G_2$ starts to enter alveoli (stage D). The $\dot{V}_{G_1}$ when $P_{ETCO_2}$ values start to increase corresponds to the alveolar ventilation ($\dot{V}_A$). At this point, all of $VD_{AN}$ is occupied by $G_2$ (stage C).

concentration of $O_2$ ($F_{AO_2}$) (Comroe, 1956; Somogyi *et al.* 2005). We therefore designate mixed alveolar gas as 'neutral' with respect to any effect it will have on the concentrations of alveolar gases, and formulate the following rule that applies to the SGD circuit.

Rule 2: *A gas can be considered 'neutral' with respect to* $\dot{V}_A$ *if its concentration is equal to that in the mixed alveolar gas. Similarly, any component of a gas mixture can be considered 'neutral' with respect to* $\dot{V}_A$ *if the concentration of that component gas is equal to that in the mixed alveolar gas.*

The formulation of Rule 2 extends the argument presented in the preceding paragraph by introducing the concept of a 'component gas'. From the previous discussion, it should be clear that expired (alveolar) gas is 'neutral' with respect to the alveolar exchange of both $O_2$ and $CO_2$. Moreover, these two component gases may be treated independently in terms of their neutrality. For example, if $G_2$ has the same $CO_2$ concentration as that of mixed alveolar gas but an $O_2$ concentration equal to that of air, then $G_2$ is neutral only with respect to $CO_2$. In this case, increasing $\dot{V}_E$ does not affect $F_{ETCO_2}$, but does increase $F_{ETO_2}$ as if breathing air. The converse argument can be made for making $G_2$ neutral with respect to $O_2$ and not $CO_2$.

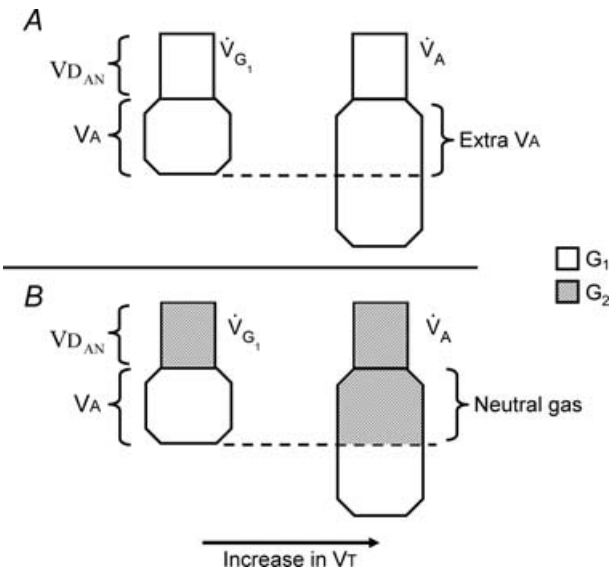


**Figure 3. The effect of changes in tidal volume ($V_T$) on alveolar ventilation when breathing on a sequential gas delivery (SGD) circuit**

When the flow of Gas 1 exceeds alveolar ventilation (panel *A*), the increase in $V_T$ causes $G_1$ trapped in the anatomical dead space ($VD_{AN}$) to enter alveoli ($V_A$), providing extra alveolar ventilation. If the flow of $G_1$ is equal to or less than alveolar ventilation (panel *B*), all of $VD_{AN}$ is filled with the previously exhaled gas ($G_2$) that is 'neutral' with respect to alveolar ventilation (see Rule 2 in text). An increase in $V_T$ causes $G_2$ to enter $V_A$, but because the volume of $G_1$ available for gas exchange is not altered, alveolar ventilation does not change.

## Independence of end-tidal gas concentrations from changes in $\dot{V}_E$

$F_{ETO_2}$ and $F_{ETCO_2}$ change from one breath to the next in spontaneously breathing subjects due to variations in $V_T$. For example, increasing $V_T$ increases $F_{ETO_2}$ and decreases $F_{ETCO_2}$. For a subject breathing via an SGD circuit, when $\dot{V}_{G_1}$ exceeds $\dot{V}_A$, an increase in $V_T$ draws $G_1$ from the $VD_{AN}$ into the alveoli, thereby increasing $\dot{V}_A$. This situation is equivalent to the subject breathing normally without the SGD circuit (Fig. 3*A*). By contrast, with $\dot{V}_{G_1}$ set at or below $\dot{V}_A$, $VD_{AN}$ is filled with previously exhaled gas (Fig. 2, stages C and D) that is 'neutral' with respect to $\dot{V}_A$ (Rule 2). Therefore in this situation, while a larger $V_T$ draws gas from $VD_{AN}$ into the alveoli (Fig. 3*B*), the composition of gas in $VD_{AN}$ is neutral and so does not change $F_{ETO_2}$ and $F_{ETCO_2}$. Thus, $F_{ETO_2}$ and $F_{ETCO_2}$ are determined only by $\dot{V}_{G_1}$ (Rule 1) which remains constant, unaffected by the increase in VT. A similar argument can be made for changes in respiratory frequency; as respiratory frequency increases, each breath will get a reduced fraction of the $\dot{V}_{G_1}$ and a complementary increase in $\dot{V}_{G_2}$. No matter how much $\dot{V}_E$ increases, the net $\dot{V}_A$ cannot exceed $\dot{V}_{G_1}$. From this argument we can formulate the following rule that applies to the SGD circuit.

Rule 3: *If* $\dot{V}_{G_1}$ *is less than or equal to* $\dot{V}_A$, $F_{ETO_2}$ *and* $F_{ETCO_2}$ *are independent of* $\dot{V}_E$.

This rule is true with respect to both steady-state conditions and to breath-by-breath analysis. For example, if the peak inspiratory flow on any one breath exceeds $\dot{V}_{G_1}$, then the balance of the breath will be made up by the 'neutral' gas from the expiratory reservoir and the $\dot{V}_A$ will remain constant.

The principles expounded above can be illustrated by formulating some example questions, and answering them serves to introduce Rule 4.

Example 1: a subject's normal $\dot{V}_A$ is $5\,l\,min^{-1}$ and $P_{ETCO_2}$ is 40 mmHg. An SGD circuit is placed on the subject's face, and the unfamiliarity of the situation causes the subject to breathe at $8\,l\,min^{-1}$. If $G_1$ is air, what $\dot{V}_{G_1}$ will maintain isocapnia: is it 5 or $8\,l\,min^{-1}$?

The correct answer is $5\,l\,min^{-1}$. In order to maintain isocapnia, we have to control the subject's $\dot{V}_A$ at the normal value. According to Rule 1, this can be done by setting $\dot{V}_{G_1}$ equal to $\dot{V}_A$.

Example 2: if the subject in example 1 doubles his $\dot{V}_E$ from 8 to $16\,l\,min^{-1}$ (while $\dot{V}_{G_1}$ remains constant at $5\,l\,min^{-1}$), will the $P_{ETCO_2}$ increase, decrease or remain constant?

