

A respiratory gas exchange simulator for routine calibration in metabolic studies

A. Huszczuk, B.J. Whipp*, K. Wasserman

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ABSTRACT: We have developed a method for simulating respiratory gas exchange for on-line calibration of metabolic measurement systems. It utilizes a pump which intakes a mixture of atmospheric air and a known flow of precision-analysed calibration gas (21% CO₂, 79% N₂). It expels the resulting mixture with flow wave form and profiles of gas concentration which closely resemble those of normal expiration. Control of the calibration mixture's inflow allows the investigator to set any desired metabolic rate regardless of the minute ventilatory rate. This separation of metabolic from ventilatory rates provides a stringent test of the computational performance of the respiratory gas exchange measurement systems. The apparatus can reproduce any range of respiratory and metabolic performance (currently ranging from 0.2–5 l·min⁻¹ O₂ uptake and CO₂ output) with accuracy $\pm 2\%$.

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Systems capable of computing pulmonary gas exchange variables, such as O₂ uptake, CO₂ output and the respiratory gas exchange ratio, on a breath-by-breath or other short time-frame basis, are becoming more commonly used in studies of physiological and pathophysiological function at rest and during exercise. These systems typically utilize rapidly responding gas analysers coupled to airflow or volume transducers and a computer which is provided with additional, precalibrated information on the instrument's performance characteristics such as transport delays, linearity and response kinetics.

Calibration of such systems has typically involved characterization of the performance of its component parts and validation of the whole-system results in the steady-state against the more conventional techniques such as the "Douglas Bag" method.

It would, therefore, be of considerable practical utility, and also improve the confidence of interpreting non-steady state physiological responses, if a reliable and easy to use calibration system were available, which would provide a precise equivalent of pulmonary O₂ uptake and CO₂ output over a wide range of "metabolic rates".

We have therefore developed such a device for the routine calibration of breath-by-breath, or other, gas exchange systems.

Methods

The respiratory gas exchange simulator is based on the principle that a precisely-known flow of CO₂ (ml·min⁻¹) can be presented to the measurement system

($\dot{V}_{\text{CO}_2\text{c}}$) with a within-breath wave form which mimics that of expired gas and utilizes selected "breath" volumes (V_T) delivered at various respiratory rates. As $\dot{V}_{\text{CO}_2\text{c}}$ is known one can assess how accurately the measured \dot{V}_{CO_2} ($\dot{V}_{\text{CO}_2\text{m}}$) recovers the known flow. Similarly a precisely-known flow of N₂ (and CO₂ in this case) can be utilized to displace O₂ and hence simulate O₂ "consumption".

The device is comprised of three functional systems (fig. 1). Specific components of the device shown in figure 1 are denoted in the following text in parentheses:

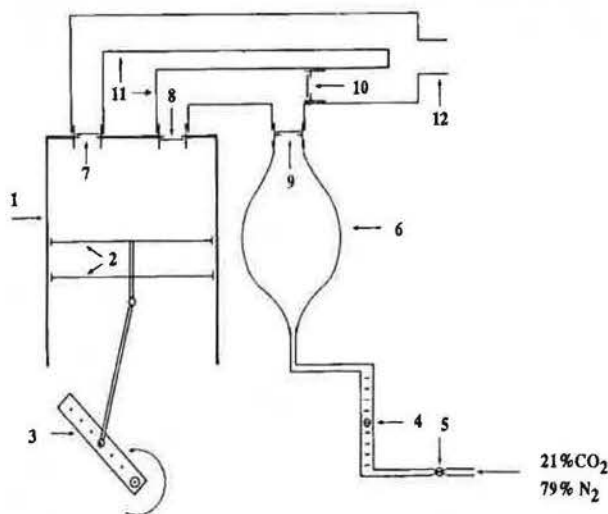


Fig. 1. – Schematic diagram of the calibrator. See methods for description.

The pumping system consists of a cylinder (1), two piston discs (2) spaced 5 cm apart for better sealing and guidance, and a crank arm (3) (allowing selection of a range of tidal volume settings) which is mounted on the shaft of a source of rotary motion. This is adjustable within a range of 5–60 rev·min⁻¹.

