Effects of ventilation on cardiac output determined by inert gas rebreathing

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Summary

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Key words

breathing frequency; hyperventilation; oxygen uptake; pulmonary blood flow; respiratory dead space One of the most important methodological problems of the foreign gas rebreathing technique is that outcome of the measurements depends on procedural variables such as rebreathing frequency (RF), rebreathing bag volume (V_{reb}) , lung volume at start of rebreathing and intervals between measurements. Therefore, in 10 healthy males we investigated the effects of changes in ventilation pattern on cardiac output (CO) estimated by an N₂O-rebreathing technique. Reducing the rebreathing volume ($V_{\rm reb}$) from 1.5 to 1.0 l diminished CO by 0.5 ± 0.2 l min⁻¹, whereas an increase in V_{reb} from 1.5 to 2.5 l had no effects. CO was 1.0 \pm 0.2 l min $^{-1}$ higher when, rebreathing was performed after a forced expiration than following a normal tidal expiration. Serial determinations of CO required a 3-min interval between the measurements to avoid effects of recirculation of N2O. Changing RF from 15 to 30 breaths min⁻¹ or adding serial dead space by up to 600 ml did not affect the determination of CO. In conclusion, the rebreathing procedure for determination of CO at rest should be performed following a normal tidal expiration with a rebreathing bag volume of between 1.5 and 2.5 l and with manoeuvres separated by at least 3-5 min. Variations in RF within the physiological range from 15 to 30 breaths min⁻¹ do not affect outcome of the measurements.

Introduction

Inert gas rebreathing is a well-established method for determining effective pulmonary blood flow (Q_{ep}) , which, in the absence of intrapulmonary shunts, equals cardiac output (CO). The method is reliable and easy to use without risks and discomfort to the subject. During the past decades, the procedure has been shown to be precise and reproducible during rest and exercise in healthy and diseased individuals (Sackner, 1987; Clemensen et al., 1994; Warburton et al., 1999; Reutershan et al., 2003a, 2004; Gabrielsen et al., 2002).

However, it is important to define the fundamental weaknesses of the method when it is used to estimate CO from Q_{ep} . Several methodological factors, such as rebreathing frequency (RF), rebreathing bag volume (V_{reb}) and lung volume at start of rebreathing, could induce either true changes or cause errors in the estimation of Q_{ep} . Furthermore, underestimation of Q_{ep} and thus CO could arise from the presence of blood soluble gas in the venous circulation caused by recirculation during rebreathing or by inadequate wash out

of the gases between the rebreathings. Although these potential confounding effects have previously been investigated in studies by a theoretical approach (Petrini et al., 1978, 1983; Hook & Meyer, 1982; Boutellier & Farhi, 1986a; Verbanck & Paiva, 1994) the clinical data from human studies are sparse and incomplete (Triebwasser et al., 1977; Bonde-Petersen et al., 1980; Petrini et al., 1982; Kallay et al., 1985; Boutellier & Farhi, 1986b; Christensen et al., 2000).

Theoretically, the rebreathing method is limited by the presence of ventilation-perfusion inhomogeneities as seen in pulmonary diseases. (Hook & Meyer, 1982). The influence of additional dead space, which induces delayed gas mixing due to changed ventilatory pattern, has not been evaluated previously in a clinical setting.

In this study, we therefore tested how variations in methodological variables modulate determination of CO by N_2O rebreathing to decide which procedure would be the best suited for obtaining the most reliable results. By using young healthy non-smoking males as subjects we were able to exclude any significant effects of pulmonary shunting, which

could have induced discrepancy between the measured $Q_{\rm ep}$ and CO.

Methods

Experimental procedures

Ten healthy males [age 27 ± 2 years (range 20-35), height 185 \pm 3 cm (range 175–192) and weight 82 ± 2 kg (range 70–95)] participated in the experiment. During all of the experiments, room temperature was kept between 24 and 26°C and humidity between 15 and 40%. Written informed consent was obtained, when the subjects had read a description of the experimental protocol, which had been approved by the Ethics Committee of Copenhagen (KF 01-215/01) and was in compliance with the Declaration of Helsinki.