As long as $\dot{V}_{G_1}$ is set at the subject's $\dot{V}_A$, doubling $\dot{V}_E$ (from 8 to $16\,l\,min^{-1}$) will only result in a proportional increase in $\dot{V}_{G_2}$ (from 3 to $11\,l\,min^{-1}$). Since $G_2$ gas is previously expired gas and therefore 'neutral' with respect to $\dot{V}_A$ (Rule 2) and $\dot{V}_{G_1}$ is unchanged ($5\,l\,min^{-1}$ during both protocols), $P_{ETCO_2}$ remains constant (Rule 3).

Example 3: suppose that in Example 2, both $\dot{V}_{G_1}$ (5 l min$^{-1}$ of air) and $\dot{V}_{G_2}$ (11 l min$^{-1}$ of previously exhaled gas) were premixed and delivered together to the $G_1$ port. What happens to $P_{ETCO_2}$ (note, $CO_2$ is now present in the inspired gas)?

It is perhaps not intuitively obvious, but $P_{ETCO_2}$ does not change. $P_{ETCO_2}$ is determined by $\dot{V}_A$, and in an SGD circuit, because $G_2$ has no effect on the $P_{ETCO_2}$ (Rule 2), $\dot{V}_A$ is determined entirely by $\dot{V}_{G_1}$ (Rule 1). Mixing $\dot{V}_{G_1}$ and $\dot{V}_{G_2}$ does not change $\dot{V}_{G_1}$, so that administering the two flows together results in the same $P_{ETCO_2}$ as delivering them sequentially. The counterintuitive concept in this example is that $P_{ETCO_2}$ does not change despite the presence of $CO_2$ in the inspired gas!

This does not contradict our contention that the order of presentation of gases to the lungs is important for maintaining control of end-tidal gas concentrations. Although $G_1$ in this example contains $CO_2$, we are still assuming that it is inhaled first, reaches the alveoli and establishes the alveolar ventilation for its component gases. Any additional gases that are inhaled as $G_2$ are 'neutral' with respect to gas exchange, and allow the alveolar ventilation to be fixed independent of minute ventilation.

The argument illustrated by Example 3 can be expressed by the following rule that applies to the SGD circuit, and is further illustrated in Example 4 that follows.

Rule 4: *If $CO_2$ is present in $\dot{V}_{G_1}$, then $\dot{V}_{G_1}$ can be separated into two virtual compartments: a 'fresh gas flow' (with no $CO_2$) that determines $\dot{V}_A$ for $CO_2$ elimination, and a 'neutral gas flow' (with a $CO_2$ concentration equal to that of the neutral gas). Similarly, the $O_2$ in $\dot{V}_{G_1}$ can be divided into 'fresh gas' and 'neutral gas' components.*

Example 4: a subject whose $\dot{V}_A$ is 5 l min$^{-1}$ is breathing on an SGD circuit at a $\dot{V}_E$ equal to 10 l min$^{-1}$. Initially, $G_1$ is air and $\dot{V}_{G_1}$ is 5 l min$^{-1}$. The subject's resting $F_{ETCO_2}$ is 0.056 ($P_{CO_2} = 40$ mmHg). Using these data, the following questions can be answered utilizing the rules and equations previously derived.

First, what is the subjects $\dot{V}_{CO_2}$? The answer may be derived using the equation:

$$\dot{V}_{CO_2} = \dot{V}_A \times \left(F_{ACO_2} - F_{ICO_2}\right) \quad (3)$$

and where $F_{ETCO_2} \approx F_{ACO_2}$, and $\dot{V}_{G_1} = \dot{V}_A$. In this case, $\dot{V}_{CO_2} = 5 \times (0.056–0) = 0.280$ l min$^{-1}$.

Second, if $\dot{V}_{CO_2}$ is constant, what happens to $F_{ETCO_2}$ if the fractional concentration of $CO_2$ in $G_1$ is changed from 0 to 0.021? Rearranging the equation (3) as:

$$F_{ACO_2} = \left(\dot{V}_{CO_2}/\dot{V}_A\right) + F_{ICO_2}, \quad (4)$$

then $F_{ETCO_2} = (0.280/5) + 0.021 = 0.077$ (i.e. $P_{CO_2} =$ 55 mmHg).

Finally, what happens to $F_{ETCO_2}$ if the $\dot{V}_{G_1}$ is increased to 8 l min$^{-1}$? Increasing $\dot{V}_{G_1}$ from 5 to 8 l min$^{-1}$ increases $\dot{V}_A$ from 5 to 8 l min$^{-1}$ (Rule 1) (assuming $\dot{V}_E$ is not limiting). Using equation (4), $F_{ETCO_2} = (0.280/8) + 0.021 = 0.056$ (i.e. $P_{CO_2} = 40$ mmHg).

From this example we note that $F_{ETCO_2}$ when $\dot{V}_{G_1} = 8$ l min$^{-1}$ and $F_{CO_2}$ in $G_1 = 0.021$, is the same as that when $\dot{V}_{G_1} = 5$ l min$^{-1}$ and $F_{CO_2}$ in $G_1 = 0$. This conclusion may be stated as a general principle for $CO_2$: the net $\dot{V}_A$ resulting from a $\dot{V}_{G_1}$ with any $F_{CO_2}$ can be determined by dividing $\dot{V}_{G_1}$ into a virtual component with no $CO_2$ and a virtual component with $CO_2$ at a concentration identical to that of 'neutral' gas. The virtual component volume with no $CO_2$ provides the effective $\dot{V}_A$ for $CO_2$ (i.e. $CO_2$ exchange). The remaining virtual component with the neutral $CO_2$ makes no contribution to $CO_2$ exchange.

This principle is the basis for using a SGD circuit to adjust $F_{ETCO_2}$ to a targeted value and maintain it in the face of changes in breathing pattern. For $\dot{V}_{G_1}$ less than $\dot{V}_A$, $\dot{V}_{G_1}$ and the concentration of $CO_2$ in $G_1$ can be used to manipulate $\dot{V}_A$ for $CO_2$ independent of $\dot{V}_E$. By the same argument, $\dot{V}_{G_1}$ and its $O_2$ concentration can be manipulated to change $\dot{V}_A$ for $O_2$. In this way the obligatory link between $F_{ETCO_2}$ and $F_{ETO_2}$ can be dissociated so as to also allow independent targeting of $F_{ETO_2}$. A final example demonstrates this latter aspect.

Example 5*:* a subject ($\dot{V}_A = 5$ l min$^{-1}$) is breathing on a SGD circuit at 15 l min$^{-1}$. Initially, $G_1$ is air, $\dot{V}_{G_1} = 5$ l min$^{-1}$, and resting $F_{ETO_2}$ is 0.16.