The gas feeding system composed of a variable-area flowmeter (rotameter) (4), precision needle valve (5) and a flexible bag or bladder (6) for controlled supply and temporary storage of the calibration gas mixture (21% CO₂, 79% N₂).

The valving and interconnecting system composed of four one-way valves (7–10) and gas conduits (11) (arranged to fulfil functional integrity of the apparatus) which enable generation of the flow and respiratory gas patterns typical of human (and mammalian) breathing (fig. 2) at the interface (12).

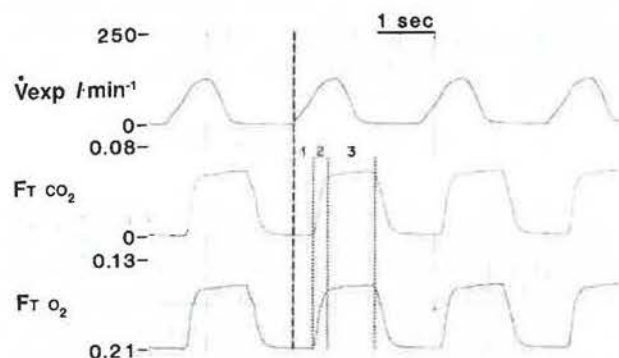


Fig. 2. — An example of expiratory flow (\dot{V}_{exp}) measured by pneumotachometer (Fleisch No. 3) and respiratory gas patterns measured by mass spectrometry (Perkin-Elmer, MGA-1100) using the calibrating device. Fr: fractional tidal concentrations of gas. Note the temporal delay (1) between the beginning of expiration (dashed line) and the expiratory deflections (first dotted line) of gas concentrations which results from the sampling line transit time and deadspace clearance delays. Also note that the following dotted lines demarcate phases equivalent to the mixing of deadspace and alveolar gas (2) and the subsequent alveolar plateau (3).

Principle of operation

If all the inspired oxygen were to be extracted by the metabolic processes, breathing air, this would result in approximately 21% CO₂ with respiratory exchange ratio $R=1$. This gas composition (*i.e.* 21% CO₂, 79% N₂) was, therefore, chosen as the standard metabolic calibration medium since only $R=1$ assures equality of inspired and expired volumes and obviates potentially significant errors [1] which can result when \dot{V}_{O_2} is determined by the most commonly used unidirectional (usually expiratory) measurement of respired volumes. Consequently, 1 l·min⁻¹ flow of this standard calibration gas mixture simulates metabolism at the rate of 210 ml·min⁻¹ for \dot{V}_{CO_2} and approximately 210 ml·min⁻¹ for \dot{V}_{O_2} (209.5 to be precise). In other words, this represents 21% of that gas

mixture's rate of "bleed". Therefore, the rotameter must be precision-calibrated for the above composition of gases or carefully recalibrated by the user. Understandably, high confidence in these values is essential.

