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J Appl Physiol 103:867-874, 2007. First published Jun 7, 2007; doi:10.1152/japophysiol.01106.2006

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Simultaneous determination of the accuracy and precision of closed-circuit cardiac output rebreathing techniques

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Submitted 2 October 2006; accepted in final form 30 May 2007

Jarvis SS, Levine BD, Prisk GK, Shykoff BE, Elliott AR, Rosow E, Blomqvist CG, Pawelczyk JA. Simultaneous determination of the accuracy and precision of closed-circuit cardiac output rebreathing techniques. *J Appl Physiol* 103: 867–874, 2007. First published June 7, 2007; doi:10.1152/jappphysiol.01106.2006.—Foreign and soluble gas rebreathing methods are attractive for determining cardiac output (\dot{Q}_c) because they incur less risk than traditional invasive methods such as direct Fick and thermodilution. We compared simultaneously obtained \dot{Q}_c measurements during rest and exercise to assess the accuracy and precision of several rebreathing methods. \dot{Q}_c measurements were obtained during rest (supine and standing) and stationary cycling (submaximal and maximal) in 13 men and 1 woman (age: 24 ± 7 yr; height: 178 ± 5 cm; weight: 78 ± 13 kg; $\dot{V}_{O_{2max}}$: 45.1 ± 9.4 ml·kg⁻¹·min⁻¹; mean \pm SD) using one-N₂O, four-C₂H₂, one-CO₂ (single-step) rebreathing technique, and two criterion methods (direct Fick and thermodilution). CO₂ rebreathing overestimated \dot{Q}_c compared with the criterion methods (supine: 8.1 ± 2.0 vs. 6.4 ± 1.6 and 7.2 ± 1.2 l/min, respectively; maximal exercise: 27.0 ± 6.0 vs. 24.0 ± 3.9 and 23.3 ± 3.8 l/min). C₂H₂ and N₂O rebreathing techniques tended to underestimate \dot{Q}_c (range: 6.6–7.3 l/min for supine rest; range: 16.0–19.1 l/min for maximal exercise). Bartlett's test indicated variance heterogeneity among the methods ($P < 0.05$), where CO₂ rebreathing consistently demonstrated larger variance. At rest, most means from the noninvasive techniques were $\pm 10\%$ of direct Fick and thermodilution. During exercise, all methods fell outside the $\pm 10\%$ range, except for CO₂ rebreathing. Thus the CO₂ rebreathing method was accurate over a wider range (rest through maximal exercise), but was less precise. We conclude that foreign gas rebreathing can provide reasonable \dot{Q}_c estimates with fewer repeat trials during resting conditions. During exercise, these methods remain precise but tend to underestimate \dot{Q}_c . Single-step CO₂ rebreathing may be successfully employed over a wider range but with more measurements needed to overcome the larger variability.

foreign gas rebreathing; physiological gas rebreathing; direct Fick; thermodilution

CARDIAC OUTPUT (\dot{Q}_c), the volume of blood pumped by the heart each minute, can be measured several ways, both invasively and noninvasively. Each technique has advantages and limitations that may restrict its application during exercise. The direct Fick method has been implemented in humans in clinical environments since 1940 (21); together with the thermodilution method, they are considered “gold standard” \dot{Q}_c techniques. These methods, however, are expensive, require medical expertise, and are invasive,

limiting their widespread utility (44). For instance, occasional reported complications associated with these gold standards include arrhythmias and pulmonary artery or right ventricle perforation (30, 40).

Rebreathing techniques, employing foreign or physiological tracers, are attractive alternatives because their relative risk is considerably less (44). Pulmonary blood flow may be estimated by rebreathing a gas mixture containing a foreign, soluble gas and measuring the rate of disappearance of this gas (often determined by mass spectrometry; Ref. 42). Foreign gases [such as acetylene (C₂H₂) and nitrous oxide (N₂O)] are commonly used in rebreathing techniques because they are inert, soluble, and enter the blood stream via pulmonary diffusion but do not bind with hemoglobin (44). Often an inert insoluble gas (e.g., He, Ar, CH₄, or SF₆) is added to the gas mixture to determine system (bag/lung) volume and adequacy of gas mixing in the lungs (42). Alternatively, the rate of accumulation of a physiological soluble gas [carbon dioxide (CO₂)] in the rebreathing mixture may be employed. In normal subjects, pulmonary blood flow is proportional to \dot{Q}_c (44). That is, if no diffusion limitation or physiological shunt is present, the rate of uptake of the foreign gas is a function of 1) the solubility coefficient of the gas, 2) pulmonary blood flow (cardiac output), and 3) lung tissue volume (37, 42).

Techniques based on these theories have been implemented in clinical settings (27), in exercise physiological research, during ground-based deconditioning studies (22), in low-earth orbit (39), and post spaceflight (34, 39). Previous studies have compared criterion methods against gas rebreathing techniques (13, 25, 32, 35) and others have examined these methods during exercise (23), but a simultaneous comparison of multiple rebreathing techniques has not been conducted over a wide range of postures and metabolic states. Thus the purpose of this investigation was to compare simultaneously obtained criterion and rebreathing data, during rest and exercise, to provide a determination of the accuracy and precision of these techniques.