First, what is the subject's $\dot{V}_{O_2}$? The answer may be derived as before but using the equation:

$$\dot{V}_{O_2} = \dot{V}_A \times \left(F_{IO_2} - F_{AO_2}\right) \quad (5)$$

and assuming that $F_{ETO_2} \approx F_{AO_2}$.· $F_{IO_2}$ is fractional concentrations of $O_2$ inspired gas. Assuming that $F_{IO_2}$ is 0.21 (concentration of $O_2$ in air), $F_{ETO_2} \approx F_{AO_2}$, and that $\dot{V}_{G_1} = \dot{V}_A$, then $\dot{V}_{O_2} = 5 \times (0.21 - 0.16) = 0.250$ l min$^{-1}$.

Second, if $\dot{V}_{O_2}$ is constant, what happens to $F_{ETO_2}$ if the fractional concentration of $O_2$ in $G_1$ is changed from 0.21 to 0.18? Rearranging the equation (5) as:

$$F_{AO_2} = F_{IO_2} - \left(\dot{V}_{O_2}/\dot{V}_A\right), \quad (6)$$

and assuming $F_{ETO_2} \approx F_{AO_2}$, then $F_{ETO_2} = 0.18 -$ $(0.250/5) = 0.13$.

Finally, what happens to $F_{ETO_2}$ if $\dot{V}_{G_1}$ is increased by 8 l min$^{-1}$? According to Rule 1, in a SGD circuit $\dot{V}_{G_1}$ determines $\dot{V}_A$. So when $\dot{V}_{G_1}$ is increased from 5 to 13 l min$^{-1}$, then $\dot{V}_A$ increases from 5 to 13 l min$^{-1}$. Using equation (6); $F_{ETO_2} = 0.18 - (0.250/13) = 0.16$.

This example is the converse of the previous example for $CO_2$ and illustrates the same principle, but this time for $O_2$. $F_{ETO_2}$ when $\dot{V}_{G_1} = 13$ l min$^{-1}$ and $F_{O_2}$ in $G_1 = 0.18$ is the same as that when $\dot{V}_{G_1} = 5$ l min$^{-1}$ and the $F_{O_2}$ in $G_1 = 0.21$. Thus, a $\dot{V}_{G_1}$ with any $F_{O_2}$ can be separated into two virtual components: (1) a virtual flow of gas with an $F_{O_2}$ concentration equal to that of the neutral gas, and (2) a virtual flow of gas with an $F_{O_2}$ different from that of the neutral gas that will constitute $\dot{V}_A$ for $O_2$ (i.e. $O_2$

exchange). This principle for $O_2$ is analogous to Rule 4 for $CO_2$, and can be stated as Rule 5 for any gas in SGD circuits as follows:

Rule 5: *$\dot{V}_{G_1}$ can be arithmetically separated into two components: one with the same composition as the neutral gas – neutral $\dot{V}_{G_1}$ ($\dot{V}_{G_1,n}$); the other with a composition different from the neutral gas – fresh $\dot{V}_{G_1}$ ($\dot{V}_{G_1,f}$), which constitutes $\dot{V}_A$.*

It follows from the above arguments that in a SGD circuit the following three parameters can be manipulated to control $P_{ETCO_2}$ and $P_{ETO_2}$ independent of $\dot{V}_E$:

(1) $\dot{V}_{G_1}$ – changes in $\dot{V}_{G_1}$ affect *both* $P_{ETCO_2}$ and $P_{ETO_2}$, as long as $\dot{V}_{G_1} \leftrightharpoons \dot{V}_A$ ;

(2) $F_{CO_2}$ in $\dot{V}_{G_1}$ – this will allow independent control of $\dot{V}_A$ for $CO_2$, and hence $P_{ETCO_2}$, if $\dot{V}_{G_1}$ remains constant;

(3) $F_{O_2}$ in $\dot{V}_{G_1}$ – this will allow independent control of $\dot{V}_A$ for $O_2$, and hence $P_{ETO_2}$, if $\dot{V}_{G_1}$ remains constant.

In the preceding discussion we assigned gas flows and concentrations in a SGD breathing circuit as $\dot{V}_A$, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$. We can now use the known relationships between $\dot{V}_A$, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ to $F_{ETCO_2}$ and $F_{ETO_2}$ to determine $\dot{V}_{G_1}$ and its composition to attain target end-tidal gas concentrations (see Appendix A for a full derivation of the equations).

For $F_{ETCO_2}$:

$$F_{ACO_2} = F_{G_1CO_2} + \left(\dot{V}_{CO_2}/\dot{V}_{G_1}\right) \quad \text{(Appendix A, eqn (A3))}$$

where $F_{ACO_2}$ is the target fractional alveolar concentration of $CO_2$, $F_{G_1CO_2}$ is the fractional concentration of $CO_2$ in $\dot{V}_{G_1}$ and $\dot{V}_{CO_2}$ is the minute flux of $CO_2$ at the lungs (which is equal to minute metabolic $CO_2$ production at steady state).

For $F_{ETO_2}$:

$$F_{AO_2} = F_{G_1O_2} - \left(\dot{V}_{O_2}/\dot{V}_{G_1}\right) \quad \text{(Appendix A, eqn (A5))}$$

where $F_{AO_2}$ is the target alveolar fractional concentration of $O_2$, $F_{G_1O_2}$ is the fractional concentration of $O_2$ in $\dot{V}_{G_1}$ and $\dot{V}_{O_2}$ is the minute flux of $O_2$ at the lungs (equal to minute metabolic $O_2$ consumption at steady state).

Although resting $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ can be easily estimated from the subject's age, height and weight using standard tables (Nunn, 1993), they can also be conveniently measured using an SGD circuit (see Appendix B).

## Apparatus

We built a custom three-gas blender to allow us to control the composition and flow of $G_1$. The blender incorporates precise flow meters to measure flow (TSI 4100, TSI, Shoreview, MN, USA), voltage controlled orifices to control the flow (VSO NC-6511-VE-Q8, Pneutronics, Hollis, NH, USA), and gas sensors for $CO_2$ (IR1507, Servomex, Fairfax, CA, USA) and $O_2$ (UFO130-2, Teledyne-AI, City of Industry, CA, USA). An electronic pressure transducer (Model 163PC01D36, Honeywell, NJ, USA) sensing pressure in the face mask was used to detect inspiration and expiration. Expiratory $V_T$ was measured using a turbine (Universal Ventilation Meter, VacuMed, Ventura, CA, USA).