Eighteen hours before the study commenced, the subjects were not allowed to perform any kind of exercise or to ingest beverages containing caffeine. On the morning of the study, the subjects ingested a light breakfast at 7:00 AM before arriving at the laboratory at 7:30 AM. The subjects were then weighed and placed upright in a comfortable armchair and rested for 30 min before the start of the experiment.

From 8:00 to 11:00 AM the subjects, while seated, performed the scheduled procedures. We used a standard procedure with a $V_{\rm reb}$ of 1.5 l and a rebreathing period of 30 s following a normal tidal expiration. A similar procedure has previously been evaluated against the direct Fick and thermodilution method for determination of CO with satisfactory results (Reutershan et al., 2003a,b, 2004; Gabrielsen et al., 2002). Finally, a breathing rate of 20 per minute was chosen. All rebreathing procedures were performed in a closed system (ventilation through the nose was prevented by the use of a nose-clip), with a gas mixture of 28% $O_2,\,0.5\%~N_2O$ and $0.1\%~SF_6$ in N_2 from atmospheric air, in a 4-l anti-static rubber bag. The rebreathing bag was emptied completely at each breath. To ensure adequate washout of N₂O between measurements, the alveolar N2O concentration before the rebreathing procedure was required to be less than 1/200 of the N_2O concentration in the rebreathing bag (0.5%).

We examined the effects of changes in rebreathing procedures on CO by varying the following variables at random order within each series of testing:

Rebreathing volume: The volume in the rebreathing bag was set at 1.0, 1.5, 2.0 and 2.5 l.

Dead space: By connecting plastic pipes of 0, 200, 400 and 600 ml air volume between the mouthpiece and rebreathing bag, dead space was expanded.

Rebreathing frequency: The breathing frequency was set at 15, 20, $25 \text{ and } 30 \text{ min}^{-1}$ by asking the subjects to breathe according to the rhythm of a metronome.

Lung volume at start of rebreathing: The rebreathing procedure was commenced following a (i) full expiration in which case the lung volume equalled residual volume, (ii) tidal expiration [lung volume = Functional Residual Capacity (FRC)] and finally, (iii) tidal inspiration.

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Intervals between measurements: The rebreathing procedures were separated by 5, 3, 2.5, 2 and 1.5 min respectively.

Equipment

The rebreathing system consisted of a three-way respiratory valve connecting a mouthpiece and a 4-l anti-static rubber bag, which was connected to an infrared photo-acoustic gas analyser (Innocor, Innovision A/S, Odense, Denmark). A negligible amount of gas (120 ml min^{-1}) was removed during rebreathing at the mouthpiece for continuous analysis of gas concentrations. The infrared photo-acoustic technique has previously been described in detail by Clemensen *et al.* (1994). Oxygen concentration was determined by Laser Diode Absorption Technology in a commercial analyser (Model X2004, Oxigraf Inc., Mountain View, CA, USA) integrated into the gas analyser.

Calculations

All calculations were performed according to the single-alveolus one-compartment lung model (Clemensen *et al.*, 1994). CO was calculated from the rate of uptake of N₂O into the blood as expressed from the slope of the regression line through the logarithmically transformed end-expiratory (alveolar) N₂O concentrations plotted against time after correction for volume changes using end-expiratory SF₆ (blood insoluble gas) concentrations. Likewise, oxygen uptake (Vo₂) was calculated from the total volume of the rebreathing system and the rate of uptake of O₂ [slope of the best fit regression line through the end-expiratory (alveolar) O₂ concentrations plotted against time after correction for volume strength of O₂ [slope of the best fit regression line through the end-expiratory (alveolar) O₂ concentrations plotted against time after correction for volume changes by end-expiratory SF₆ concentrations].

