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F. Prieur · T. Busso · J. Castells · R. Bonnefoy
H. Benoit · A. Geyssant · C. Denis

A system to simulate gas exchange in humans to control quality of metabolic measurements

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Abstract We have developed a gas exchange simulation system (GESS) to assess the quality control in measurements of metabolic gas exchange. The GESS simulates human breathing from rest to maximal exercise. It approximates breath-by-breath waveforms, ventilatory output, gas concentrations, temperature and humidity during inspiration and expiration. A programmable motion control driving two syringes allows the ventilation to be set at any tidal volume (V_T), respiratory frequency (*f*), flow waveform and period of inspiration and expiration. The GESS was tested at various combinations of V_T (0.5–2.5 l) and *f* (10–60 stroke · min^{-1}) and at various fractional concentrations of expired oxygen (0.1294–0.1795); and carbon dioxide (0.0210–0.0690) for a pre-set flow waveform and for expired gases at the same temperature and humidity as room air. Expired gases were collected in a polyethylene bag for measurement of volume and gas concentrations. Accuracy was assessed by calculating the absolute and relative errors on parameters (error = measured−predicted). The overall error in the gas exchange values averaged less than 2% for oxygen uptake and carbon dioxide output, which is within the accuracy of the Douglas bag method.

Key words Human breathing simulation · Oxygen uptake validity · Metabolic measurement

F. Prieur · T. Busso · J. Castells · R. Bonnefoy ·
H. Benoit · A. Geyssant · C. Denis
Laboratoire de Physiologie-Groupement d'Interêt
Public Exercice, Faculté de Médecine
Saint-Etienne, 15 rue Ambroise Paré,
F-42023 Saint-Etienne Cedex 2, France

F. Prieur (✉)
Centre Hospitalier Universitaire de Saint-Etienne,
Pavillon 12 Hôpital de St Jean Bonnefonds,
F-42055 Saint-Etienne Cedex 2, France

Introduction

Metabolic function is commonly assessed during exercise in physiological research and clinical investigation. Accurate measurements of ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) are needed. The complexity and diversity of methods employed for these measurements may lead to inaccuracies due to errors in the measurement of volume or flow, calibration of analysers (errors or too infrequent calibration), humidity and temperature of expired gas, linearity and response times of analysers and leaks in the respiratory circuit. These errors may contribute to explaining the differing results which have been obtained by different laboratories, or measurement systems (Jones and Kane 1979).

Each component of a measuring system can be tested separately using calibration gases, a calibration syringe or pump and it has been shown that the performance of the whole system can be evaluated during human exercise against a reference method (Wasserman et al. 1994). Measurements can be made using the reference and the system to be tested simultaneously or sequentially. Simultaneous measurements are the most reliable for quality control assessment. When simultaneous measurements are not possible (depending on the methods to which the systems are referred), sequential measurements should be used. Sequential measurements require the assumption of a true steady state, and this assumption can be a source of error. The inherent variability of metabolism even during a steady state can prevent an accurate comparison, and the lack of a steady state above the anaerobic threshold has been shown to preclude evaluation of any system at a high intensity of exercise (Whipp and Wasserman 1972).

The conventional Douglas bag method has been employed as a reference system and has allowed comparison of $\dot{V}O_2$ calculated from an expiratory gas sample taken for at least 15–30 s (Versteeg and Kippersluis 1989). However, it has been reported that the conventional

Douglas bag method may not be a reliable reference method at high oxygen concentrations (Welch and Pedersen 1981) as this method overestimates $\dot{V}O_2$ in hyperoxia. This error occurs because the gas in the bag is contaminated with a small volume of ambient air.

A practical reference system could involve replacing the human subject by a mechanical system which can simulate a metabolic rate, a method which several authors have developed. Boutellier et al. (1981) have described a system with a double-piston pump allowing the simulation of respiration at low ventilations. Foster and Norton (1983) and Huszczuk et al (1990). have each developed methods with a pumping system providing high ventilations at a pre-set metabolic level. Recently, Gore et al. (1997) have improved the device of Huszczuk et al. (1990) with a calibrator that simulates very high metabolic rates. The device described by Huszczuk et al. (1990) and Gore et al. (1997) allows a metabolic rate to be pre-set independently of the $\dot{V}_E$. However, these systems have not reproduced the temperature and water vapour pressure of expired gases in humans. Because these factors could contribute to measurement inaccuracy, we have developed a simple device that provides a pre-set metabolic rate with expired gases warmed and fully saturated with water vapour. Inspired and expired gas mixtures are separated to obtain inspired gases at room temperature and expired wet gases at a temperature of approximately 30°C. The system is computerized to set ventilatory parameters at each respiratory cycle (tidal volume, V_T breathing frequency, f, lengths of inspiratory and expiratory phases).