MATERIALS AND METHODS

Subjects

Thirteen men and one woman (age: 24 ± 7 yr; height: 178 ± 5 cm; weight: 78 ± 13 kg; $\dot{V}_{O_{2max}}$: 45.1 ± 9.4 ml·kg⁻¹·min⁻¹; mean \pm SD) volunteered to participate. All subjects were healthy, nonsmoking

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individuals that were recruited from the surrounding community. Most were active in recreational sports; no one was a competitive athlete at the time of the study. Volunteers received a physical exam, performed a maximal exercise test ($\dot{V}O_{2\max}$), and performed 5–10 \dot{Q}_c rebreathing maneuvers during screening visits to become familiar with the procedures. Each subject was studied on a single day within 2 wk of screening. All aspects of this study were approved by the Institutional Review Board at the Presbyterian Hospital of Dallas and the University of Texas Southwestern Medical Center.

Criterion Techniques: Direct Fick and Thermodilution

Direct Fick. A flow-directed thermistor-tipped pulmonary artery catheter was inserted from the antecubital fossa and advanced under fluoroscopic guidance into the main or proximal right pulmonary artery. Samples of pulmonary artery blood were withdrawn for determination of mixed venous oxygen content ($C\bar{v}O_2$) in the middle of the 1-min Douglas bag collection. Hemoglobin concentration and oxyhemoglobin saturation were determined using co-oximetry (IL 482, Instrument Laboratories). \dot{Q}_c was determined by using the Fick equation: $\dot{Q}_c = \dot{V}O_2 / (CaO_2 - C\bar{v}O_2)$, where CaO_2 is arterial oxygen content with SaO_2 derived from ear oximetry (Ohmeda 3700 ear probe), and $\dot{V}O_2$ is oxygen uptake determined by open-circuit spirometry (Douglas bags).

Thermodilution. Determinations were based on the temperature changes recorded at the pulmonary artery after 10 ml of 0°C isotonic saline was injected into the right atrium. Saline was stored in an ice bath until just before use. Careful attention was paid to minimize the time between removal of the syringe from the ice bath and injection into the right atrium. All curves were inspected visually, and only curves with apparent exponential decay were used for data analysis. The average of three measurements was used for each determination. \dot{Q} was calculated by a Baxter cardiac output computer using the modified Stewart-Hamilton equation: $\dot{Q} = [V(T_B - T_1)K_1K_2] / \int \Delta T_B(t) dt$, where V is volume of isotonic saline injected; T_B is temperature of blood; T_1 is temperature of injectate; and K_1 and K_2 are constants.

Gas Rebreathing: Foreign and Physiological Soluble Gases

Five independent investigative teams developed six rebreathing methods: one- N_2O , four- C_2H_2 , and one- CO_2 (revised single step). As the principle underlying these techniques is mass balance, they are fundamentally similar. In this investigation, the differences were the choice of soluble gas (CO_2 vs. N_2O vs. C_2H_2), the insoluble gas to determine system volume (Ar or He), and the analysis software independently developed by each team and used in their respective laboratories. To provide a simultaneous comparison, data were acquired using a gas mixture of O_2 40%, CO_2 0%, N_2 balanced, Ar 5%, He 9%, N_2O 2%, C_2H_2 0.600%. The gas mixture contained two inert insoluble gases since determinations with the C_2H_2 and N_2O rebreathing methods use He as an insoluble gas, whereas the CO_2 method used Ar. Each investigative team independently calculated \dot{Q}_c from the gas concentrations obtained during the same rebreathing maneuver. The rebreathing bag was pre-filled so that subjects rebreathed 2.5 liters of the gas mixture during the resting conditions (supine and standing) and 3.0–3.5 liters during exercise for 25 s at a rate of 22 breaths/min. Gas concentrations were continuously analyzed via mass spectrometry (MGA-1100, Perkin Elmer). This combination of gas mixtures, bag volume, rebreathing time, and breathing frequency was devised to accommodate, to the greatest extent possible, all techniques within the experimental design. A turbine flowmeter (VMM-400, Interface Associates) was included between the subject's mouth and the rebreathing valve for those implementations requiring a volume/time signal. The catheter transit time was measured in response to a step change in gas concentration to align volume and gas concentration signals temporally.

N_2O . This method has been used previously to obtain measurements in astronauts, both pre- and in-flight, for evaluating the effects of microgravity on \dot{Q}_c (34). \dot{Q}_c measurements were determined by using the Sackner algorithm by fitting a line over all of the alveolar plateau regions from expiration after clearing the deadspace. \dot{Q}_c was calculated as: $\dot{Q}_c = [(V_A \times 760) / \alpha_{N_2O} (F_{AN_2O}^{intercept} / F_{AN_2O}) (P_A - P_{H_2O})] \times [\Delta \ln(F_{AN_2O} / F_{AN_2O}^{intercept}) / \Delta t]$, where \dot{Q}_c is pulmonary capillary blood flow; V_A is alveolar volume (STPD) determined by He dilution; α_{N_2O} is the Bunsen solubility coefficient for N_2O (0.407); F_{AN_2O} is the alveolar fraction of N_2O , corrected for He dilution (F_{AN_2O} is the initial fraction and $F_{AN_2O}^{intercept}$ is the intercept value corrected for timing); and $P_A - P_{H_2O}$ is barometric pressure of the dry gas mixture (38).