To ensure adequate mixing of the rebreathing gas with air in the lungs we excluded the first part of the end expiratory concentration curve, where the peak-to-peak variation of the SF_6 concentration was more than 15%. Hence, the first two breaths were omitted in 97% of the standard rebreathing procedures. To examine how the number of breaths used for calculation of CO influenced the results, we included from two to six breaths in the calculations of all of the standard measurements. All other calculations of CO were performed using data of three expirations.

Statistics

Data are presented as mean \pm SEM. A one-way ANOVA for repeated measurements with the variable as main variate and the intervention as factor was used to evaluate the effects of the interventions on CO. Statistically significant differences between mean values were evaluated by a post hoc multiple range test (Newman–Keuls). If no significant changes were observed by the ANOVA, the relative changes in the main variables due to the interventions were concluded to be negligible, if the variation were < $\pm 10\%$ in comparison with the standard procedure.

Results

All subjects completed the study. In general, the determinations of CO and Vo₂ were only affected modestly by changes in the ventilatory patterns:

Rebreathing frequency: Variations in rebreathing rate from 15 to 30 breaths min^{-1} induced no physiologically relevant changes neither in CO nor Vo_2 (Table 1).

Rebrathing volume: Changing the rebreathing volume from 1.0 to 2.5 l progressively increased CO and Vo_2 (Table 1). However, these changes were only modest with a variation in CO from -0.5 ± 0.2 to $0.1 \pm 0.1 \text{ l} \text{ min}^{-1}$ in comparison with CO of the standard procedure. Likewise, Vo_2 increased only moderately from -0.02 ± 0.01 to $0.05 \pm 0.01 \text{ l} \text{ min}^{-1}$ (Table 1).

Lung volume at start of rebreathing: When the rebreathing manoeuvre was started following a forced expiration (lung volume = 1.74 ± 0.12 l), CO and Vo₂ were 1.0 ± 0.2 and 0.10 ± 0.03 l min⁻¹ higher, respectively, than compared with the values during standard conditions (lung volume = 3.08 ± 0.13 l). Rebreathing following a normal tidal inspiration (lung volume = 4.10 ± 0.23 l) induced no changes in CO or Vo₂ (Table 1).

Dead space: Adding from 0 to 600 ml dead space did not affect the calculation of CO or the Vo_2 (Table 1).

Intervals between rebreathings: Reducing the interval between two rebreathing procedures progressively diminished CO in an almost linear fashion (Fig. 1a) although significant only when measurements were performed <3 min apart. However, CO was

Table 1	Cardiac outpu	it and o	oxygen	uptake	during	variation
ventilato	ry patterns.					

Interventions	CO (l min ⁻¹)	V_{0_2} (l min ⁻¹)	
Rebreathing frequenc	y		
15	5·8 ± 0·4	0.39 ± 0.01	
20	5.9 ± 0.3	0·39 ± 0·02	
25	5.5 ± 0.4	0.40 ± 0.02	
30	5.5 ± 0.5	0.39 ± 0.01	
Rebreathing bag volu	me (ml)		
1000	$6.0 \pm 0.4*$	0.39 ± 0.01	
1500	6.5 ± 0.3	0.41 ± 0.02	
2000	6.6 ± 0.3	0.41 ± 0.01	
2500	6.6 ± 0.4	0·46 ± 0·02*	
Lung volume before :	rebreathing (l)		
RV (1.73)	$6.4 \pm 0.3*$	0·46 ± 0·03*	
FRC (3.08)	5.4 ± 0.3	0·37 ± 0·02	
INSP (4.01)	5.5 ± 0.5	0.41 ± 0.04	
Applied dead space (i	ml)		
0	6.0 ± 0.4	0·41 ± 0·02	
200	5.8 ± 0.4	0.39 ± 0.02	
400	6.0 ± 0.3	0.38 ± 0.01	
600	5·9 ± 0·3	0.37 ± 0.02	

Values are mean \pm SE. RV, residual volume; FRC, functional residual volume; INSP, lung volume after a normal tidal inspiration. *Significant difference (P<0.05) in comparison with the standard procedure. Values in italics represent the standard procedure.