A 12-bit digital-to-analog converter (DAQCard-6024E, National Instruments, Austin, TX, USA) interfaced the measurements with a laptop computer, where input/output signal processing, data analysis and all calculations were carried out by a specially written computer program (LabView, National Instruments, Austin, TX, USA). $CO_2$ and $O_2$ concentrations and mouth pressure data were digitized and recorded continuously at 40 Hz. The pressure transducer signal was used to calculate respiratory rate ($f$) and to help identify end-tidal values from raw $CO_2$ and $O_2$ data. $V_T$ and $f$ were used to calculate $\dot{V}_E$. Breath-by-breath $P_{ETCO_2}$, $P_{ETO_2}$, $f$, $V_T$ and $\dot{V}_E$ were recorded continuously. $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were calculated as the product of $\dot{V}_{G_1}$ and the absolute difference between the concentrations of $CO_2$ and $O_2$ in $G_1$ and those in the mixed expired gas (see Appendix 2). Given the target $P_{ETCO_2}$ and $P_{ETO_2}$, and the measured $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, the program calculated $\dot{V}_{G_1}$, $F_{G_1CO_2}$ and $F_{G_1O_2}$ from Appendix A equations (A3) and (A5). Fractional concentrations were converted to partial pressures using the dry barometric pressure on the day of the experiment. Appropriate corrections were made to convert from atmospheric temperature, pressure, saturation (ATPS) to body temperature, pressure, saturation (BTPS).

A commercial SGD circuit (Hi-Ox$^{80}$, VIASYS HealthCare, Yorba Linda, CA, USA) was modified by attaching the turbine and an expiratory gas reservoir in series to its expiratory limb. Gas was sampled from the mask or the expiratory gas reservoir. The $G_1$ outlet of the gas flow controller was attached to the fresh gas inlet of the SGD circuit.

## Protocol

After receiving institutional Research Ethics Board approval, we obtained a signed informed consent from six healthy subjects (5 males, 1 female; age $24.7 \pm 4.4$ years, height $178.3 \pm 8.7$ cm, weight $70.7 \pm 8.5$ kg; means $\pm$ S.D.) to participate in the study. All procedures conformed with the Declaration of Helsinki. Subjects were seated comfortably in a chair and the face mask applied. The elastic straps on the mask were tightened to assure a good seal to the face. If required, adhesive tape (Tegaderm, 3M Health Care, St Paul, MN, USA) was used to seal any leaks. $\dot{V}_{G_1}$ was

initially set to 8 l min$^{-1}$ of air. Subjects were allowed to acclimatize to breathing on the circuit for at least 10 min. Once $P_{ETO_2}$ and $P_{ETCO_2}$ stabilized (less than 2 mmHg variability over 2 min), the three-way stopcock attached to the gas sampling port of the device was turned so that gas was sampled from the expiratory reservoir. Values for $F_{CO_2}$ and $F_{O_2}$ from the expiratory reservoir averaged over at least 30 s were used to calculate $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ (see Appendix 2 for details). Once $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were measured, the sampling port was redirected to sample expired gas at the face mask. $\dot{V}_{G_1}$, $F_{G_1CO_2}$ and $F_{G_1O_2}$ were then altered according to the principles described above, to achieve target values of $P_{ETCO_2}$ and $P_{ETO_2}$.

A total of three experiments were performed (Fig. 4). In experiment I, we maintained normoxia ($P_{ETO_2} =$ 100 mmHg) while targeting two levels of $P_{ETCO_2}$, returning to baseline $P_{ETCO_2}$ between each target level. The first target $P_{ETCO_2}$ level (I-$T_1$) was 5 mmHg above initial baseline followed by a targeted return to baseline (I-$B_2$). The second target $P_{ETCO_2}$ (I-$T_2$) was 10 mmHg above baseline (I-$B_2$) followed by a return to baseline (II-$B_1$). In experiment II, $P_{ETO_2}$ was controlled during normocapnia ($P_{ETCO_2} = 40$ mmHg). The first target $P_{ETO_2}$ (II-$T_1$) was 100 mmHg above baseline (II-$B_1$) followed by a return to baseline (II-$B_2$). The second target $P_{ETO_2}$ (II-$T_2$) was 200 mmHg above baseline (II-$B_2$) followed by a return to baseline (III-$B_1$). In experiment III, both $P_{ETCO_2}$ and $P_{ETO_2}$ were targeted simultaneously. The first target levels (III-$T_1$) were a change of $P_{ETCO_2}$ and $P_{ETO_2}$ from baseline (III-$B_1$) to +5 and +100 mmHg, respectively, followed by a return to baseline (III-$B_2$). The second target levels (III-$T_2$) were a change of $P_{ETCO_2}$ and $P_{ETO_2}$ from baseline (III-$B_2$) to +10 and +200 mmHg, respectively, followed by a return to baseline (III-$B_3$). To demonstrate the versatility and robustness of the method targeting various levels of $P_{ETCO_2}$ and $P_{ETO_2}$ we performed experiments I–III sequentially, maintaining baseline and target $P_{ETCO_2}$ and $P_{ETO_2}$ values for a duration of 30 s.

We entered the same target $P_{ETCO_2}$ and $P_{ETO_2}$ levels and sequence duration for each subject. Given the subject's $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ the computer automatically chose the $\dot{V}_{G_1}$, $F_{G_1O_2}$ and $F_{G_1CO_2}$ sequence required to carry out all three experiments using Appendix A eqns (A3) and (A5). All calculations were done prospectively prior to the start of experiment and feedback control was not used during the experiment. In order to produce rapid changes in end-tidal gases, we used an 'overshooting' technique (Banzett *et al.* 2000) by targeting higher-than-required end-tidal values for the first 2–3 breaths for rising gas concentrations and lower-than-required values for the first 2–3 breaths on descending gas concentrations. $\dot{V}_{G_1}$ was arbitrarily raised to 15 l min$^{-1}$, a value above the resting $\dot{V}_E$ of all subjects, in order to speed up transitions between steady-states. The inspiratory reservoir was placed loosely on the palm of the subject's hand and the subject was instructed to breathe such that the inspiratory reservoir was empty at the end of most breaths. As a result, the baseline $\dot{V}_E$ during the experiment was at least 15 l min$^{-1}$ or more in all subjects (Fig. 5).

## Subject safety

The composition of $G_1$ can be controlled by mixing pure $O_2$, $CO_2$ and $N_2$. Because accidental inspiration of either pure $CO_2$ or pure $N_2$ can cause lethal hypoxaemia, we only used gas mixtures containing at least 10% $O_2$. We further limited the $CO_2$ source gas to 40% $CO_2$ (10% $O_2$, balance $N_2$) to prevent an accidental inspiration of high concentrations of $CO_2$. These restrictions placed significant limits on the $P_{ETO_2}$ and $P_{ETCO_2}$ values that could be targeted and complicated the calculations of the combinations of flow of the source gases required to