The first three breaths of each maneuver were discarded for this method's analysis because thorough mixing of the bag-lung system had not been achieved. Thus, only the breaths containing stable He concentrations were used to determine \dot{Q}_c . N_2O disappearance curves were calculated using a least-squares fit and the disappearance curve's intercept was shifted to *time zero* (3). *Time zero* was defined as the midpoint of the rapid rise in N_2O concentration of the first test inspiration.

C_2H_2 . Similar to N_2O rebreathing, \dot{Q}_c determinations with C_2H_2 rebreathing used He to compute alveolar volume by $V_A = [I[He] / F[He]] \times \dot{V}_I$, where $I[He]$ is initial fraction of inspired He; $F[He]$ is final He fraction; and \dot{V}_I is inspired volume in liters (STPD). The differences in determining \dot{Q}_c from each C_2H_2 rebreathing method are outlined below.

C_2H_2 (method 1). \dot{Q}_c determinations for this method were identical to the N_2O method described above. The equation used to calculate \dot{Q}_c was identical except that the solubility coefficient for C_2H_2 (0.768) was adjusted accordingly.

C_2H_2 (method 2). This C_2H_2 rebreathing method has been previously used to determine \dot{Q}_c before and after spaceflight (31). It was the only fully automated method, providing valve switching (Hans Rudolph Series 2540) to connect the inspiratory circuit to the rebreathing bag. Since this method does not require a pre-filled bag, the inspired fraction of C_2H_2 was calculated from the volume weighted integral of $[C_2H_2]$ measured during the first inspiration of a known mixture. The rate of C_2H_2 absorption into blood was computed from the regression slope of the logarithm of regressed end-tidal C_2H_2 fractions. The end-tidal points were selected by the software based on Sackner's criterion, only for breaths where a stable $[He]$ had been established (38). *Time zero* was defined from the initial rapid rise in C_2H_2 concentration (point at which inspired acetylene concentration exceeded 0.0025%), less the time required to inspire the sum of the measured mouthpiece and estimated physiological deadspace volume.

C_2H_2 (method 3). This implementation was originally published by Triebwasser et al. (42) and used more recently in a study that examined cardiac atrophy during 6° head-down bed rest (5). C_2H_2 and He concentrations were averaged during the last 40 ms of each expiration, as determined by the zero crossing of the flowmeter. The slope of the change in $[C_2H_2]$ over time was derived during each breath from the end respiratory gas concentrations (42). Since there is some uptake, albeit small, of C_2H_2 by the lung parenchyma upon the first inspiration, the intercept was back extrapolated to determine *time zero* by: $intercept = (V_s) / \{V_s + \alpha_i [(P_A - P_{H_2O}) / (760)]\} \times V_t$, where V_s is system volume (alveolar + bag); α_i is Bunsen solubility coefficient for C_2H_2 (0.768); $P_A - P_{H_2O}$ is barometric pressure of the dry gas mixture; and V_t , which can be estimated by $V_t = [V_s / (intercept - 1) / (0.768)] \times [760 / (P_A - P_{H_2O})]$ (42). Finally, to calculate \dot{Q} , the following equation was used: $\dot{Q} = \{[(V_s / intercept) \times (760 / P_A - P_{H_2O})] / 0.700\} \times (-m)$, where $-m = \{[\ln(F_{A2} \times F_{He1}) / (F_{A1} \times F_{He2})] / (t_2 - t_1)\}$ was estimated over several breaths obtained by linear regression and the slope of the concentration ratio over time, F_{A1} and F_{He1} and F_{A2} and F_{He2} are the fractional C_2H_2 and He concentrations for the first and second samples, respectively; and $t_2 - t_1$ was the time in seconds between the two samples (42). Additionally, a partition coefficient of 0.700 for C_2H_2 between gas and blood was used (42).

C_2H_2 (method 4). This method was developed as a prototype. Determinations made with this prototype method used a C_2H_2 re-breathing technique similar to the Sackner implementation described above.

CO_2 (single step). Although several different CO_2 rebreathing methods have been developed (e.g., Refs. 10, 20), only the modified one-step method was employed in this investigation because its initial conditions and rebreathing technique were compatible with the other methods under study. This method has been used to determine \dot{Q}_c under a number of altered environmental conditions that include microgravity (39), water immersion, and head-down tilt (29). None of the other CO_2 rebreathing methods could have been used in this investigation because they require a separate, steady-state measurement of CO_2 production, and several rely on equilibration of CO_2 in the gas and blood or unique respiratory maneuvers.

The modified one-step rebreathing maneuver is based on the fact that any CO_2 leaving the blood during rebreathing enters either the gas phase or the tissue stores. For the i th breath once the rebreathing bag and lung gas are well mixed, the mass balance of CO_2 states that $\dot{Q}_c \cdot (C_vCO_2 - C_cCO_2)(t_{i+1} - t_i) = V_{gas}^{i+1} \cdot FCO_2^{i+1} - V_{gas}^i \cdot FCO_2^i + V_t \cdot (FCO_2^{i+1} - FCO_2^i)$, where V_{gas} is the total gas volume, rebreathing bag + lung, FCO_2^i is the fraction of CO_2 in the gas phase at time t_i , and V_t is the volume of lung tissue expressed as equivalent gas volume.

A breath is defined to begin at the onset of the alveolar plateau. Because the rebreathing bag is empty at the end of inspiration, the gas sample is representative of the system. A fitted dissociation curve is applied to each value of $P_{A_{CO_2}}$ during the breath and the values are averaged to give $C_cCO_2^i$; $P_{A_{CO_2}}$ is either the measured value during expiration, or the linear interpolation between end expiration and the start of the next alveolar plateau during inspiration. V_{gas} was calculated for each breath using the mass balance of N_2 and Ar, and, in this study, corrected for the gases not usually in the rebreathing mix for this method.