Figure 1 (a) Cardiac output (CO) and (b) oxygen uptake (Vo_2) determined by N_2O rebreathing when the interval between procedures is gradually narrowed. Values are mean \pm SEM. *Significant difference from baseline (start) values (P<0.05).

reduced by $-0.4 \pm 0.1 \text{ l min}^{-1}$ after a 3-min break (P = 0.17). In contrast, Vo₂ was not affected by varying the intervals between the procedures (Fig. 1b).

Number of breaths included for calculation of CO: In the 90 measurements performed during standard conditions (rebreathing following a normal tidal expiration, $V_{\rm reb} = 1.5$ l and RF = 20 breaths min⁻¹), CO remained unchanged when calculated on the basis of three to five breaths. When including data from six expirations, CO decreased significantly although very modestly (0.1 ± 0.1 l min⁻¹). Vo₂ remained unchanged when an increasing number of breaths were used as basis for the calculations.

Discussion

In this study, we evaluated how changes in ventilatory variables affect the determination of CO by inert gas

rebreathing. In conclusion, we recommend that rebreathing procedures at rest should be performed following a normal tidal expiration with a rebreathing bag volume of between 1.5 and 2.5 l and with consecutive procedures separated by at least 5 min. Varying the RF within the normal physiological range $(15-30 \text{ breaths min}^{-1})$ does not affect the outcome of the measurements.

Increasing $V_{\rm reb}$ from 1.0 to 2.5 l progressively increased both CO and Vo2. The increased CO is in fact a true physiological phenomenon during high-volume hyperventilation and has likewise been demonstrated by invasive methods (Donovan et al., 1962; McGregor et al., 1962; Cummin et al., 1986). This increase can be explained by a higher respiratory work (Milic-Emili & Petit, 1960) or by a passive increase in venous return due to increased thoracic movements and a decreased intrapleural pressure that expands the heart and central vessels (Cummin et al., 1986). Furthermore it is not established whether hypocapnia per se increases CO during hyperventilation (McGregor et al., 1962; Cummin et al., 1986). However, this potential mechanism might be of less importance during rebreathing, where arterial CO₂ is changing from hypocapnia to hypercapnia (Matalon et al., 1982). Regardless of the mechanisms, however, our results are in accordance with those of previous investigations of rebreathing (Overland et al., 1981; Boutellier & Farhi, 1986b; Kallay et al., 1985).

Increasing RF from 15 to 30 did neither change CO nor Vo_2 . Hyperventilation due to a high breathing frequency, has by invasive means (Matalon *et al.*, 1982) and by rebreathing (Kallay *et al.*, 1985; Boutellier & Farhi, 1986b) been shown to change CO only moderately if at all. In one study (Triebwasser *et al.*, 1977) where a higher CO was reported at increasing breathing rate, the changes were insignificant, when the rate was kept between 15 and 25 breaths min⁻¹. The small effect of breathing frequency on CO could be explained by an unchanged average intrapleural pressure and thereby unchanged venous return.

The rebreathing procedure is traditionally commenced following a normal tidal expiration, when the lungs contain a gas volume close to FRC. It could be argued that it might be advantageous to expire maximally before rebreathing to obtain a more complete mixing of rebreathing gas with air in the lungs. However, it has only been investigated during rebreathing in one study by Kallay et al. (1985) that reported no significant effects of increasing the lung volume by 3 l (seated position) before rebreathing, when $V_{\rm reb}$ was kept unchanged. We observed a significantly higher CO and Vo2, when the rebreathing procedure was performed following a full expiration than compared with procedures following a normal tidal expiration or inspiration. Respiratory work is minimized when breathing is performed around a lung volume equal to FRC, where the relaxation pressure is zero. Thus, it is likely that the alterations we observed in CO and Vo2 during variations in breathing patterns reflect true physiological and not methodological changes. Therefore, at rest it is recommendable to begin the rebreathing procedure following a normal tidal expiration.

