

Determining Cardiac Output by Carbon Dioxide Rebreathing in Patients With Sleep Apnea-Hypopnea Syndrome

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The objective of the present study was to determine the relation between resting cardiac output in patients with sleep apnea-hypopnea syndrome but without arterial hypertension or heart failure as measured indirectly by the carbon dioxide rebreathing method and left ventricular function evaluated by transthoracic echocardiography. We also compared the variability and reproducibility of the measurements obtained by the equilibrium and exponential methods. In patients with sleep apnea-hypopnea syndrome there was a modest but significant association between resting cardiac output and left ventricular shortening fraction ($r=0.690$; $P=.001$) and left ventricular ejection fraction ($r=0.690$; $P=.001$). In addition, mean (SD) cardiac output obtained by the equilibrium method showed a lower coefficient of variability (0.21 [0.08]) than that of the exponential method (0.16 [0.09]) ($P<.01$) as well as a narrower reproducibility interval.

Key words: Cardiac output. Carbon dioxide rebreathing. Stroke volume. Sleep apnea-hypopnea syndrome. Left ventricular function. Variability.

Determinación del gasto cardíaco mediante reinhalación de CO₂ en pacientes con síndrome de apneas-hipopneas durante el sueño

El objetivo del presente estudio ha sido relacionar la medida indirecta del gasto cardíaco por reinhalación de anhídrido carbónico en reposo en pacientes con síndrome de apneas-hipopneas durante el sueño sin hipertensión arterial ni insuficiencia cardíaca, con la función ventricular izquierda valorada mediante ecocardiografía transtorácica. También se comparan la variabilidad y la reproducibilidad de las medidas obtenidas por el método del equilibrio y por el método exponencial. En pacientes con síndrome de apneas-hipopneas durante el sueño se evidencia una relación moderada pero significativa del gasto cardíaco en reposo (método de equilibrio) con las fracciones de acortamiento ($r = 0,690$; $p < 0,001$) y de eyección del ventrículo izquierdo ($r = 0,690$; $p < 0,001$). Además, el gasto cardíaco obtenido por el método de equilibrio mostró un menor coeficiente de variabilidad que por el obtenido por el método exponencial ($0,21 \pm 0,08$ frente a $0,16 \pm 0,09$; $p < 0,01$), así como un menor intervalo de reproducibilidad.

Palabras clave: Gasto cardíaco. Reinhalación de CO₂. Volumen sistólico. Síndrome de apneas durante el sueño. Función ventricular izquierda. Variabilidad.

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS), characterized by repeated episodes of complete or partial interruption of airway flow during sleep, constitutes a major health problem due to its high prevalence (around 3% of the middle-aged population) and associated morbidity and mortality.^{1,2} While traffic or work accidents due to excessive daytime sleepiness

cause some deaths, most mortality is the result of cardiovascular complications. The association between sleep apnea and heart failure has been described in recent decades. This frequent association is of particular importance due to the high prevalence of both entities, the overlapping of several pathophysiological mechanisms, and the possibility of applying therapeutic measures useful for both disorders.³

Although the gold-standard procedure for measuring cardiac output (Qt) is the direct Fick method, which requires cardiac catheterization, there are several indirect procedures such as echocardiography or radioisotope techniques. Several decades ago, Jones⁴ developed a method for estimating Qt by means of carbon dioxide (CO₂) rebreathing, which makes it possible to establish a balance between alveolar and

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mixed venous CO₂ pressures. In subsequent years, 2 modalities of this procedure, the equilibrium method and the exponential method, were established and applied in several different clinical situations.^{5,6} To our knowledge, however, no specific information is available concerning the use of these techniques in patients with OSAHS.

The objectives of the present study were to compare the variability and reproducibility of the equilibrium and exponential methods of CO₂ rebreathing in patients with OSAHS and to determine the relation between measurements obtained by these techniques and left ventricular function parameters evaluated by echocardiography.

Patients and Methods

Thirty-two patients with OSAHS with normal blood pressure and without heart failure and 13 control subjects were included in the study (Table 1). All patients gave their signed consent to the study, which was approved by the hospital ethics committee.

The study was carried out in 2 phases. In the first, we determined the relation between resting Qt measured by the equilibrium method of CO₂ rebreathing and parameters obtained by echocardiography. In the second, we compared the coefficient of variability and the reproducibility interval of the exponential and equilibrium methods of measuring resting Qt by CO₂ rebreathing. This second phase was carried out in a subsample consisting of 14 patients with OSAHS (13 men and 1 woman) with a mean (SD) age of 53 (12) years and a mean apnea-hypopnea index of 50.5 (27.4) as well as in a subsample of 8 healthy men with a mean age of 51 (10) years and a mean apnea-hypopnea index of 2.1 (1).