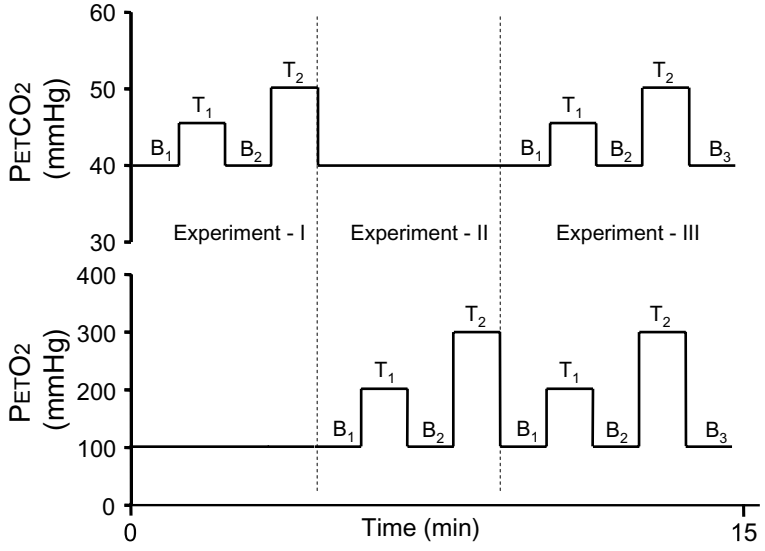


**Figure 4. Experimental protocol**
A total of three experiments were performed. During experiment I $P_{ETCO_2}$ was varied to + 5 (I-$T_1$) and + 10 mmHg (I-$T_2$) from baselines (I-$B_1$ and I-$B_2$) before being returned to baseline II-$B_1$. During experiment II $P_{ETO_2}$ was varied to +100 (II-$T_1$) and +200 mmHg (II-$T_2$) from baselines (II-$B_1$ and II-$B_2$) before being returned to baseline III-$B_1$. During experiment III, both $P_{ETCO_2}$ and $P_{ETO_2}$ were varied simultaneously to the same targets as those attained during experiments II and III.

**Table 2. Intra-subject steady-state variability in $P_{ETCO_2}$, $P_{ETO_2}$ and $\dot{V}_E$**

| Subject | $P_{ETCO_2}$ (mmHg) | $P_{ETO_2}$ (mmHg) | $\dot{V}_E$ (l min$^{-1}$) |
|---|---|---|---|
| 1 | 0.2 (0.1–0.8) | 0.6 (0–6.3) | 3.4 (1.9–7.6) |
| 2 | 0.3 (0.1–0.5) | 0.7 (0–8.4) | 2.8 (1.6–4.3) |
| 3 | 0.2 (0.1–1.3) | 0.9 (0.3–5.7) | 2.7 (1.6–8.9) |
| 4 | 0.2 (0.1–1.5) | 1.2 (0.3–3) | 1.7 (1–5.3) |
| 5 | 0.2 (0.1–0.7) | 1 (0.3–6.2) | 2.8 (1.6–7.7) |
| 6 | 0.2 (0.1–0.6) | 1.9 (0.3–7) | 1.8 (1.1–3.7) |

Data are median (range) of standard deviations.

attain the target $F_{G_1O_2}$ and $F_{G_1CO_2}$. To make sure that our algorithms for these complex functions resulted in safe inspired gas concentrations at all combinations of target values, we added a series of alarm features designed to indicate when the calculated $F_{G_1O_2}$ and $F_{G_1CO_2}$ were not attainable with our series of gas mixtures, or the actual inspired concentrations were outside the designated safe range.

### Statistical analysis

One-way repeated measures analysis of variance (1-way RMANOVA) was used to compare initial baseline $P_{ETCO_2}$ and $P_{ETO_2}$ (stage I-$B_1$) to the rest of the corresponding baseline $P_{ETCO_2}$ (stages I-$B_2$, II-$B_1$, II-$T_1$, II-$B_2$, II-$T_2$, III-$B_1$, III-$B_2$ and III-$B_3$) and $P_{ETO_2}$ (stages I-T1, I-$B_2$, I-$T_2$, II-$B_1$, II-$B_2$, III-$B_1$, III-$B_2$ and III-$B_3$). Dunnett's test was used for *post hoc* comparison when necessary. A *t* test was used to compare the $P_{ETCO_2}$ values reached at stages I-$T_1$ and I-$T_2$ to those at stages III-$T_1$ and III-$T_2$, respectively. Similarly, the $P_{ETO_2}$ values attained at stages II-$T_1$ and II-$T_2$ were compared to those at stages III-$T_1$ and III-$T_2$, respectively. Statistical significance was assumed when $P < 0.05$.

## Results

Individual results for all subjects are shown in Fig. 5. Intra-subject steady-state variabilities in $P_{ETCO_2}$, $P_{ETO_2}$ and $\dot{V}_E$ are summarized in Table 2. Target and measured $P_{ETCO_2}$ values from all stages in all experiments for all subjects were pooled and are presented in Fig. 6. Experimental data for both $P_{ETCO_2}$ and $P_{ETO_2}$ (filled circles in Fig. 6) closely followed the target values (continuous line). The average absolute difference between target and measured values for $P_{ETCO_2}$ was 1 mmHg, and for $P_{ETO_2}$ was 4 mmHg. $P_{ETCO_2}$ varied by ± 1 mmHg and $P_{ETO_2}$ by ± 5.6 mmHg (S.D.) over the 30 s stages.