Determination of CO by inert gas rebreathing is based on the assumption that there is no rebreathing gas in the alveoli before start of the rebreathing; otherwise CO will be underestimated. When performing multiple rebreathings, there must be an adequate period between the procedures for elimination of the soluble gas. The length of this period depends on the amount of gas present in the blood after rebreathing (depends on the duration of the procedure and concentration of the gas) and of gas elimination following rebreathing (depends on CO, ventilation and gas solubility in blood). Our results demonstrate that it is necessary to separate the measurements by at least 3 min to avoid recirculation of N2O. By shortening the rebreathing period from 30 to 20 s, the soluble gas concentration in blood can become lower and less time will be required for elimination. As expected, the determination of Vo₂ was unaffected by narrowing the time period between procedures.

The physiological dead space and that of the equipment do not constitute a methodological problem for determination of CO by rebreathing in healthy humans (Petrini et al., 1978; Badgwell & Heavner, 1990). In the present study, an additional serial dead space of up to 600 ml did not affect the determination of CO or Vo2, even though total dead space (physiological + equipment + applied) constituted up to 50% of tidal volume. Despite delayed gas mixing requiring exclusion of data from 3 to 4 of the initial breaths in the calculation, the determination of CO and Vo_2 was unaffected. Although this model does not constitute a direct model for increased physiological dead space, it reveals that the effects of late mixing of rebreathing gases are negligible. This is in accordance with theoretical studies of simple lung models in which an uneven distribution of ventilation and perfusion only modestly affected CO (Petrini et al., 1978; Hook & Meyer, 1982; Kallay et al., 1985). In a clinical study (Kallay et al., 1987) of patients with mild to moderate obstructive and restrictive pulmonary disease, CO determined by C2H2rebreathing and by indicator-dilution method exhibited a fair agreement. In contrast, Pierce et al. (1987) underestimated CO by freon-rebreathing compared with the CO by direct Fick method in patients with mild obstructive pulmonary disease. However, the use of freon in rebreathing procedures has been shown to underestimate CO probably due to the heavier molecule resulting in uneven distribution throughout the lungs (Bonde-Petersen et al., 1980). Therefore, it might be possible to apply the rebreathing technology in patients with pulmonary disease but further clarification must be obtained for this purpose.

To avoid errors, CO should ideally be calculated from the slope of the logarithmically transformed end-expiratory N_2O disappearance curve in the period from adequate gas mixing to the moment of soluble gas recirculation. We did not use the data from the initial breaths, where the peak-to-peak variation in the SF₆ concentration was more than 15% of the concentration at

equilibrium excluding two breaths in 97% of the standard procedures. The absolute values and variation of CO remained unchanged including from three to five breaths in the calculation (Fig. 1). Thus, the majority of the rebreathing procedures (>95%) can be completed within five to six breaths with a total duration of <20 s. This should be sufficient to avoid the influence recirculating rebreathing gases that have been detected by invasive means (Werko *et al.*, 1949; Chapman *et al.*, 1950; Matalon *et al.*, 1982) in the pulmonary artery 10–14 s after initiation of rebreathing and remained at negligible concentrations for additionally 5–10 s.

 Vo_2 decreases as the calculation period is extended but the difference is small (<30 ml) and without physiological significance. In all rebreathing procedures the final alveolar oxygen pressure was beyond 140 torr which have been demonstrated to be a critical determinant for precision of the method (Kallay *et al.*, 1990). Thus, when calculating CO and Vo_2 , it seems adequate to include only three breaths allowing the exclusion of three breaths if initial gas mixing is slow.

Conclusion

The rebreathing procedure for determination of CO and Vo_2 should be performed following a normal tidal expiration with a rebreathing bag volume of between 1.5 to 2.5 l and with the procedures separated by at least 3 min. Changes in RF within the physiological range (15–30 breaths min⁻¹) do not affect the outcome of the measurements.

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