Transthoracic second-harmonic, 2-dimensional M-mode Doppler echocardiography using a Sonos 5500 system (Hewlett Packard, Andover, Maine, USA) was performed with patients in supine and left lateral decubitus, using short-axis and long-axis parasternal, apical, and subcostal views. Left ventricular end-systolic dimensions and end-diastolic posterior wall and interventricular septum thickness were measured in accordance with the recommendations of the American Society of Echocardiography.⁷ Left ventricular

systolic function was evaluated by calculating the left ventricular shortening fraction and left ventricular ejection fraction.⁸ The studies were carried out using simultaneous bipolar lead monitoring and all measurements were the result of averaging the values obtained in 3 cardiac cycles.

Qt was measured twice with an Oxycon Alpha system (Jaeger, Würzburg, Germany), using the equilibrium and the exponential techniques in random order. In the equilibrium technique, patients rebreath from a bag filled with 1.5 times their tidal volume of room air and a mixture of 20.9% oxygen and 8.5% CO₂ and nitrogen until a plateau in expired CO₂ fraction is reached.⁵ This plateau is considered to reflect the equilibrium between alveolar and mixed venous CO₂ pressures, the point that equilibrium PCO₂ is determined.⁵ In the Defares or exponential technique, however, the rebreathing bag contains a lower concentration of CO₂ (0%-5%). The CO₂ concentration increases progressively during the rebreathing maneuver and the exponential regression curve is used to extrapolate the point of equilibrium and calculate equilibrium PCO₂.⁶

For both techniques, rebreathing periods lasting a maximum of 20 seconds were repeated and continuous recording of expired CO₂ fraction was performed. Once equilibrium PCO₂ had been determined, Qt was calculated using the Fick method, whereby Qt is equal to CO₂ production (V̇CO₂) (measured directly before the beginning of the rebreathing maneuver) divided by the difference between mixed venous and arterial CO₂ contents as expressed in the equation⁴:

$$Qt = V'CO_2 / C_vCO_2 - CaCO_2$$

Arterial CO₂ content (C_aCO₂) is calculated from PaCO₂, which in turn is estimated from end-tidal CO₂ pressure.⁴ Finally, mixed venous CO₂ content (C_vCO₂) is calculated from venous CO₂ pressure, which in turn is calculated from equilibrium PCO₂.⁴ Stroke volume was calculated from simultaneous recording of heart rate. We also calculated cardiac index (Qt/body surface area) and stroke volume index (stroke volume/body surface area).

Results

Resting Qt in patients with OSAHS was lower than in healthy controls (Table 1). Compared to the control group, the group of patients with OSAHS showed greater thickness of the left ventricular posterior wall (10.6 [0.2] mm compared to 9.3 [0.4] mm; *P*<.01) and of the interventricular septum (10.7 [0.2] mm compared to 9.4 [0.4] mm; *P*<.01), as well as greater ventricular mass (213 [7] g compared to 174 [7] g; *P*<.01) and a lower left ventricular ejection fraction (67.1% [0.7%] compared to 70.3% [1.8%]; *P*<.05).

In patients with OSAHS there was a modest but significant correlation between resting Qt and stroke volume determined by CO₂ rebreathing (equilibrium method), left ventricular shortening fraction (*r*=0.648; *P*<.001, and *r*=0.567; *P*<.01, respectively), and left ventricular ejection fraction (*r*=0.690; *P*<.001, and *r*=0.584; *P*<.01, respectively) (Table 2). We also determined correlations between Qt and stroke volume values, corrected for body surface area, and left ventricular function parameters (Table 2).

TABLE 1
Patient Characteristics, Mean Arterial Pressure,
and Left Ventricular Function*

	OSAHS	Control	P
Men, %	97	100	NS
Age, years	53 (13)	50 (8)	NS
Height, cm	170 (7)	172 (6)	NS
Weight, kg	88 (14)	81 (11)	NS
BMI, kg/m ²	30.3 (3.9)	27.4 (3.3)	.027
Smokers, %	48	50	NS
AHI	45.3 (26.4)	2.1 (1)	.000
LVEF, %	67.1 (0.7)	70.3 (1.8)	.043
Daytime MAP, mm Hg	94 (7)	92 (6)	NS
Nighttime MAP, mm Hg	86 (8)	82 (8)	NS
Qt, L/min	4.86 (2.01)	6.08 (2.47)	.039

*Data are expressed as means (SD) unless otherwise noted. BMI indicates body mass index; AHI, apnea-hypopnea index; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; Qt, cardiac output; OSAHS, obstructive sleep apnea-hypopnea syndrome; NS, not significant.