This study was carried out to check this gas exchange simulation system (GESS) under normal use and with expired gases at ambient temperature and humidity. The coherence of the breath-by-breath waveforms was checked as was the system for leaks. The dead-space volume was evaluated. The accuracy of the simulated gas exchange parameters was then assessed for overall and physiological data. Lastly, the advantages and disadvantages of GESS over other simulation systems were examined.

Methods

System

The GESS is shown in Fig. 1. A programmable motion control (Warner Electric, SLO-SYN SS20001) (*a*) drives two rigidly coupled 3-1 syringes (Hans Rudolph, series 5530, *b*, *c*). The motion control is programmed with specific software (Warner Electric, MS2000 Development Software). The V_T and f are set by programming the pump amplitude, speed and displacement acceleration. A pneumatic directional control valve (Hans Rudolph, three-way sliding-type valve, series 8600, *d*) is reset at each transition between inspiration and expiration. This directional valve is driven by an automated controller (Hans Rudolph, series 4285B, *e*). The three valves (Hans Rudolph, two-way non-rebreathing valve, series 2730, (*f*, *g*, *h*) do not open until a critical pressure is reached. The system is connected to two polyethylene bags (2000 l, *i*, *j*) filled with appropriate gas mixtures. Gas mixture I simulates inspiratory gas and E simulates expiratory gas. During inspiration,

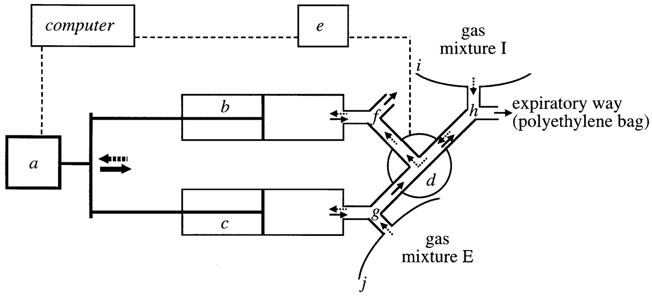

Fig. 1 Diagram of gas exchange simulation system. *Dotted arrows* gas flow during inspiration *solid arrows* gas flow during expiration. *a* motion control, *b c* 3-1 syringes, *d* pneumatic directional control valve, *e* automated controller for directional valve, *f g h*, two-way non-rebreathing valves, *i j* polyethylene bags (2000 1)

syringe *b* is filled with gas mixture I through valve *h*. At the same time, syringe *c* is filled directly with gas mixture E. During expiration, syringe *b* is emptied directly into the room, while syringe *c* sends gas mixture E through valve *h*.

Experiment procedure

The conventional Douglas bag method was used to determine the volume of the system dead space, the volume of ambient air in the Douglas bag and the accuracy of GESS at various metabolic levels. The GESS was tested at five values of V_T (0.5, 1, 1.5, 2, 2.5 1) and six values of f (10, 20, 30, 40, 50 and 60 strokes · min^{-1}). Therefore, GESS worked at 30 different combinations of V_T and f corresponding to $\dot{V}_E$ from 5 to 150 l · min^{-1}. These 30 combinations were repeated six times using six different fractional concentrations of oxygen and carbon dioxide FO_2, FCO_2, respectively; gas mixture E mixture 1: $F_{O_2} = 0.1294$, $F_{CO_2} = 0.0210$; mixture 2: $F_{O_2} = 0.1401$, $F_{CO_2} = 0.0293$; mixture 3: $F_{O_2} = 0.1502$, $F_{CO_2} = 0.0385$; mixture 4: $F_{O_2} = 0.1589$, $FCO_2 = 0.0502$; mixture 5: $F_{O_2} = 0.1704$, $F_{CO_2} = 0.0594$; mixture 6: $F_{O_2} = 0.1795$, $F_{CO_2} = 0.0690$). For each GESS simulation, gas mixture I was room air and gas mixture E was at the same temperature and humidity as room air.