Mixing of the bag-lung system was assessed from the concentration of Ar; in general, the gases were well mixed after the third breath. The same mass balance equation was applied also to the first, poorly mixed breaths in toto, with t_0 as the end-tidal point before rebreathing. This yields a system of equations in the unknowns (\dot{Q}_c , C_vCO_2 , and V_t) to be rearranged and solved by linear regression methods. In the usual implementation of this method, the breathing frequency and rebreathing times are set to obtain at least 12 breaths and nine equations per rebreathing maneuver, but in this multi-method trial we compromised with eight to nine complete breaths and six or seven equations.

The original one-step method (28) needs a rebreathing bag large enough that FCO_2 remains below FCO_2^0 , the normal end-tidal value, for three or four breaths. To obviate the need to consider tissue stores of CO_2 , that method then measures the amount of CO_2 added to the gas phase only in the time from the start of the hyperventilation of rebreathing at t_0 to the time when FCO_2 in the system again reaches FCO_2^0 . C_cCO_2 is obtained for the measurement period as in the modified method, but C_vCO_2 is obtained, using the dissociation curve, from a calculated equilibrium $P_{eq}CO_2$ obtained by extrapolation to the PCO_2 at which the slope of the curve of end-tidal values would equal zero. However, in the modified one-step method used in these experiments, C_vCO_2 is estimated as the CO_2 content remaining in the blood after its passage through the lungs, not as equilibrated CO_2 content. The assumption is made that alveolar and mixed capillary PCO_2 are the same, but CO_2 is leaving the blood throughout the measurements and full oxygen saturation is ensured because the rebreathing starts with 40% oxygen.

Resting Conditions: Supine and Standing

After catheter placement, the subjects rested quietly for 30 min while under observation. Subjects were then taken to the lab to be

instrumented with ECG and noninvasive blood pressure monitoring (Suntech 4240).

\dot{Q}_c was collected during supine rest, standing rest, submaximal exercise on a cycle ergometer at 100 W, and during maximal exercise. The supine resting protocol began with 2 min of allowing the subject to reach steady state, 1 min to obtain mixed venous samples, 1 min rebreathing, and then 1 min of thermodilution measurements. This cycle was repeated until four measurements were collected. The subject was then asked to move into the standing position and allowed 5 min to achieve steady state, after which the same protocol was repeated. Once the standing measurements were obtained, we allowed 15 min to prepare for the exercise protocol.

Exercise Conditions: Submaximal and Maximal

The subject exercised at 100 W on a cycle ergometer for 15 min, while \dot{Q}_c was collected four times, every 3 min, in the same manner as above. This workload was chosen because it allowed all subjects to maintain steady state for at least 15 min. To obtain the maximal exercise \dot{Q}_c measurement, the subject continued to exercise at the end of the submaximal bout while the workload was increased by 20 W/min until maximal effort was achieved. \dot{Q}_c was collected once during maximal exercise.

Statistical Analysis

Each investigative team acquired analog representations of gas concentrations for subsequent digital analysis with their own unique software. The derived values for \dot{Q}_c were then consolidated and analyzed with a condition \times technique analysis of variance. When significant main effects were observed, comparisons between the criterion techniques (direct Fick and thermodilution) and the rebreathing methods were assessed using Tukey's honestly significant difference. Bartlett's test with post hoc analysis was used to determine whether significant differences in variance existed (47). Average fractional deviations were calculated to determine whether gas rebreathing techniques fell within an a priori determined acceptable margin of accuracy (10%) compared with our criterion methods. In all cases, differences with $P < 0.05$ were considered significant.

RESULTS

Of the 182 \dot{Q}_c determinations for each method, 91% of direct Fick data were appropriate for analysis; that is, they did not fall outside of three standard deviations from the mean or were not missing data points. Similarly, 96% were used for thermodilution, 94–96% for C_2H_2 and N_2O rebreathing, and 71% for CO_2 rebreathing.

An identity plot is shown in Fig. 1 for direct Fick vs. thermodilution. The slope of this relationship was not significantly different from the line of identity. Bland-Altman analysis (Fig. 2) revealed no systematic differences between the two techniques.

Table 1 and Fig. 3 portray the means compared in the analysis of variance (standing, supine, submaximal exercise, and maximal exercise). Significant differences were observed between all techniques (criterion and rebreathing; $P < 0.05$). In particular, the single-step CO_2 rebreathing method was generally greater than the other rebreathing techniques. All foreign gas techniques (C_2H_2 and N_2O) had a propensity to underestimate \dot{Q}_c during submaximal and maximal exercise, compared with direct Fick and thermodilution ($P < 0.05$). Single-step CO_2 rebreathing was not different from thermodilution during exercise, while all C_2H_2 and N_2O techniques were different from both criterion techniques. During submaximal exercise, direct Fick and thermodilution were significantly different.

