Do rebreathing manoeuvres for non-invasive measurement of cardiac output during maximum exercise test alter the main cardiopulmonary parameters?

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Abstract

Background: Inert gas rebreathing has been recently described as an emergent reliable non-invasive method for cardiac output determination during exercise, allowing a relevant improvement of cardiopulmonary exercise test clinical relevance. For cardiac output measurements by inert gas rebreathing, specific respiratory manoeuvres are needed which might affect pivotal cardiopulmonary exercise test parameters, such as exercise tolerance, oxygen uptake and ventilation vs carbon dioxide output (VE/VCO_2) relationship slope.

Method: We retrospectively analysed cardiopulmonary exercise testing of 181 heart failure patients who underwent both cardiopulmonary exercise testing and cardiopulmonary exercise test+cardiac output within two months (average 16 ± 15 days). All patients were in stable clinical conditions (New York Heart Association I–III) and on optimal medical therapy.

Results: The majority of patients were in New York Heart Association Class I and II (78.8%), with a mean left ventricular ejection fraction of 31 ± 10%. No difference was found between the two tests in oxygen uptake at peak exercise (1101 (interquartile range 870–1418) ml/min at cardiopulmonary exercise test vs 1103 (844–1389) at cardiopulmonary exercise test-cardiac output) and at anaerobic threshold. However, anaerobic threshold and peak heart rate, peak workload (75 (58–101) watts and 64 (42–90), $p < 0.01$) and carbon dioxide output were significantly higher at cardiopulmonary exercise testing than at cardiopulmonary exercise test+cardiac output, whereas VE/VCO_2 slope was higher at cardiopulmonary exercise test+cardiac output (30 (27–35) vs 33 (28–37), $p < 0.01$).

Conclusion: The similar anaerobic threshold and peak oxygen uptake in the two tests with a lower peak workload and higher VE/VCO_2 slope at cardiopulmonary exercise test+cardiac output suggest a higher respiratory work and consequent demand for respiratory muscle blood flow secondary to the ventilatory manoeuvres. Accordingly, VE/VCO_2 slope and peak workload must be evaluated with caution during cardiopulmonary exercise test+cardiac output.

Keywords

Cardiac output, cardiopulmonary exercise test, inert gas rebreathing

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Background

Cardiac output (CO) is an essential parameter in the assessment of cardiac diseases,[1,2] and it represents an added value in severity and risk stratification of heart failure (HF) patients.[3,4] CO estimation from oxygen uptake (VO_2) has been proposed albeit without a relevant clinical application.[5,6] Indirect surrogate parameters, such as oxygen pulse or stroke work index, have been proposed, but again with limited clinical usefulness. Until recently, reliable CO measurements during exercise in HF have been obtained only by invasive methods.[7] Nowadays, CO during exercise can be determined through inert gas rebreathing (IGR) (Innocor Rebreathing System, Innovision A/S, Odense, Denmark).[8–13] IGR needs three to five respiratory cycles to obtain nitric oxide (N_2O) washout at a predetermined breathing frequency. Although we previously demonstrated that other respiratory manoeuvres, such as maximal flow-volume loops collected during a maximal exercise test, do not alter the main cardiopulmonary exercise test (CPET) parameters,[14] it is unknown whether rebreathing manoeuvres affect pivotal CPET parameters, such as VO_2 at the anaerobic threshold and at peak and the ventilation vs carbon dioxide output (VE/VCO_2) slope. Indeed, these parameters are considered among the most relevant data obtainable from CPET in HF patients.[15,16]

Aim

We investigated whether CPET parameters are influenced during exercise by IGR manoeuvres needed for CO determination.

Methods

Patient population

We retrospectively analysed clinical data of 181 consecutive HF patients (154 men and 27 women) who were evaluated at our unit. All patients underwent two CPETs with (CPET+CO) and without CO determination (CPET) by IGR within two months of each other (average 16 ± 15 days). All patients were in a stable clinical condition, in New York Heart Association (NYHA) functional class I–III, capable of performing a standard CPET and rebreathing manoeuvres. Exclusion criteria were left ventricular ejection fraction $> 50\%$ at baseline echocardiographic examination, presence of primary pulmonary hypertension, pulmonary embolism or any concomitant disease per se influencing exercise capacity. All patients underwent a complete clinical evaluation (including NYHA functional class, resting haemoglobin, and brain natriuretic peptide levels), conventional transthoracic echocardiography, standard spirometry, CPET and CPET + CO is cardiopulmonary exercise test + cardiac output measurement (CPET+CO).