There were 30 series of six GESS simulations made using six combinations of V_T and f and the same gas mixture E. Expired gases were collected in a polyethylene bag through the expiratory way of valve *h* and during the time required to collect a theoretical volume of 60 l. This collecting time (24 s–12 min) was dependent on V_T and f (i.e. $\dot{V}_E$). The order of combinations was chosen to obtain an increase in $\dot{V}_E$. The volume of gas collected in the bag was measured in a Tissot spirometer (200 l) after the work of GESS at six different combinations. The F_{O2} was measured with a paramagnetic O_2 analyser (Servomex, cell 1155B) and FCO_2 with an infrared CO_2 analyser (Normocap Datex). Analysers were calibrated for each series of six GESS simulations with two calibration gases, whose compositions were determined by the method of Scholander (1947) (gas 1: $F_{O2} = 0.2188$, $F_{CO2} = 0.00$; gas 2: $F_{O2} = 0.0013$, $F_{CO2} = 0.0500$). The fractions of O_2 and CO_2 in bag *i* and *j* were measured after each analyser calibration procedure to check that no gas mixture E had flowed into bag *i* and that no gas mixture I had flowed into bag *j* due to overpressure and backflow in corresponding valves *h* and *g*.

The GESS can provide expired gases warmed and saturated with water vapour. This feature requires GESS and the bag *j* to be in a room kept at 30°C while bag *i* is at ambient temperature. The gas mixture E in bag *j* is prepared in the warmed room and water vapour produced with an autoclave is introduced into the bag. Thus the expiratory bag and the GESS are kept at 30°C throughout the working period. In this condition expired gases are at 30°C and fully saturated with water vapor while inspired gases are at ambient temperature.

We did not test these temperature and water vapour features in the present study. Validation of GESS consisted principally of determining the accuracy of ventilatory output and mean expired gas fractions. The $\dot{V}_E$ was dependent on V_T and f; mean fractional concentrations in expired gas of oxygen (F_EO_2 and carbon dioxide (F_ECO_2) were dependent on the dead space and the volume of contaminating ambient air; temperature and humidity (kept stable) have no direct influence on these parameters (when the conventional volume conversions are made for the calculation and when gas fractions are measured on dried gases).

Effect of the contaminating volume on gas exchange variables

The volume of gas mixture E collected in the Douglas bag was contaminated by a small volume of gas mixture I at each expiration. This contamination is due to a volume (v) of "pollution" (p) that occurs at each cycle (c) of V_T (ie V_{pc}) and is composed of the valve h (housing and mouth port tube) and the exhalation port tube of the directional valve d. The volume (V_{p_c}) was estimated to be 125 ml from the physical characteristics of the valves. Contamination with dead-space gas happened at each respiratory cycle and its influence on the gas fraction collected in the bag depended on the number of respiratory cycles (n) and V_T. Contamination also occurred when the polyethylene Douglas bag (D) was used to collect expired gases, due to the volume of the exhalation port tube of the valve h, the volume of the rigid collar of the bag and the incomplete removal of gas from the bag before its connection to the expiratory way. Hence, this volume of contamination due to the Douglas bag (V_{pD}) happened once during the sampling time.

If $V_{P_{tot}}$ is the total volume of contamination:

$$V_{P_{tot}} = n \cdot V_{P_c} + V_{P_D} \quad (1)$$

and the F_EO_2 measured in the polyethylene bag depends on V_{Ptot}:

$$\bar{F}_EO_2 = [(F_{BIO_2} \cdot V_{p_{tot}} + (F_{BEO_2}) \cdot (V_{tot} - V_{P_{tot}})]/V_{P_{tot}} \quad (2)$$

where V_{tot} is the total volume of expired gas collected in the Douglas bag and measured in the Tissot spirometer, $F_{BI}O_2$ is the O_2 fraction of gas mixture I, and $F_{BE}O_2$ is the O_2 fraction of gas mixture E.

From Eq. 2 $V_{P_{tot}}$ was calculated for each combination as:

$$V_{P_{tot}} = V_{tot} \cdot (\bar{F}_EO_2 - F_{BEO2})/(F_{BI}O_2 - F_{BE}O_2) \quad (3)$$

The regression line between V_{tot} and n was then drawn. As shown in Eq. 1 V_{P_c} and V_{P_D} were the slope and the intercept of this line, respectively.