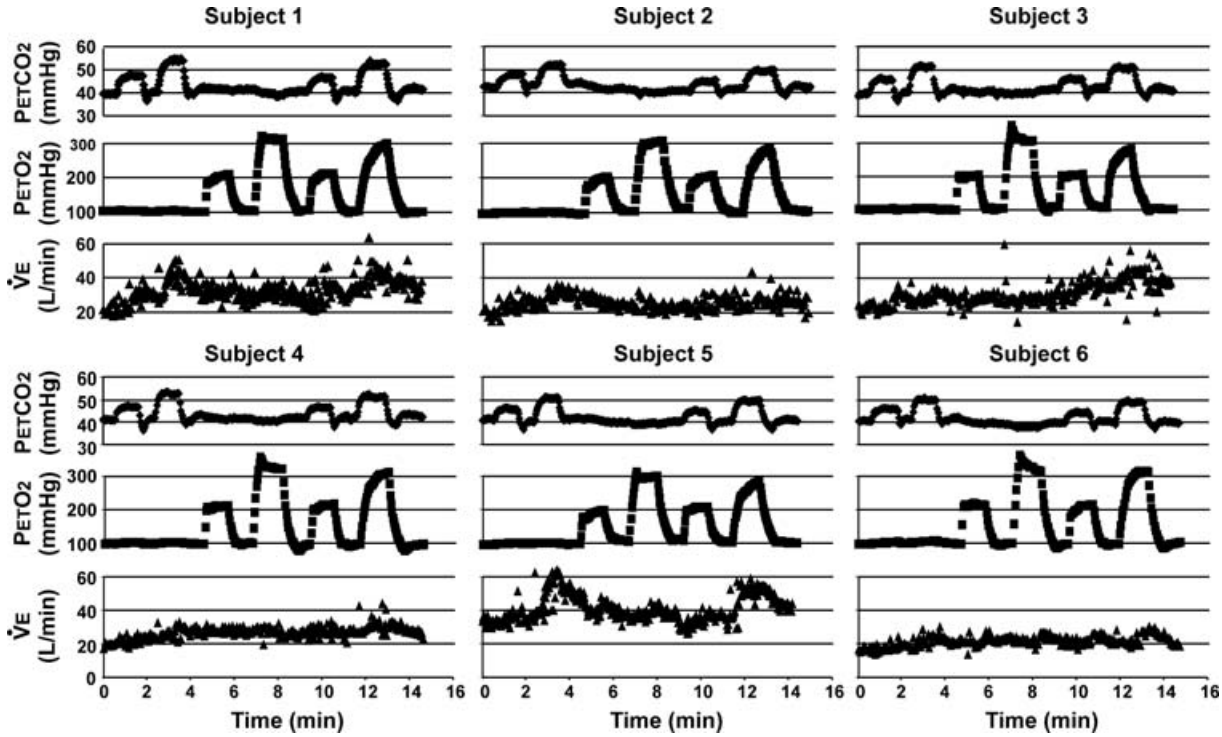


**Figure 5. End-tidal partial pressure of $CO_2$ ($P_{ETCO_2}$) and $O_2$ ($P_{ETO_2}$) and minute ventilation ($\dot{V}_E$) data from all subjects**

Note that subjects were asked to empty the inspiratory reservoir at the end of most breaths. Since $\dot{V}_{G_1}$ was set to 15 l min$^{-1}$ in order to speed up transitions between steady-states, the baseline $\dot{V}_E$ was at least 15 l min$^{-1}$ or greater in all subjects. As a result, the normal increases in ventilation that would be seen during a significant hypercapnic challenge and natural breathing are not observed in this experiment.

This degree of control of end-tidal gases was obtained despite large inter- and intrasubject variability in $\dot{V}_E$ (Fig. 5). $P_{ETO_2}$ (1-way RMANOVA, $P = 0.136$) and $P_{ETCO_2}$ (1-way RMANOVA, $P = 0.01$, Dunnett's test $P > 0.05$) returned to baseline after each targeted value. There were also no differences between $P_{ETCO_2}$ in stages I-T1 and III-$T_1$ (paired $t$ test, $P = 0.061$) and $P_{ETO_2}$ in stages II-T1 and III-$T_1$ (paired 2 tail $t$ test, $P = 0.249$). The only statistically significant differences were observed between stages I-T2 and III-$T_2$ for $P_{ETCO_2}$ (paired 2 tail $t$ test, $P < 0.001$) and stages II-$T_2$ and III-$T_2$ for $P_{ETO_2}$ (paired 2 tail $t$ test, $P = 0.019$).

## Discussion

### Main findings

In this study we demonstrate that $P_{ETCO_2}$ and $P_{ETO_2}$ can be repeatedly targeted independently and maintained for at least 30 s in spontaneously breathing subjects using a SGD breathing circuit. Previous methods for end-tidal forcing have used closed loop feedback methods to control end-tidal gas concentrations. This is the first demonstration of an effective method of prospectively targeting end-tidal gas values and attaining them in an open loop fashion. The measured experimental data followed the targeted values closely, i.e. $\pm 1$ mmHg for $P_{CO_2}$ and $\pm 4$ mmHg for $P_{O_2}$ so that the variability in the partial pressures of end-tidal gases at each stage was minimal, despite substantial variability in $\dot{V}_E$.

### Improvement over previous methods

In their study, Banzett *et al.* (2000) successfully demonstrated the 'clamping' characteristics of the SGD circuit, i.e. they successfully maintained $P_{ETCO_2}$ and $P_{ETO_2}$ constant despite significant changes in ventilation. In our study we extended the functionality of the SGD circuit by demonstrating 'targeting', i.e. how a series of target $P_{ETCO_2}$ and $P_{ETO_2}$ values can be attained independent of each other and independent of $\dot{V}_E$. Our findings are notable in that the 'targeting' and 'clamping' were achieved without use of any feedback algorithms. This is in contrast to dynamic end-tidal forcing that uses advanced prediction–correction schemes to target and control end-tidal gases. Since our method does not rely on feedback control, it is also 'protected' from the usual problems associated with feedback control, such as signal drift, phase lags and instability, leading to signal oscillations (Smith *et al.* 1978). This may prove useful in applications such as MRI, where the presence of high magnetic fields dictates that all measurement apparatus have to be situated in the control room for safety and interference-prevention purposes. As a result, several gas sampling lines have to be extended from the control room to the MRI suite delaying expired gas analysis and thereby complicating feedback control.

In the present study we used an automated gas sequencer that included $CO_2$ and $O_2$ gas analysers and a stand-alone pneumotachometer. In contrast to dynamic end-tidal forcing that requires these apparatus for feedback control, our method only uses them to record the end-tidal and ventilation data. Furthermore, gas flows in our method only have to match the subject's minute ventilation (5–15 l min$^{-1}$, depending on the protocol). In contrast, the end-tidal forcing technique requires gas flows that are high enough to meet individual peak inspiratory flows that can be as high as 50–300 l min$^{-1}$. This makes our method less bulky and more suitable for use in clinical settings.

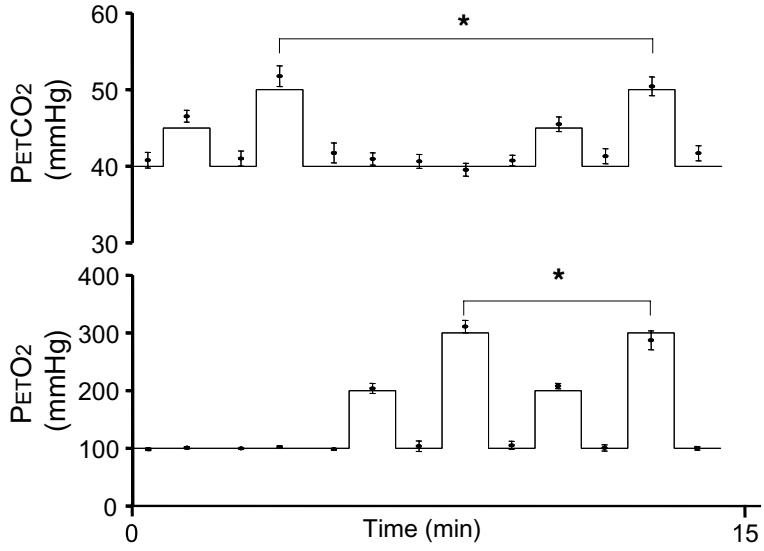


**Figure 6. Pooled end-tidal $P_{CO_2}$ and $P_{O_2}$ data from all subjects**
Continuous lines represent ideal target responses at each stage of the protocol. Circles represent experimental data (mean ± S.D.). *Statistically significant differences ($P < 0.05$).