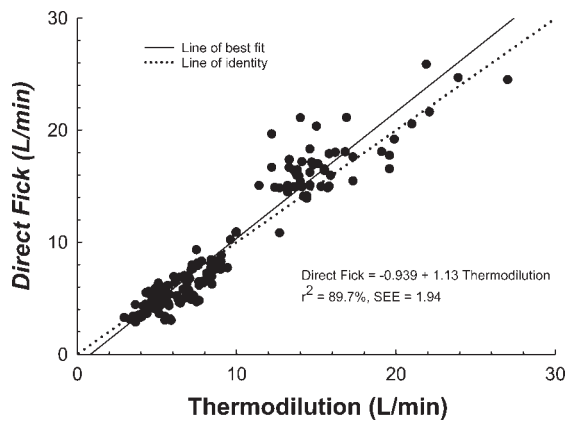


Fig. 1. Identity plot of direct Fick vs. thermodilution. The dashed line represents the line of identity and the solid line represents the line of best fit by linear least squares regression. The slope of the line of best fit for direct Fick vs. thermodilution was not statistically different from the slope of the line of identity (slope = 1).

Table 1 provides additional results where the within-method variability of each technique was compared. Bartlett's test indicated variance heterogeneity among the techniques ($P < 0.05$). Further inspection showed larger variance with the single-step CO_2 rebreathing method, which is shown in Table 1 and Fig. 4. In general, during rest, the foreign gas rebreathing techniques had lower variance than did direct Fick (Table 1); however, this difference did not exist during exercise.

Figures 5 and 6 illustrate the average fractional deviations, by method, from the criterion techniques. Resting conditions provide the most reasonable estimates of noninvasive cardiac output measurement, with most techniques (3 of 7 during supine rest and 6 of 7 during standing) falling within 10% of our criterion values for direct Fick. Similarly, 6 of 7 of the techniques during supine rest fell within 10% of criterion means and 6 of 7 during standing rest for thermodilution. During submaximal and maximal exercise conditions, however, all rebreathing techniques fell above or below the $\pm 10\%$ range, with the exception of single-step CO_2 rebreathing.

DISCUSSION

The present study was designed to compare eight techniques of \dot{Q}_c measurement in humans during different resting (supine

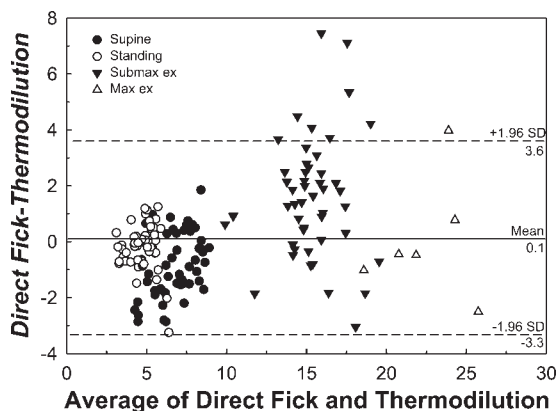


Fig. 2. Bland-Altman plot for direct Fick and thermodilution. These criterion methods show agreement during resting conditions, but tended to differ during submaximal exercise.

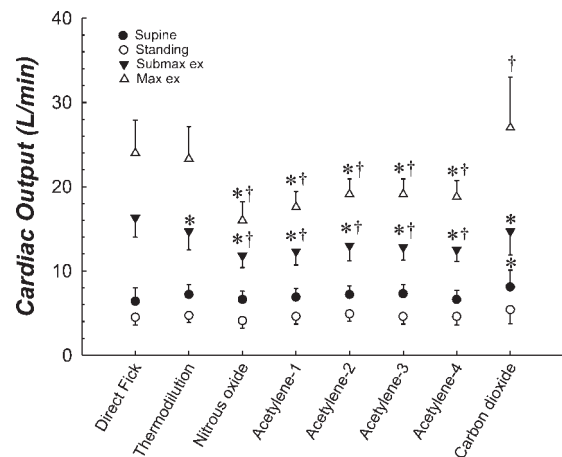


Fig. 3. Cardiac output during each condition, by method. ANOVA indicated that the interaction between condition and method was significant ($P < 0.05$). C_2H_2 and N_2O tend to underestimate cardiac output, while single-step CO_2 rebreathing tends to overestimate cardiac output compared with the criterion methods. This difference is especially clear during maximal exercise. *Different from direct Fick, $P < 0.05$; †different from thermodilution, $P < 0.05$.

and standing) and exercise (submaximal and maximal) conditions. Direct Fick and thermodilution served as criterion techniques, where foreign and physiological soluble gas rebreathing techniques were systematically compared with our criterion methods.

Direct Fick vs. Thermodilution

Our data agree with the established values in the literature relative to oxygen consumption (see Table 1) for a given condition (rest or exercise; Refs. 1, 12, 18). We found that direct Fick and thermodilution were not statistically different during rest (standing or supine) or maximal exercise. However, we found that during submaximal exercise, direct Fick was statistically higher than thermodilution. Complete consensus does not exist among investigations that have examined the relationship between direct Fick and thermodilution. Some have reported agreement (15), while some investigations (13, 43) reported that thermodilution overestimates \dot{Q}_c compared with direct Fick and others reported that thermodilution underestimates \dot{Q}_c (11).