Statistics

Analysis of variance with one factor (time of gas fraction measurement) was employed to test the contamination of gas mixtures I and E. The predicted value of $\dot{V}_E$ was calculated with the settings of V_T and f. The $V_{P_{tot}}$ was estimated and the predicted value of $\bar{F}_EO_2$ was calculated using Eq. 2 (the predicted value of $\bar{F}_ECO_2$ was calculated using Eq. 2 for CO_2). The predicted value of $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated using the predicted values of $\dot{V}_E$, $\bar{F}_EO_2$ and $\bar{F}_ECO_2$ and using the equations: $\dot{V}O_2 = \dot{V}_E \cdot [((1 - \bar{F}_EO_2 - F_ECO_2)/(1 - F_IO_2 - F_ICO_2)) \cdot F_IO_2 - \bar{F}_EO_2]$ and $\dot{V}CO_2 = \dot{V}_E \cdot [\bar{F}_ECO_2 - F_ICO_2 \cdot (1 - \bar{F}_EO_2 - \bar{F}_ECO_2/(1 - F_IO_2 - F_ICO_2)$ where F_IO_2, F_ICO_2 are the fractional concentrations of oxygen and carbon dioxide in inspired air, respectively]. The errors on parameters between the measured and predicted values were calculated as the difference (measured – predicted), which is the absolute error. This error was expressed as a percentage of the measured value and calculated as [100 · (measured −predicted)/measured], which is the relative error, because a wide range of $\dot{V}_E$, $\dot{V}O_2$ and $\dot{V}CO_2$ were tested. The error on parameters and 0 were compared using Student's t-test on one group to determine any bias in the prediction of variables produced by GESS. Average values were considered significantly different at $P < 0.05$. The coefficient of variation of $\dot{V}_E$ was calculated over the six GESS simulations at each combination of V_T and f. The average coefficient of variation of $\dot{V}_E$ was then calculated.

Results and discussion

Breath-by-breath waveforms

The use of a programmable motion control to drive the syringes which change the volumes allows the simulation of human breathing during exercise. The periods and flow waveforms for inspiration and expiration were set by programming the speed and acceleration of the motion control. Figure 2 shows examples of breath-by-breath waveforms delivered by GESS. Acceleration and deceleration settings of the motion control were varied to show the different resulting flow waveforms. There was a delay between the inspiratory and expiratory flow due to the time required to change the directional valve d. The gas concentration waveforms were somewhat different from human patterns. The slope at the beginning of the expiration was steeper in GESS. There was a plateau is our GESS model, whereas the continuous alveolar gas exchange that occurs in human breathing causes a slight incline in the CO_2 plateau and a slight decline in the O_2 plateau.

Airtightness of the system

Valves g and h did not open until a critical pressure was reached, but we were concerned about gas flowing into bags j and i, especially at high $\dot{V}_E$. Too high a pressure in valves h and g could occur, making gas flow into bags i and j. The contamination of gas mixtures I and E was tested by measuring the gas fractions in each bag at regular intervals. The was no significant effect of time on the measured gas fraction of inspiratory and expiratory gas mixtures. Gas mixtures remained stable during the run of GESS, showing that the system was airtight.

Volume and ventilatory output

The accuracy of the expired gas volume produced by the system was assessed with a Tissot spirometer. The GESS worked at various $\dot{V}_E$ over the time required to collect the expected gas volume of 60 l. The average volume measured was 59.62 (SD 0.89) l, which was significantly different from the expected volume ($P < 0.001$), showing a slight bias on the volume produced. Part of the variability could have been due to the accuracy of the Tissot spirometer (about ± 1%) and part to the accuracy of the syringe (±0.2%). Table 1 shows the absolute and relative error on $\dot{V}_E$. The relative error was significantly lower than 0, showing that $\dot{V}_E$ was overestimated by 0.53 (SD 1.51)%. The reproducibility of $\dot{V}_E$, assessed