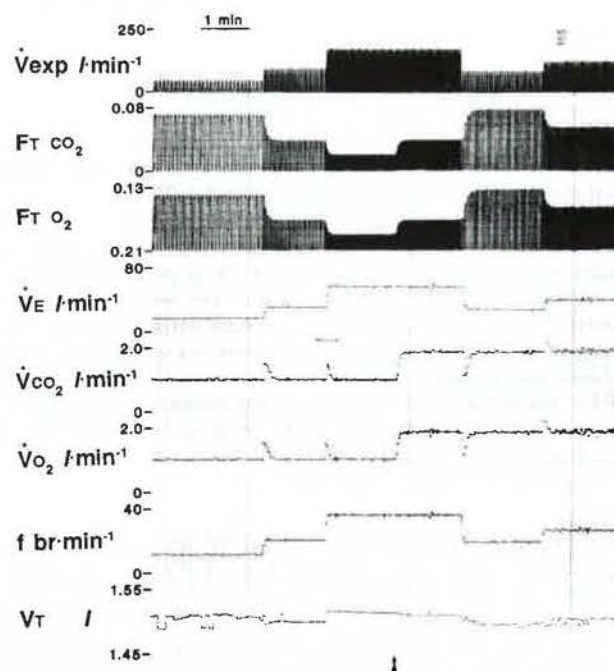


Fig. 3. — An on-line, breath-by-breath computation of minute ventilation (\dot{V}_E), CO₂ production (\dot{V}_{CO_2}), O₂ consumption (\dot{V}_{O_2}), breathing frequency (f) and tidal volume (V_T) of the respiratory variables simulated by the calibrator (three top traces). The stroke volume of the calibrator was set at 1.5 l and maintained throughout. The calibration gas mixture was 21% CO₂, 79% N₂ and its initial flow was set at 4,980 ml·min⁻¹; at arrow, it was increased to 9,205 ml·min⁻¹. The minute ventilatory rate was changed by adjusting the breathing (pumping) frequency. As a result the magnitudes of expiratory flow and gas concentrations were inversely related so their product (\dot{V}_{CO_2} and \dot{V}_{O_2}) would have remained unchanged if the computations were being performed correctly. Due to the gas-filled dead space of the calibrator the tidal changes in gas concentrations could not follow rapid changes in respiratory flow rates instantaneously; this resulted, as shown, in exponential transitions and, therefore, transient deviations from the preset metabolic rates. However, note that following these brief consequences of a wash-out (or wash-in) process, the computed \dot{V}_{CO_2} and \dot{V}_{O_2} remained practically unchanged despite threefold changes in ventilation (see text for further details).

Furthermore, the titratable continuous "metabolic flow" needs a temporary storage space (much like that created by body fluids) in order to be smoothly combined with the intermittent pattern of respiratory flows - here simulated by the reciprocating pump. This function is subserved by the expandable bladder which undergoes complete evacuation of its contents with every inspiratory phase of the respiratory cycle (*i.e.* the downward stroke of the piston in fig. 1). The complete operational cycle of the calibrator proceeds as follows: the

inspiratory phase begins with the uppermost position of the piston and the now-expanding cylindrical space is being filled with a mixture of the bladder contents (via valves 9 and 8) and atmospheric air (route 12→10→8). Upon reaching the lowermost position of the piston, the expiratory phase begins and the just-formed gas mixture is now exhaled (route 7→12) into the measurement system being calibrated; the bladder, therefore, provides temporary storage for the incoming "metabolic flow" to be dealt with during the subsequent inspiratory phase.

Results

Varying the minute respiratory flows (\dot{V}_E) will affect the rate of dilution of the calibration gas mixture by the atmospheric air and consequently change the O_2 and CO_2 fractional concentrations of the exhaled composition. But, importantly, this should not change the computed minute flows of these gases (\dot{V}_{O_2} and \dot{V}_{CO_2}). Two different metabolic rates are shown in figure 3. These are each delivered at three different pumping rates with fixed V_T at 1.5 l. Initially the metabolic rate simulated by the calibrator was set at $1,046 \text{ ml}\cdot\text{min}^{-1}$ (i.e. $4,980 \times 0.21$) for \dot{V}_{CO_2} and $1,043 \text{ ml}\cdot\text{min}^{-1}$ (i.e. $4,980 \times 0.2095$) for \dot{V}_{O_2} . Our breath-by-breath system under calibration computed the average values, over three different breathing frequencies, to be as follows: $\dot{V}_{CO_2} = 1,031 \pm 6$ (SD) $\text{ml}\cdot\text{min}^{-1}$, $\dot{V}_{O_2} = 1,032 \pm 9 \text{ ml}\cdot\text{min}^{-1}$ and $V_T = 1,507 \pm 6 \text{ ml}$. At the arrow, the metabolic rate was increased to $1,933 \text{ ml}\cdot\text{min}^{-1}$ for \dot{V}_{CO_2} and $1,928 \text{ ml}\cdot\text{min}^{-1}$ for \dot{V}_{O_2} , which were computed as $1,903 \pm 13 \text{ ml}\cdot\text{min}^{-1}$ and $1,900 \pm 8 \text{ ml}\cdot\text{min}^{-1}$, respectively with the mean $V_T = 1,502 \pm 6 \text{ ml}$. It is both apparent from figure 3 and supported by the small standard deviation of the mean results, that the process is independent of the particular ventilatory magnitude and pattern or difference in the "respired" gas concentrations.