It has been suggested that thermodilution measurements may provide inaccurate estimates because this method relies on heat as a marker. During injection of a cold indicator, not all heat transfer can be accounted for; potential sources of error include heat gain during handling of the injectate (36), heat transfer through the vessel wall, or heat exchange with the air in the lungs (24). It is also possible that the development of tricuspid regurgitation during exercise (4) could compromise the measurement of \dot{Q}_c by thermodilution (8). It is most likely, however, that the differences seen during submaximal exercise in our study, for several reasons, are best explained by measurement error in the variables used to calculate direct Fick. Direct Fick presumes that steady-state conditions are maintained throughout the determinations, an assumption that is violated as exercise intensity increases (44). Additionally, although oxygen uptake during rest and exercise was consistent within each condition (refer to Table 1), erroneous measurements in oxygen content of arterial or mixed venous blood could affect

Table 1. Comparison of cardiac output determined with criterion and soluble gas rebreathing methods

Method	Condition							
	Standing Rest				Supine Rest			
	Mean, l/min	SD	Bartlett's Test	$\dot{V}O_2$, l/min	Mean, l/min	SD	Bartlett's Test	$\dot{V}O_2$, l/min
Direct Fick	4.5	0.9	‡	0.47±0.06	6.4	1.6		0.44±0.06
Thermodilution	4.7	0.8	‡		7.2	1.2	‡	
N ₂ O	4.1	0.9	‡		6.9	1.0	*‡	
C ₂ H ₂ -1	4.6	0.9	‡		6.9	1.0	*‡	
C ₂ H ₂ -2	4.9	0.9	‡		7.2	1.0	*‡	
C ₂ H ₂ -3	4.6	0.9	‡		7.3	1.1	‡	
C ₂ H ₂ -4	4.6	1.0	‡		6.6	1.1	‡	
CO ₂	5.4	1.7			8.1*	2.0		

Method	Condition							
	Submaximal Exercise				Maximal Exercise			
	Mean, l/min	SD	Bartlett's Test	$\dot{V}O_2$, l/min	Mean, l/min	SD	Bartlett's Test	$\dot{V}O_2$, l/min
Direct Fick	16.0	2.3		1.75±0.16	24.0	3.9		3.49±0.43
Thermodilution	14.7*	2.2			23.3	3.8		
N ₂ O	11.8*†	1.4	*†‡		16.0*†	2.2		
C ₂ H ₂ -1	12.2*†	1.7	‡		17.6*†	1.8		
C ₂ H ₂ -2	13.0*†	1.8	‡		19.1*†	1.8	‡	
C ₂ H ₂ -3	12.8*†	1.5	*‡		19.1*†	2.3		
C ₂ H ₂ -4	12.5*†	1.4	*†‡		18.8*†	1.9		
CO ₂	14.7*	2.8			27.0†	6.0		

*Different from direct Fick, $P < 0.05$; †different from thermodilution, $P < 0.05$; ‡different from CO₂ rebreathing, $P < 0.05$.

\dot{Q}_c when using the direct Fick method (11). These errors generally are magnified when the $a\text{-}\bar{v}O_2$ difference is small, since the error in measurement of oxyhemoglobin saturation has the potential to be a large part of the $a\text{-}\bar{v}O_2$ difference. It should also be noted that we used pulse oximetry to measure arterial oxygen saturation in this study to avoid the requirement for arterial catheterization.

We acknowledge the potential error introduced by estimating arterial oxygen content from pulse oximetry. However, previous investigators have evaluated the accuracy of the Ohmeda 3700 pulse oximeter and have concluded it provides reasonable estimates of arterial oxygen saturation. Powers et al. (33) examined its usefulness during graded exercise on a cycle

ergometer, finding that the Ohmeda 3700 was accurate during exercise in nonsmoking individuals. Additionally, Kagle et al. (19) exposed a group of healthy volunteers to steady-state hypoxic and rapidly declining hypoxic conditions, noting that the Ohmeda 3700 ear probe was accurate throughout an arterial oxygen saturation range of 90–100%. At rest and during submaximal exercise, any differences between pulse oximetry and “true” arterial saturation were likely to be small, although more significant differences could be present at higher levels of exercise (46). Moreover, if pulse oximetry data were inaccurate, the direct Fick \dot{Q}_c would be expected to be biased high, yet thermodilution and direct Fick were in agreement in all conditions except for submaximal exercise. Additionally, no