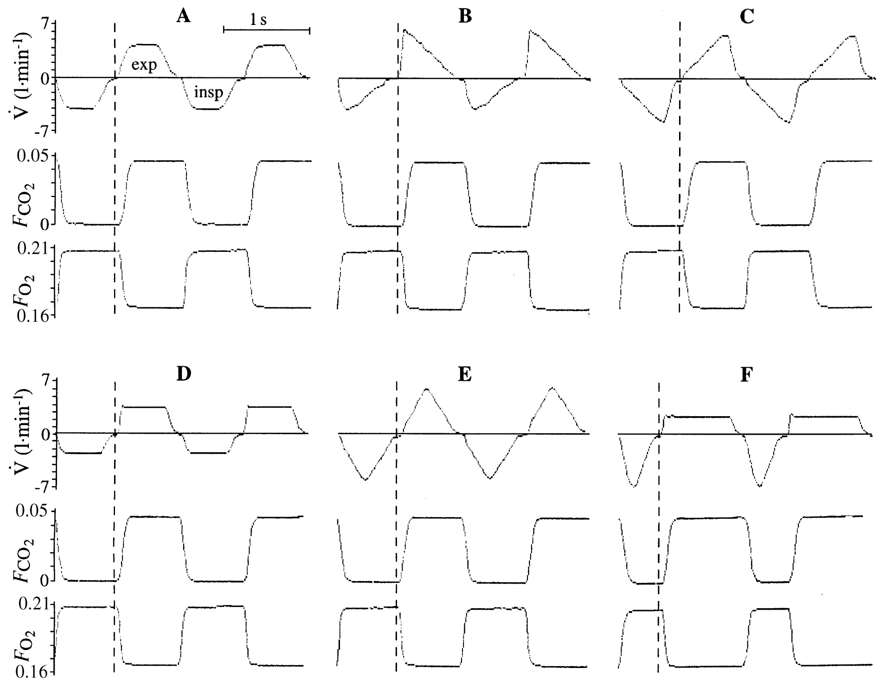

Fig. 2 Example of breath-by-breath waveforms delivered by gas exchange simulation system (GESS) and measured with an exercise testing system (MedGraphics, CPX/D system). The GESS worked at frequency = 40 stroke · min^{-1} and tidal volume = 2 l. *Panels A* shows the flow waveform used in the validation study. Dotted lines identify the start of the first expiratony phase at each panel. $\dot{V}$ Flow, F_{O2} fraction, F_{CO2} fraction, *exp* expiratory phase, *insp* inspiratory phase, CO_2 vertical dotted line?

by calculating the average coefficient of variation, was 0.99 (SD 0.54)%, showing that the $\dot{V}_E$ provided by GESS was reproducible.

Contamination volumes

The regression line between $V_{P_{tot}}$ and n (number of respiratory cycles) was given by the equation: $V_{P_{tot}}$ (ml) $= 129 \cdot n + 644$, with $r = 0.99$; the 95% confidence interval for the slope was 127–131 ml. The slope of this line gave V_{P_c} (129 ml) because dead-space gas modified the expired gas fractions at each expiration. This was close to the 125-ml volume corresponding to the physical characteristics of the valves. The intercept gave an estimation of the mean contaminating volume of the collection system ($V_{P_D} = 644$ ml), and the 95% confidence interval for the intercept was 508–780 ml. The V_{P_D} was composed of the exhalation port tube volume of the valve *h*, the volume of the rigid collar of the bag and the incomplete removal of gas in the bag. The physical value of the exhalation port tube volume was about 60 ml; for the rigid collar of the bag it was about 180 ml. The physical value for the volume corresponding to the incomplete removal of gas in the bag is difficult to establish. Although the estimated volume of about 400 ml [i.e. 644 – (60 + 180)] seems large, it was obvious that a volume of gas still remained in the bag during the flushing procedure in the Tissot spirometer.

Fractional concentration of expired gas

The predicted values of $\bar{F}_EO_2$ and $\bar{F}_ECO_2$ were calculated using V_{P_c} and V_{P_D} as described above (129 and 644 ml, respectively). Table 1 shows the error on $\bar{F}_EO_2$ and $\bar{F}_ECO_2$. The errors on the two gases were significantly different from 0 showing that $\bar{F}_EO_2$ was underestimated by 0.0001 (SD 0.0004), and that $\bar{F}_ECO_2$ was overestimated by 0.0004 (SD 0.0005). The variability of the

Table 1 Absolute and relative errors on variables produced by the gas exchange simulation system. $\bar{F}_EO_2$ Mean expired O_2 fraction, $\bar{F}_ECO_2$ mean expired CO_2 fraction, $\dot{V}_E$ ventilation (ambient temperature and pressure, saturated), $\dot{V}O_2$ O_2 uptake, $\dot{V}CO_2$ CO_2 output. Errors were computed as: (measured value – predicted value). *n* was 179 for $\dot{V}_E$ and 178 for $\bar{F}_EO_2$, $\bar{F}_ECO_2$, $\dot{V}O_2$ and $\dot{V}CO_2$