### Modification of the method for studies of ventilation

In the present study the subjects increased their $\dot{V}_E$ above their resting values by hyperventilation. This was done in order to shorten the lung washout time and thereby speed up transitions between steady-states. As a result, the subjects' $\dot{V}_E$ were not allowed to vary naturally. If it is desirable to study the natural ventilatory responses to changes in end-tidal gases, however, the subject can be asked to breathe normally and $\dot{V}_{G_1}$ can be set equal to subject's $\dot{V}_A$ (which can be estimated from standard tables or from subject's $\dot{V}_{CO_2}$ and $P_{ETCO_2}$). With an SGD circuit, $P_{ETCO_2}$ and $P_{ETO_2}$ will become independent of $\dot{V}_E$ as soon as the $\dot{V}_{G_1}$ is set equal to subject's $\dot{V}_A$ (Rule 3). The experimenter (or computer) can then adjust the concentrations of $CO_2$ and $O_2$ in $\dot{V}_{G_1}$ using eqns (A3) and (A5) (from Appendix A) to produce desired changes in the $P_{ETCO_2}$ and $P_{ETO_2}$, while recording the natural ventilatory response of the subject. In theory, a specific pattern of changes can be preprogrammed into the computer to attain desired input functions (e.g. linear, step-like, sinusoidal, etc.).

### Independent control of end-tidal gases

SGD circuits have been used previously to control $P_{ETCO_2}$ independently of ventilation (Sato *et al.* 1992; Sommer *et al.* 1998; Banzett *et al.* 2000; Vesely *et al.* 2001). However, changes in $P_{ETCO_2}$ resulted in tandem changes in $P_{ETO_2}$ and both were dependent on the flow of 'fresh gas' (i.e. $\dot{V}_{G_1}$) into the circuit. We used the unique property of the SGD circuit to dissociate this obligatory link between $P_{ETCO_2}$ and $P_{ETO_2}$. With the SGD circuit, the volume of fresh gas available to the alveoli for gas exchange is fixed by $\dot{V}_{G_1}$. We introduce here the concept of 'neutral gas' to rationalize the relationship between $F_{CO_2}$ and $F_{O_2}$ in $\dot{V}_{G_1}$ and the target $P_{ETCO_2}$ and $P_{ETO_2}$. The property of the SGD circuit that permits fixing $\dot{V}_A$ independent of ventilation allows changes in end-tidal gas concentrations to be sustained in the face of the inevitable ventilatory responses to the induced changes in $P_{ETO_2}$ and $P_{ETCO_2}$.

### Composition of $G_2$

In the present study, the composition of $G_2$ was passively adjusted during each breath by providing the subject's own expiratory gases for rebreathing. It is possible to use an external source for $G_2$, for example from a pressurized tank via a demand regulator (see Sommer *et al.* 1998), if one needs to control only one of the end-tidal gases. However, the composition of $G_2$ can be such that any of its component gases are 'neutral' with respect to the alveolar gas.

The circuit used in the present study could be modified by placing a $CO_2$ scrubber in the bypass conduit, and in this configuration, any $G_2$ that is inhaled from the expiratory reservoir will have all its $CO_2$ removed, thereby providing 'extra' $\dot{V}_A$ for $CO_2$ exchange. Because the $O_2$ concentration of $G_2$ will still approximate that of the alveolar gas, $G_2$ remains 'neutral' with respect to $O_2$. In such a SGD circuit a subject can hyperventilate and reduce $P_{ETCO_2}$ to an extent determined by minute ventilation yet maintain $P_{ETO_2}$ constant throughout. To make a circuit that does the reverse – allows $P_{ETO_2}$ to vary with ventilation but maintain isocapnia – one simply uses a Sommer circuit (Sommer *et al.* 1998) and provides $G_2$ with $F_{O_2}$ equal to that in $G_1$ and 'neutral' $F_{CO_2}$.

### Limitations and further suggestions

In the course of developing the theoretical basis of our method we made the simplifying assumption that the inhaled gas is distributed exclusively to anatomical dead space and alveoli. In reality, however, some of the inhaled gas will be distributed to the physiological dead space, which would confound the targeting of $P_{ETCO_2}$ and $P_{ETO_2}$. However, other methods of controlling end-tidal gases including the end-tidal forcing will be equally affected by physiological dead space.

In the present study, we only tested the newly described 'targeting' characteristics of an SGD circuit that permit independent control of $P_{ETCO_2}$ and $P_{ETO_2}$. 'Clamping' characteristics of an SGD circuit were previously validated by Banzett *et al.* (2000) and Somogyi *et al.* (2005).

It is important to point out that errors in the measurement of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ will likely affect the targeting, but not the 'clamping', characteristics of the circuit. In our experience, however, small changes in $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ have minimal effect on the outcome of the study. However, this requires further formal investigation, perhaps during steady-state exercise studies.

The SGD circuit used in the current study does not behave ideally. During the rebreathing phase of inspiration, any $G_2$ flowing through the bypass conduit into the inspiratory side of the circuit is 'contaminated' by $G_1$ flowing constantly into the inspiratory reservoir. This limitation may be overcome by temporarily shutting off $\dot{V}_{G_1}$ during the rebreathing phase of inspiration and then delivering a compensatory higher flow during the first second of expiration to maintain an average $\dot{V}_{G_1}$. We suggest that this limitation may have only a small effect and its compensation may not be necessary in all circumstances, but we did not verify this notion in the present study.

The method we used targets the equilibrium steady state $P_{ETCO_2}$ and $P_{ETO_2}$. Depending on the size of the transition and how long it is to be maintained, further accommodation must be made for filling or emptying body stores of $CO_2$ and $O_2$. Rapid changes in $O_2$ can be induced and maintained relatively easily because only

the fast compartment, consisting of the lung and possibly the blood, need be accounted for. On the other hand, the body has large $CO_2$ stores (~120 l) (Cherniack & Longobardo, 1970). For a rapid up or down transition, only the fast compartment (i.e. the lung) needs to be taken into account. However, if a change to a higher $P_{CO_2}$ level is to be sustained indefinitely, the transition to that equilibrium state should take into account the slower compartments (i.e. blood, tissue). Since metabolic $CO_2$ production is small (~0.240 l min$^{-1}$) relative to $CO_2$ stores (~ blood 2.7 l, tissues ~120 l), filling of slower compartments can take a long time. This time can be shortened by supplying $CO_2$ to inspired gas from an external source. The same reasoning applies when a sustained transition to a new lower equilibrium $P_{CO_2}$ is required. In this case, as before, the initial rate of change in the transition is determined by the emptying of the fast compartment. For more sustained reductions in $P_{CO_2}$ the kinetics of emptying the slower body stores (i.e. blood and tissue) need be taken into account. The $\dot{V}_A$ required to sustain a targeted lower $P_{CO_2}$ will consist of the $\dot{V}_A$ required to remove the $CO_2$ produced by metabolism plus the 'extra' $\dot{V}_A$ needed to remove the $CO_2$ delivered to the lungs from the slower compartments of the $CO_2$ stores (blood and tissue).