Discussion

The calibration of a breath-by-breath, mixing chamber or a flow through metabolic measurement equipment generally consists of a series of standard checks designed to verify the performance of gas sensors (with precision-analysed gas mixtures) and flow or volume sensors (with large syringes of a known volume displacement). These are often supplemented with additional measurements such as the phase misalignment between flow and gas signals, which result from both transit delays to the gas sensors and their response dynamics. In addition, information is provided with respect to barometric pressure, humidity and temperature of ambient air. In other words, the user assumes that the system is free from serious computational errors, software inadequacies or trivial physical leaks. This is usually answered by resorting to numerous collections of expired gas and manual calculations. However, this itself has the potential for errors, requires time-consuming repetitive collections of expired gas and also needs a human subject willing to give up the time to serve as a metabolizing source. A tireless

substitute for a human subject in which the respiratory and metabolic rates can be pre-set independently, and maintained within a calibration accuracy of 1% over the desired time frame would be an ideal solution.

There have been previous successful attempts to simulate human metabolic gas exchange [2, 3] for the purpose of testing various designs of protective breathing apparatus (e.g. for miners, firefighters, etc) (the authors are grateful to Dr J. Pawelczyk for drawing this to their attention). These devices, however, in addition to their technical complexity, and hence cost, were not designed directly as calibrators - that is, the gas flows to the devices were modified as needed during the operation, to establish the required exchange rate when there was a discrepancy between the intended values and those actually delivered; they did not directly provide the required standard input to serve as the frame-of-reference for the appropriateness of the calculations.

Other investigators, however, have attempted to provide such a calibrator. For example, BOUTELIER *et al.* [4] have described a respiratory simulator "exhaling" a pre-mixed O_2 - CO_2 - N_2 gas mixture. Consequently the metabolic rate was strictly dependent on ventilation, i.e. none could be independently controlled.

FOSTER and NORTON [5] developed a "standard artificial Lung", consisting of a reciprocating piston pump connected in series with a mixing chamber and a two-way respiratory valve. N_2 and CO_2 flowed into the mixing chamber, mixed with inhaled atmospheric air, and subsequently exhaled. The tidal volumes (V_T) (hence ventilation \dot{V}_E) were therefore dependent on the respiratory rate and the rates of N_2 and CO_2 flows.

Our system overcomes these technical flaws and provides a pre-set level of "metabolic rate" which is independent of the minute or stroke flow of gas, as shown in figure 3. In this case, there were no perceptible changes in the measured metabolic rate despite threefold changes in ventilation. This latter feature, we feel, provides a further and stringent test of the accuracy of the computation. Flow or volume sensor nonlinearities, and their influence on the computed metabolic rate, will become apparent as a range of flows or volumes is utilized.

The calibration limits of such a system naturally depend upon the precision of the gas mixtures used and the appropriateness of the rotameters.

Practical considerations

Parts and components. The major component of the calibrator is the pumping system. It has to be leak-free, its volume displacement (V_T) has to be known precisely and it must be able to provide a sufficient span of pumping rates. A typical volume respirator can be sufficient for this purpose.

The rotameter must be accurate to at least $\pm 1\%$ and cover the $1\text{--}24 \text{ l}\cdot\text{min}^{-1}$ range of flows, although half of this range is satisfactory for most applications. These are generally equipped with a needle valve or other means of precise flow adjustment.

The gas storage bag, or bladder made of flexible rubber or plastic, is commonly used in pulmonary medicine and anaesthesiology. We recommend 3 l as the optimal volume.

The valving system can be assembled either with four one-way valves or with two two-way breathing valves (one combining functions of valves 8 and 9 and the other pf valves 7 and 10 in figure 1). Any typical valve of 2–3 cm internal diameter is adequate.

Flow and volume calibration. It is imperative that the flow of the calibration gas mixture and the stroke (tidal) volume of the exhaled gases be known with high accuracy. This can be achieved with a rolling seal or a wedge spirometer (at least 10 l of volume) equipped with an electric volume transducer. Using 21% CO₂ in N₂ mixture, multiple gas collections over measured periods of time can be performed for various rotameter readings (settings) so that the regression line can be derived. Similarly, for the V_T calibration, multiple air collections over a known number of pumping cycles can be obtained in order to determine the exact stroke volume for a given setting and its statistical variability. For all gas collections, one should make sure that the line between the source of gas (an outlet of a rotameter or a pump) and the inlet port of the spirometer collecting it must offer as little resistance to flow as possible in order to avoid artefacts associated with gas compression.