		$\bar{F}_EO_2$	$\bar{F}_ECO_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$
				ml · min^{-1}		
Absolute error	Mean	0.0001***	0.0004***	−50	−6*	−15***
	SD	0.0004	0.0005	709	36	31
				%		
Relative error	Mean	–	–	−0.53***	−0.56***	−1.48***
	SD			1.51	1.73	1.99

Asterisks denote statistical differences from 0: *$P < 0.05$, ***$P < 0.001$

mean expired gas fraction produced by GESS, and hence the accuracy of this system, depended on the precision of the analysers. As the analysers were accurate to within ± 0.0002, this could explain a part of the variability.

$\dot{V}O_2$ and $\dot{V}CO_2$

Table 1 shows the absolute and relative errors on $\dot{V}O_2$ and $\dot{V}CO_2$, which were both significantly different from 0, showing that $\dot{V}O_2$ was overestimated by 0.56 (SD 1.73)% and $\dot{V}CO_2$ by 1.48 (SD 1.99)%. These overestimations were mainly due to the overestimation of $\dot{V}_E$. The accuracy of $\dot{V}O_2$ and $\dot{V}CO_2$ produced by GESS was lower than 2%. The accuracy of the Tissot spirometer and gas analysers ensure that the conventional Douglas bag method is accurate to within $\pm 2.5\%$. This result is therefore satisfactory.

Accuracy of physiological data

Data were chosen to show the accuracy of GESS for more physiological data. Combinations of V_T and f were selected assuming that V rises faster than f when $\dot{V}_E$ increases. The measured value of $\overline{F}_EO_2$ was 0.1500–0.1800 and that of $\overline{F}_ECO_2$ was 0.02–0.0550. Measured values for $\dot{V}O_2$ and $\dot{V}CO_2$ were between 0 and 5 1 A - min^{-1}. The relative errors on $\dot{V}_E$, F_ECO_2, $\dot{V}O_2$ and $\dot{V}CO_2$ were significantly different from 0, showing that these parameters were overestimated (Fig. 3). No bias was found for $\overline{F}_EO_2$. The mean relative errors of these near physiological data (Fig. 3) were very similar to those for all data (Table 1). There was a significant relationship between the errors and the measured values for $\dot{V}O_2$ and $\dot{V}CO_2$. Hence, the relative error was linked to the metabolic rate. Nevertheless, the slopes of these regression lines were all close to 0 ($0.44\% \cdot \mathrm{min} \cdot 1^{-1}$).

Advantages and disadvantages

The GESS has several advantages over other gas exchange simulation systems, and particularly over that of Huszczuk et al. (1990). Firstly, it can provide warm expired gases that are fully saturated with water vapour because two different gas mixtures are used, one for *inspired* and the other for *expired* gases. The gas mixture E