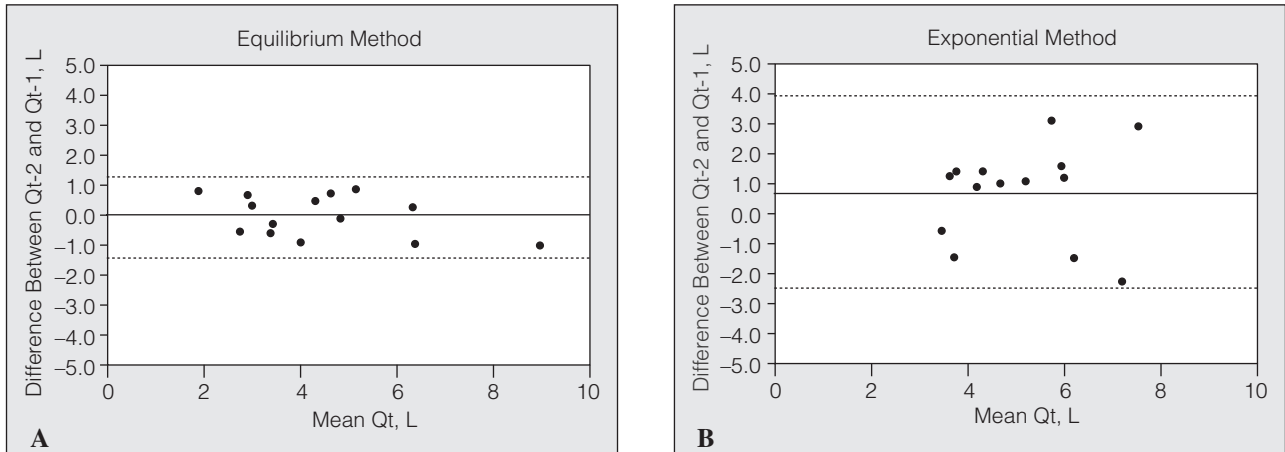


Figure 1. Reproducibility of the equilibrium (A) and exponential (B) methods of measuring cardiac output (Qt) in patients with obstructive sleep apnea-hypopnea syndrome. The continuous line represents the mean of the differences and the broken lines, the reproducibility interval at the 95% confidence level. Qt-1 indicates the first time Qt was measured, and Qt-2, the second.

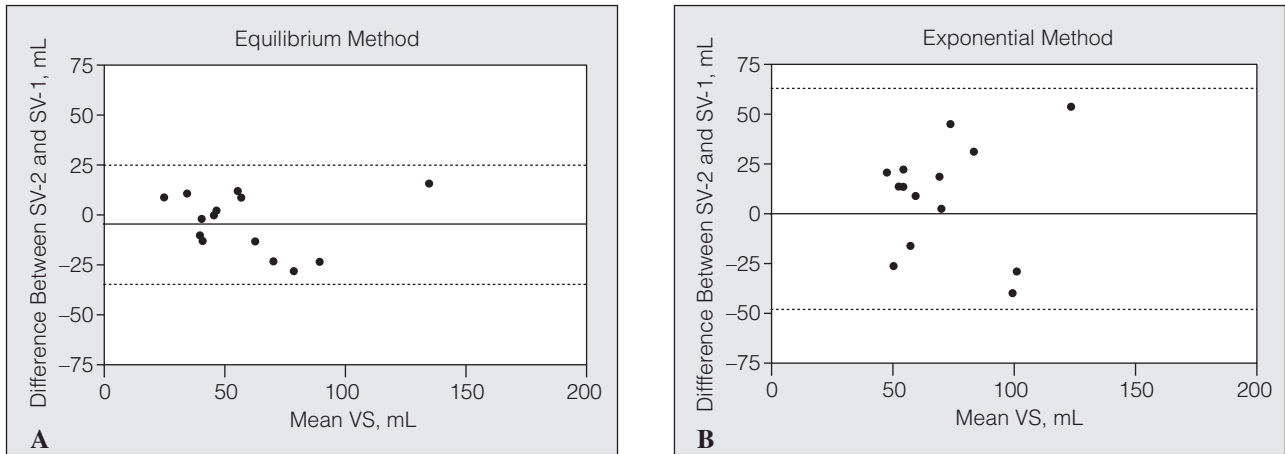


Figure 2. Reproducibility of the equilibrium (A) and exponential (B) methods of measuring resting stroke volume (SV) in patients with obstructive sleep apnea-hypopnea syndrome. The continuous line represents the mean of the differences and the broken lines, the reproducibility interval at the 95% confidence level. SV-1 indicates the first time SV was determined, and SV-2, the second.