### Conclusions

We have used a feed-forward control method to implement rapid transitions to targets for $P_{ETCO_2}$ and $P_{ETO_2}$ in spontaneously breathing subjects. The method is based on well accepted physiologic principles, and requires relatively simple, inexpensive apparatus.

## Appendix A. Derivation of the equations

It follows from Principle 5 that $\dot{V}_{G_1}$ can be separated into fresh gas component ($\dot{V}_{G_1,f}$), which is also equal to $\dot{V}_A$, and neutral gas component ($\dot{V}_{G_1,n}$), which we call 'neutral' gas ventilation, or $\dot{V}_N$. Mathematically, this can be expressed as follows.

For $CO_2$ according to mass balance:

$$\dot{V}_{G_1} \times F_{G_1CO_2} = \dot{V}_A \times F_{ICO_2} + \dot{V}_N \times F_{NCO_2} \quad (A1)$$

where $F_{G_1CO_2}$, $F_{ICO_2}$ and $F_{NCO_2}$ are the fractional concentrations of $CO_2$ in $\dot{V}_{G_1}$, $\dot{V}_A$ and $\dot{V}_N$, respectively.

Assuming that inspiratory and expiratory volumes are equal, the flux of $CO_2$ at the lungs is summarized by the following equation:

$$\dot{V}_{CO_2} = \dot{V}_A \times \left(F_{ACO_2} - F_{ICO_2}\right)$$

Solving for $F_{ICO_2}$:

$$F_{ICO_2} = F_{ACO_2} - \left(\dot{V}_{CO_2}/\dot{V}_A\right) \quad (A2)$$

Substituting eqn (A2) into eqn (A1):

$$\dot{V}_{G_1} \times F_{G_1CO_2} = \dot{V}_A \times \left(F_{ACO_2} - \left(\dot{V}_{CO_2}/\dot{V}_A\right)\right) + \dot{V}_N \times F_{NCO_2}$$

Recall that $F_{NCO_2} \approx F_{ACO_2}$ (Principle 1) and that $\dot{V}_N = \dot{V}_{G_1} - \dot{V}_A$,

$$\dot{V}_{G_1} \times F_{G_1CO_2} = \dot{V}A \times \left(F_{ACO_2} - \left(\dot{V}_{CO_2}/\dot{V}_A\right)\right) + \left(\dot{V}_{G_1} - \dot{V}_A\right) \times F_{ACO_2}$$

Solving for $F_{G_1CO_2}$, this simplifies to:

$$F_{G_1CO_2} = F_{ACO_2} - \left(\dot{V}_{CO_2}/\dot{V}_{G_1}\right) \quad (A3)$$

The above equation should hold true for any gas that is excreted by the body.

Similarly, the mass balance equation for $O_2$:

$$\dot{V}_{G_1} \times F_{G_1O_2} = \dot{V}_A \times F_{IO_2} + \dot{V}_N \times F_{NO_2} \quad (A4)$$

Since the flux of $O_2$ at the lungs can be described by the equation:

$$\dot{V}_{O_2} = \dot{V}_A \times \left(F_{IO_2} - F_{AO_2}\right),$$

and $F_{NO_2} \times F_{AO_2}$ (Principle 1),

$$F_{G_1O_2} = F_{AO_2} + \left(\dot{V}_{O_2}/\dot{V}_{G_1}\right) \quad (A5)$$

Note that the change in sign (from negative to positive) compared to analogous eqn (A3) reflects $O_2$ consumption in place of $CO_2$ production.

Equations (A3) and (A5) can be used to calculate the composition and flow of $G_1$ that will result in desired target $F_{ACO_2}$ and $F_{AO_2}$ at steady-state (fractional target concentrations can be easily converted to partial pressures by multiplying them by dry barometric pressure), if the $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are known. (Note that the desired target $F_{ACO_2}$ and $F_{AO_2}$ will only be reached if metabolic $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are equal to respiratory $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, i.e. the system is in dynamic equilibrium.)

Although $\dot{V}_{G_1}$ and target fractional concentrations used in eqns (A3) and (A5) are known, the other two parameters ($\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$) are a property of each individual subject. They are related to subject's age, body mass and height and can be easily estimated from standard tables. (Note, the values given in standard tables are at standard temperature, pressure and dry gas. They have to be converted to body temperature, pressure and saturated gas prior to use in these equations.) Alternatively, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ can be easily measured in each subject using a SGD circuit.

## Appendix B. Measurement of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ using a SGD circuit

At steady-state, metabolic $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are equal to respiratory $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$. Standard methods of estimating $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ at steady-state employ collection of the expired gas in a reservoir (e.g. Douglas bag) from a subject breathing air at rest. Since there is no $CO_2$ in the inspired gas (air), all of the $CO_2$ in the reservoir at the end of the collection period must have come from metabolic $CO_2$ production by the subject. Thus:

$$\dot{V}_{CO_2} = \left(V_{bag}/t\right) \times F_{bagCO_2} \quad \text{(A6)}$$

where $V_{bag}$ is the volume of gas in the bag at the end of the collection, $t$ is the collection time in minutes, and $F_{bagCO_2}$ is the fractional concentration of $CO_2$ in the bag. Similarly, the difference in $O_2$ concentration between air and the gas in the reservoir must be due to $O_2$ consumption by the subject. $\dot{V}_{O_2}$ can therefore be calculated as follows:

$$\dot{V}_{O_2} = \left(V_{bag}/t\right) \times \left(0.21 - F_{bagO_2}\right) \quad \text{(A7)}$$

where $F_{bagO_2}$ is the fractional concentration of $O_2$ in the bag. $F_{bagO_2}$ has to be subtracted from the fractional concentration of $O_2$ in air, which is approximately 0.21.

In the SGD circuit, all of the delivered gas, $\dot{V}_{G_1}$, eventually ends up in the expiratory reservoir. The concentrations of $O_2$ and $CO_2$ in the reservoir at any given $\dot{V}_{G_1}$ will therefore be proportional to the subject's metabolic $O_2$ consumption and $CO_2$ production. Equations (A6) and (A7) can be rewritten to apply to SGD circuit as follows:

$$\text{For } CO_2 : \dot{V}_{CO_2} = \dot{V}_{G_1} \times F_{bagCO_2}$$
$$\text{For } O_2 : \dot{V}_{O_2} = \dot{V}_{G_1} \times \left(0.21 - F_{bagO_2}\right)$$

However, the concentrations of $O_2$ and $CO_2$ in the expiratory reservoir fluctuate throughout expiration. In order to obtain a representative estimate of metabolic parameters, the concentrations of $O_2$ and $CO_2$ in the expiratory reservoir should be averaged over time (30–60 s is usually adequate). For additional confidence, repeated measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ can be made to yield average values.

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## Disclosure

A patent has been filed for the method described in the present paper, with some of the authors named as co-inventors (Marat Slessarev, Eitan Prisman, Cliff Ansel, George Volgyesi and Joseph Fisher).