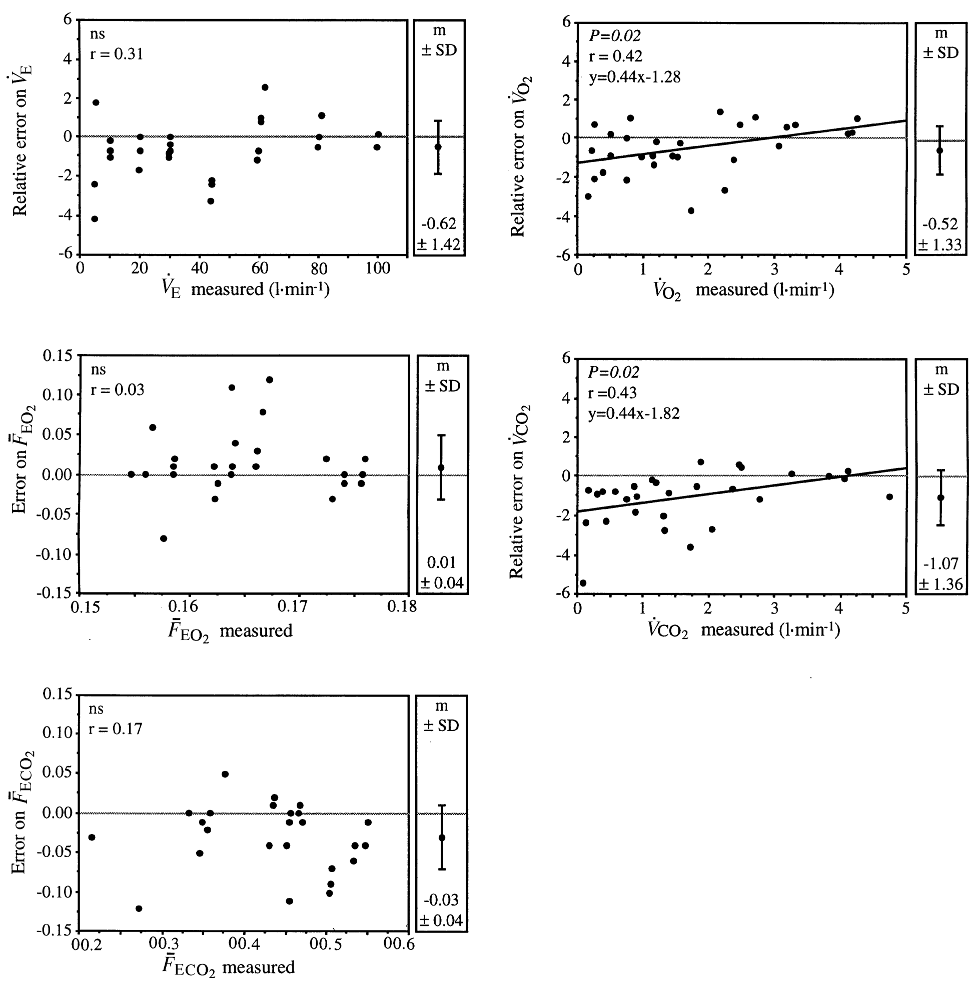

Fig. 3 Errors on variables produced by gas exchange simulation system plotted against measured values for physiological data. $n = 29$ for each parameter. The regression lines are drawn for significant correlations. The mean and the standard deviation ($m \pm SD$) are shown on the *right side of the graph*. $\dot{V}_E$ Minute ventilation, $\overline{F}_EO_2, \overline{F}_ECO_2$ mean fractional concentration of oxygen and carbon dioxide in expired air, respectively, $\dot{V}O_2$ oxygen uptake, $\dot{V}CO_2$ carbon dioxide production

in bag *j* is prepared in a room kept at 30°C and water vapour produced with an autoclave is introduced into the bag to simulate these temperature and humidity conditions. Thus the expiratory bag is kept at 30°C throughout the working period. Nevertheless this feature is an elaborate process and cannot be used easily as routine.

Secondly, GESS is able to test measurement systems in which inspired flow, expired flow, or both are measured. The device described by Gore et al. (1997), that improved on the device of Huszczuk et al. (1990) also has this capacity. Thirdly, the use of a programmable motion control allows any V_T, f and flow waveforms to be set. The disadvantages of GESS compared to the device of Huszczuk et al. (1990) are due to the larger volumes of test gases needed. Gas mixture E can readily be prepared in a 2000-1 polyethylene bag by adding the correct volume of N_2 and CO_2 in ambient air, although it is time-consuming. Several different gas mixtures E are needed to change FO_2 and FCO_2 delivered by GESS during a simulation. Polyethylene bags containing different FO_2 and FCO_2 can be successively connected to GESS to provide a metabolic rate that is independent of the $\dot{V}_E$. This process is, however, more constraining than the device of Huszczuk et al. (1990).

In conclusion, GESS is a suitable system for the quality control of measurements of respiratory gas exchange. It can be used with various metabolic measurement systems. The GESS can be used with systems measuring inspired flow, expired flow or both with the flow meter and gas sampling tube being placed between valve *d* and valve *h*. But it requires the accurate determination of the dead-space volume of the tested system apparatus (flowmeter and valve) for calculation of mean expired gas concentrations. The GESS can simulate humidity and temperature of both inspired and expired gases and provides an accurate $\dot{V}_E$ from 5 to 150 $l \cdot min^{-1}$ at any V_T and f. The overall accuracy of the gas exchange values is less than 2% for $\dot{V}O_2$ and $\dot{V}CO_2$, which is within the accuracy of the Douglas bag method.

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