Verifying the precision of the calibration gas mixture. The composition of the special calibration gas mixture can be an unexpected source of error, i.e. CO₂ values "certified" at 21% have actually varied between 20.3% and 21.5%. The investigator, therefore, needs to verify the gas composition independently.

As most existing CO₂ analysers only cover the range from 0–10%, one must resort to diluting samples of the calibration gas if appropriate chemical analysis is not available. This can be readily done by utilizing atmospheric air and using the O₂ concentration as an estimate of the proportional dilution according to the following formula:

$$\%CO_2 = D\%CO_2 / (1 - D\%O_2 / 20.95)$$

where %CO₂ denotes the actual tank concentration and D the corresponding concentrations in the diluted mixture.

Analysis of errors. We believe that the calibration device (i.e. standard) should be at least 1% accurate and, at present, this is easily achieved for any single quantity. The essence of this method of calibration is generation of a predetermined mass flow of gases that is then detected by the measurement system under calibration. However, as our standard depends upon the precision and stability of the flow and gas concentration measurements, it is itself prone to small fluctuations. In

order to avoid considerable additional expense and complexity, we settled for a measurement accuracy of $\pm 1\%$ for flow and concentration, i.e. resulting in an overall accuracy of $\pm 2\%$.

Nevertheless, this system for calibrating pulmonary gas exchange measurements is sufficiently easy to use and reliable that it is utilized routinely in the pre-test calibration. It can be set to span the extremes of expected gas exchange values, e.g. 0.2–5 l·min⁻¹ for $\dot{V}O_2$ and $\dot{V}CO_2$, ambient temperature and pressure, dry (ATPD), therefore, depending on the specific measurement system to be calibrated, appropriate corrections for temperature, humidity and barometric pressure have to be performed.

Knowing that the entire measurement and computational system is accurate to within approximately 2% of the subject's metabolic rate, allows the investigators to interpret the subject's gas exchange responses with great confidence.

References

1. Otis AB. – Quantitative relationships in steady-state gas exchange. In: Handbook of Physiology: Respiration. W.O. Fenn and H. Rahn eds. Vol 1, American Physiological Society, Washington, 1964, pp. 681–698.
2. Deno NS. – Automatic breathing and metabolic simulator: the respiring robot. *Journal of ISRP*, 1984, 2(1), 38–51.
3. Reimers SD. – The development of a new automated breathing metabolic simulator. *Journal of ISRP*, 1984, 2(1), 170–196.
4. Boutelier U, Gomez U, Mader G. – A piston pump for respiration simulation. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1981, 50(3), 663–664.
5. Foster SL, Norton AC. – A standard artificial lung for system calibration in physiological gas exchange measurements. In: Computers in critical care and pulmonary medicine, Vol. 3, S. Nair ed., Plenum Press, New York, 1983, pp. 213–220.

Un simulateur des échanges gazeux respiratoires pour la calibration de routine dans les études métaboliques. A. Huszczuk, B.J. Whipp, K. Wasserman.

RÉSUMÉ: Nous avons développé une méthode de simulation des échanges gazeux respiratoires pour la calibration des systèmes de mesures métaboliques on line. Elle utilise une pompe qui absorbe un mélange d'air atmosphérique et un débit connu d'un gaz de calibration analysé avec précision (21% de CO₂, 79% de N₂). Elle élimine le mélange qui en résulte avec des formes de vague de débit et des profils de concentration gazeuse qui ressemblent étroitement à ceux d'une expiration normale. Le contrôle du débit d'entrée des mélanges de calibration permet à l'investigateur de fixer les taux métaboliques désirés, indépendamment du taux de ventilation/minute. Cette séparation des taux métaboliques et des taux ventilatoires fournit un test rigoureux des performances en matière de computation des systèmes de mesure des échanges gazeux respiratoires. L'appareil peut reproduire toute l'étendue des performances respiratoires et métaboliques (s'étendant habituellement de 0.2 à 5 l·min⁻¹ de prise d'oxygène et d'élimination de CO₂) avec une précision de $\pm 2\%$. *Eur Respir J.*, 1990, 3, 465–468.