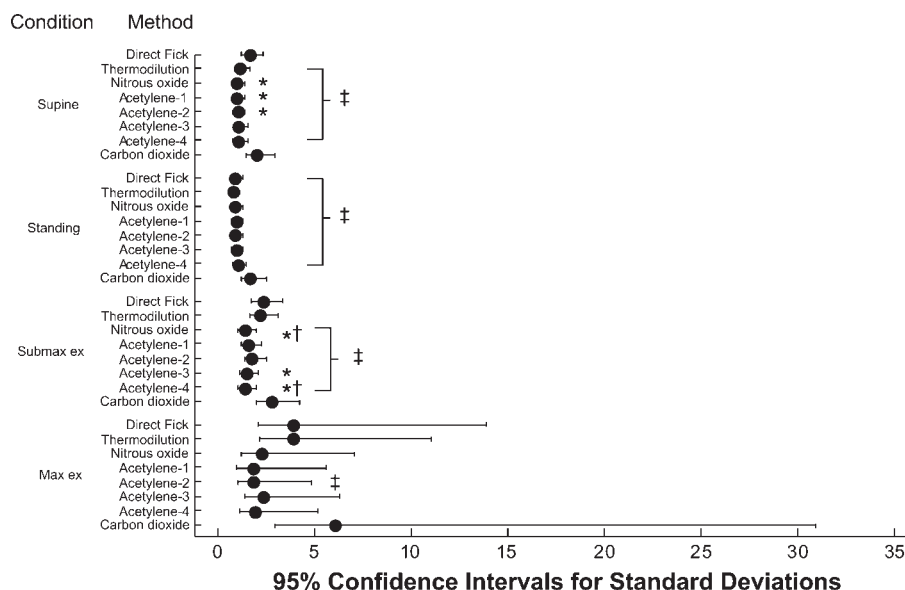


Fig. 4. 95% Confidence intervals for the standard deviations of each technique. Resting conditions provided the smallest variability in all methods. Single-step CO₂ rebreathing showed the largest variability and, in most cases, foreign gas rebreathing had lower variance than did direct Fick. Refer to Table 1 for values. *Different from direct Fick, $P < 0.05$; †different from thermodilution, $P < 0.05$; ‡different from CO₂ rebreathing, $P < 0.05$.

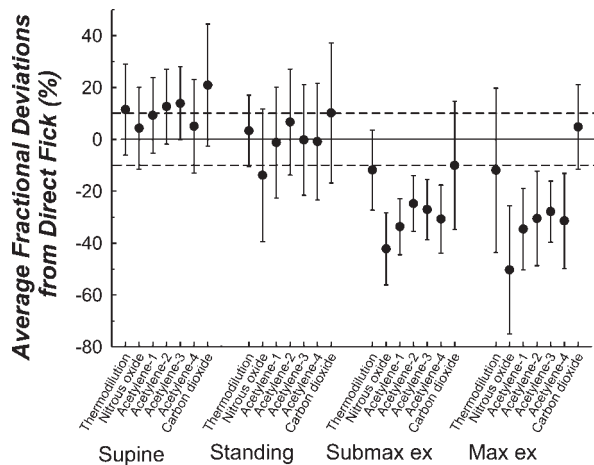


Fig. 5. Average fractional deviations from direct Fick. Resting conditions provided the most reasonable estimates of noninvasive cardiac output (\dot{Q}_c) measurement, with most techniques falling within $\pm 10\%$ of the direct Fick values. During both exercise conditions there was less agreement between gas rebreathing and direct Fick, with the exception of single-step CO_2 rebreathing, which fell within the defined as acceptable range.

subject was an endurance athlete, limiting the likelihood that true changes in arterial saturation would occur. Thus, on the basis of the analysis of the literature and our own methodology, the criterion \dot{Q}_c data are accurate.

C_2H_2 and N_2O Rebreathing vs. Criterion Techniques

The results of C_2H_2 and N_2O rebreathing were not statistically different from the criterion techniques during rest. Although previous studies support our findings (15, 16, 23), there is disagreement among the current literature, as others have claimed that foreign gas rebreathing is less accurate at rest (44). N_2O and C_2H_2 rebreathing are widely used techniques because they are reliable, less expensive than the criterion techniques, and are easy to employ (44). Reported discomforts are transient and include dizziness from hyperventilation, dyspnea from buildup of CO_2 (17), unpleasant taste from the gas mixture (26), and headache. Some have argued that C_2H_2 rebreathing is superior to N_2O because N_2O uptake may be influenced more than C_2H_2 rebreathing by factors such as blood lipid concentration (44). However, we did not find N_2O rebreathing to be different from our criterion methods and others have also reported agreement by comparing N_2O rebreathing against other gas rebreathing or dye dilution techniques (2, 48, 49). Finally, and most importantly, we did not find any evidence that the implementation of any method introduced systematic differences in these independently developed \dot{Q}_c estimates, suggesting that interlaboratory comparisons of \dot{Q}_c estimations are largely valid.

During exercise, however, we found that \dot{Q}_c as measured by C_2H_2 and N_2O rebreathing was significantly lower than both criterion methods. This is in contrast to Liu et al. (23) who reported agreement between C_2H_2 and direct Fick from resting conditions up through maximal exercise. The time requirement needed to determine \dot{Q}_c during rebreathing is an unavoidable limitation. It has been suggested that the higher velocity of blood flow during exercise shortens the recirculation time of the rebreathing gas mixture, which may underestimate \dot{Q}_c by as much as 10–20% (6, 7, 40). Thus the available sampling time

is inversely related to exercise intensity. Results from previous investigations have recommended that during maximal exercise, rebreathing measurements be made within 8 s to avoid recirculation of the rebreathing mixture (40, 49). We were unable to shorten our rebreathing time from 25 s because we needed to accommodate the requirements of the single-step CO_2 method. Additionally, we kept the breathing rate low (22 breaths/min) to minimize the increase in \dot{Q}_c associated with hyperpnea (42). This limited the number of breaths before recirculation could occur and, on average, we were able to obtain three to five data points for regression that contained breaths with adequate gas mixing. Thus the first and most plausible explanation for the underestimation we observed with C_2H_2 and N_2O rebreathing was because of recirculation of the rebreathing mixture. Limiting the analysis to the first few breaths after complete mixing has been achieved may help reduce the underestimation of the foreign gas rebreathing methods during exercise.

Second, we cannot exclude the possibility that the use of pulse oximetry to estimate arterial oxygen content introduced error. These differences should be small but a slight underestimation in oxygen saturation would lead to an overestimation in the criterion \dot{Q}_c for direct Fick. Special care was taken to follow exact procedures to ensure we obtained valid pulse oximetry data. The ear probe line was secured, head motion was kept to a minimum, and a real-time pulse oximetry tracing was monitored for any motion.