In the OSAHS group, the exponential method showed a greater coefficient of variability than did the equilibrium method in the measurement of Qt (0.21 [0.08] compared to 0.16 [0.09]; $P=0.008$), of stroke volume (0.24 [0.10] compared to 0.16 [0.09]; $P=0.039$)

and of resting cardiac index (0.21 [0.07] compared to 0.12 [0.08]; $P=0.008$). These coefficients were similar to those obtained in the control group. The exponential method also showed wider reproducibility intervals at the 95% confidence level than did the equilibrium method for both Qt (-2.51 to 3.82 L for the exponential method compared to -1.31 to 1.45 L for the equilibrium method) and for stroke volume (-46 to 63 mL compared to -34 to 27 mL, respectively) (Figures 1 and 2).

TABLE 2

Correlation Between Echocardiographic Measurements and Parameters Obtained at Rest With the Carbon Dioxide Rebreathing Technique in Patients With Obstructive Sleep Apnea-Hypopnea*

	LV Wall Thickness	LV Septum Thickness	LV Mass	LVSF	LVEF
Qt	-0.140	-0.055	-0.120	0.648‡	0.690‡
SV	-0.054	-0.077	-0.081	0.567†	0.584†
HR	-0.179	0.075	-0.077	0.188	0.190
CI	-0.103	-0.028	-0.070	0.581†	0.619†
SVI	-0.033	-0.072	-0.053	0.521†	0.533†

*Values are Pearson's correlation coefficients. Qt indicates cardiac output; SV, stroke volume; HR, heart rate; CI, cardiac index; SVI, stroke volume index; LVSF, left ventricular shortening fraction; LVEF, left ventricular ejection fraction. † $P<0.01$. ‡ $P<0.001$.

Discussion

The results of our study showed a correlation between resting Qt determined by CO₂ rebreathing and echocardiographic parameters of left ventricular systolic function. The equilibrium method showed less variability and greater reproducibility than the exponential method.

From previous studies, it was already known that the equilibrium method had greater precision and reproducibility than the exponential method both in

healthy subjects and in patients with heart disease.^{9,10} The exponential method also appears to underestimate Q_t slightly, especially compared to the direct Fick method and dye dilution techniques.^{10,11} In any event, the reliability of the 2 CO_2 rebreathing methods is similar and analogous to that of other indirect methods. In a group of 29 patients with cardiovascular disease, Franciosa et al¹⁰ observed that mean variability of 2 successive Q_t measurements was 6% (1%) with the equilibrium method, 13% (2%) with the exponential method, and 7% (1%) with the dye dilution method.

Our data showed a significant association between Q_t and stroke volume measured by CO_2 rebreathing and left ventricular function parameters (Table 2). These results are consistent with previous data from procedure validation studies. In 20 volunteers the correlation coefficient for the correlation between resting Q_t obtained with the equilibrium method and that obtained by the dye dilution technique was 0.75, and for the relation between resting Q_t obtained by the equilibrium method and that obtained by the direct Fick method, 0.8¹² Agreement of the equilibrium method with direct methods increases when patients are in a sitting position and is directly related to oxygen consumption.¹⁴

The main drawback of the equilibrium method is the sensation of dyspnea caused by the rebreathing of CO_2 , and this limits its use during maximal exercise. However, only resting values were measured in the present study, and no patients had to interrupt the test prematurely because of dyspnea.

Determining Q_t by CO_2 rebreathing allows for measurement not only at rest, but also during exercise. The precision of the method increases during exercise, as with all techniques that use rebreathing of gases to calculate Q_t .^{12,13} CO_2 rebreathing is an attractive technique, as it is noninvasive and allows early detection of alterations in Q_t response to exercise in patients with OSAHS.¹⁵ From our results, we can conclude that CO_2 rebreathing is a method that has a modest but significant correlation with echocardiographic parameters and that, of the 2 techniques available, the equilibrium

method is the one that shows less variability and greater reproducibility in determining resting Q_t in patients with OSAHS.

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