Last, it should be mentioned that gas rebreathing techniques estimate pulmonary blood flow, rather than left heart output (21). In healthy individuals without pulmonary shunts the difference between pulmonary blood flow and left heart output at rest is $<3\%$ (42).

Single-Step CO_2 Rebreathing vs. Criterion Techniques

These data have been presented in part elsewhere (28, 29). Not surprisingly, the current literature includes many relationships between CO_2 rebreathing and criterion methods similar to ours. In contrast to our findings, other investigators have

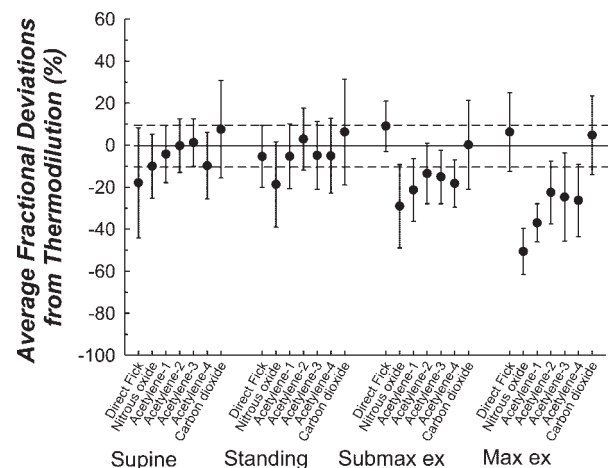


Fig. 6. Average fractional deviations from thermodilution. Resting conditions provided the most reasonable estimates of noninvasive \dot{Q}_c measurement, with most techniques falling within $\pm 10\%$ of the thermodilution values. During both exercise conditions there was less agreement between gas rebreathing and thermodilution, with the exception of single-step CO_2 rebreathing, which fell within the defined as acceptable range.

reported that CO₂ rebreathing underestimates \dot{Q}_c compared with direct Fick and thermodilution (9, 13, 25). We found that the modified single-step CO₂ rebreathing method yielded higher results than the criterion techniques, except during submaximal exercise. The most plausible explanation for this overestimation appears to stem from inaccuracies in calculating end-capillary CO₂ from end-tidal CO₂. A fitted dissociation curve was applied to each value of P_{ACO₂} during expiration (or the linear interpolation between expiration and the next alveolar plateau) and averaged to obtain C_cCO₂. The assumption that end-tidal CO₂ accurately depicts end-capillary CO₂ may introduce small errors, even in normal subjects (14).

During submaximal exercise, our data showed no significant differences between the single-step CO₂ rebreathing method and thermodilution; during maximal exercise, the single-step CO₂ method differed from thermodilution but not direct Fick. Previous studies support this finding and have indicated that during submaximal exercise the relationship between CO₂ rebreathing and other methods was better than that observed at rest (35, 45). That conclusion should be interpreted with caution, however, since the single-step CO₂ rebreathing method demonstrated the largest variability across all conditions.

Heterogeneity of Variance Between Methods

The intratechnique variance associated with CO₂ rebreathing was statistically higher than all methods during standing rest, all but direct Fick during supine rest, and all other gas rebreathing techniques during submaximal and maximal exercise. Direct Fick had the next largest variance, showing significantly larger variances, compared with C₂H₂ and N₂O rebreathing, during supine rest and submaximal exercise. Similarly, we found that during submaximal exercise, thermodilution had higher variance than C₂H₂ and N₂O rebreathing. The standard deviations calculated from our direct Fick and thermodilution data compare favorably with past investigations (7, 13, 27, 41). Thus our data suggest a distinct advantage of foreign gas rebreathing techniques over CO₂ rebreathing; since the variance of CO₂ rebreathing was approximately double that of foreign gas rebreathing, approximately four times more trials would be needed to develop a statistically reliable estimate of \dot{Q}_c .

In conclusion, we found that rebreathing techniques to determine \dot{Q}_c provide similar results in healthy volunteers; however, there are limitations that should be kept in mind. Soluble gas rebreathing, as implemented, provided accurate data at rest, whether standing or supine. Although there were slight differences in how each of the C₂H₂ cardiac outputs were computed, these values differed little from one another, leading us to conclude that variations in the way these techniques have been implemented has little impact in determining \dot{Q}_c . This finding may be particularly important when \dot{Q}_c comparisons are made in multi-site or collaborative studies. Single-step CO₂ rebreathing was accurate over a wider range (i.e., during exercise), but suffered from lesser precision. Based on these data, we suggest that foreign gas rebreathing can provide reasonable \dot{Q}_c estimates (within 10% of criterion) with relatively fewer repeat trials during resting conditions. During submaximal and maximal exercise these methods remain precise but tend to underestimate \dot{Q}_c . Single-step CO₂ rebreathing may be successfully employed over a wider range (i.e., ap-

proaching maximal exercise) but with more measurements needed to overcome variability with the method.

ACKNOWLEDGMENTS

We acknowledge the following people for their outstanding technical assistance: Paul DeFrain, Robyn Etzel, Janelle Fine, Kevin Harper, Susie McMinn, Boyce Moon, Willie Moore, and Julie Zuckerman. We also appreciate the advice and support of Charles Sawin at the NASA Johnson Space Center.

GRANTS

Supported by contract #NAS9-18440, NASA (to J. A. Pawelczyk).

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