Cardiopulmonary exercise testing

A maximal CPET was performed (229D Spectra metabolic cart, SensorMedics) on a cycle ergometer (Erg 800S, SensorMedics), using a personalised ramp protocol. The majority of patients had previous experience with the CPET in our laboratory; the other patients underwent a familiarization procedure. We analysed the CPET using a standard methodology. The CPET was self-interrupted by the patients when they claimed that had reached a maximal effort. CPET+CO was performed using the same ramp protocol. CO was measured at rest, at submaximal exercise (usually $\approx 40\%$ of exercise) and at peak. All patients underwent a few teaching sessions to be familiarised with the rebreathing manoeuvres. The IGR technique has been previously reported in detail.[17] In brief, IGR uses an oxygen-enriched mixture of an inert soluble gas (0.5% N_2O) and an inert insoluble gas (0.1% sulphur hexafluoride (SF_6)). SF_6 is insoluble in blood and used to determine lung volume. Patients have to breathe into a respiratory valve via a mouthpiece and a bacterial filter with a nose clip. At the end of expiration, the valve is activated automatically so that patients rebreathe from the prefilled bag for a period of 10–20 s. After that period, patients start breathing ambient air again. N_2O concentration decreases during rebreathing with a rate proportional to pulmonary blood flow (PBF), which is the blood flow that perfuses the alveoli participating in gas exchange, i.e. ventilated and perfused. CO is equal to PBF in the absence of pulmonary shunt flow, otherwise shunt flow can be estimated from arterial oxygen (O_2) saturation. Patients performed between 2–4 IGR manoeuvres during the exercise protocol. Both cycle ergometers were checked for calibration and no significant difference was found. Moreover VO_2 was measured during exercise, without IGR, in normal subjects with both ergometers confirming that similar data were recorded. The study was approved by our institutional ethics committee (R435/16-CCM451).

Statistical analysis

Data are reported as median and interquartile range (25–75% percentile) or as median and standard deviation (SD) as appropriate. For each parameter, the data distribution normality was tested using the Shapiro-Wilk test. The paired student's t test was used to compare normally distributed continuous variables between the CPET and CPET+CO measurements, and the

Table 1. Heart failure patients demographic characteristics.

Variables	Overall ($n = 181$) Mean ± SD
Age, years	64.6 ± 11.2
Gender (male), %	85
BMI, kg/m^2	26.2 ± 4.1
NYHA Class I, %	24.4
NYHA Class II, %	54.4
NYHA Class III, %	21.1
Haemoglobin, g/dl	14 ± 1
BNP, pg/ml	532 ± 808
LVEF, %	31 ± 10
LVEDV, ml	206 ± 75
LVESV, ml	144 ± 62
FEV1, % of predicted	83.1 ± 17.8
FVC, % of predicted	88.3 ± 16.8
β-Blockers, %	91.3
ACE-inhibitors, %	70
ARBs, %	18.1
Diuretics, %	78.8
Antialdosteronic drug, %	61.9
Digitalis, %	3.8

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; LVEDV: left ventricle end diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricle end systolic volume; NYHA: New York Heart Association; SD: standard deviation.
Bold means statistically significant ($p < 0.05$).

Wilcoxon rank sum test was used for non-normally distributed variables. Linear regression analysis with the Spearman correlation coefficient was used to evaluate the relationship between the CPET and CPET+CO measurements. Bland-Altman analysis was used to assess the intertechnique agreement by calculating the bias (mean difference) and the 95% limits of agreement

Table 3. Inter-technique comparisons between cardiopulmonary exercise test (CPET) and CPET+cardiac output (CO) measurements (linear regression and Bland-Altman analysis).

	r	Bias	LOA
VO_2 AT (ml/min)	0.72	–22	346
HR AT (bpm)	0.66	6	26
Work AT (watts)	0.64	7	33
VO_2 peak (ml/min)	0.86	19	370
HR peak (bpm)	0.78	7	28
Work peak (watts)	0.90	13	26
O_2 pulse peak (ml/beat)	0.69	−1.06	6.54
VCO_2 peak (ml/min)	0.86	108	449
VT peak (l)	0.78	0.04	0.69
VE peak (l/min)	0.78	5.3	20.0
RR peak (breath/min)	0.63	2	13
RQ peak	0.40	0.08	0.24
VE/VCO_2 slope	0.58	−1.9	12.6

AT: anaerobic threshold; HR: heart rate; LOA: limit of agreement; RQ: respiratory quotient; RR: respiratory rate; VCO_2: carbon dioxide output; VO_2: oxygen uptake; VE: ventilation; VT: tidal volume.

Table 2. Cardiopulmonary exercise test (CPET) data (CPET and CPET + cardiac output (CO)).

	CPET	CPET+CO	*p* Value
VO_2 AT (ml/min)	738 (624–966)	749 (624–967)	N.S.
HR AT (bpm)	89 (80–101)	81 (72–95)	**<0.001**
Work AT (watts)	46 (34–59)	39 (25–52)	N.S.
VO_2 peak (ml/min)	1101 (870–1418)	1103 (844–1389)	N.S.
HR peak (bpm)	112 (96–125)	101 (87–120)	**<0.001**
Work peak (watts)	75 (58–101)	64 (42–90)	**<0.001**
O_2 pulse peak (ml/beat)	10.5 (8.6–12.8)	11.8 (9.1–14.2)	**<0.001**
VCO_2 peak (ml/min)	1265 (998–1609)	1140 (863–1542)	**<0.001**
VT peak (l)	1.6 (1.3–2.0)	1.6 (1.3–2.0)	N.S.
VE peak (l/min)	51 (39–62)	44 (36–56)	**<0.001**
RR peak (breath/min)	32 (27–36)	28 (25–33)	**<0.001**
RQ peak	1.12 (1.06–1.21)	1.06 (0.97–1.13)	**<0.001**
VE/VCO_2 slope	30 (27–35)	33 (28–37)	**<0.001**

AT: anaerobic threshold; HR: heart rate; N.S.: not significant; RR: respiratory rate; RQ: respiratory quotient; VCO_2: carbon dioxide output; VE: ventilation; VO_2: oxygen uptake; VT: tidal volume.
Data are reported as median and interquartile range (25–75% percentile).

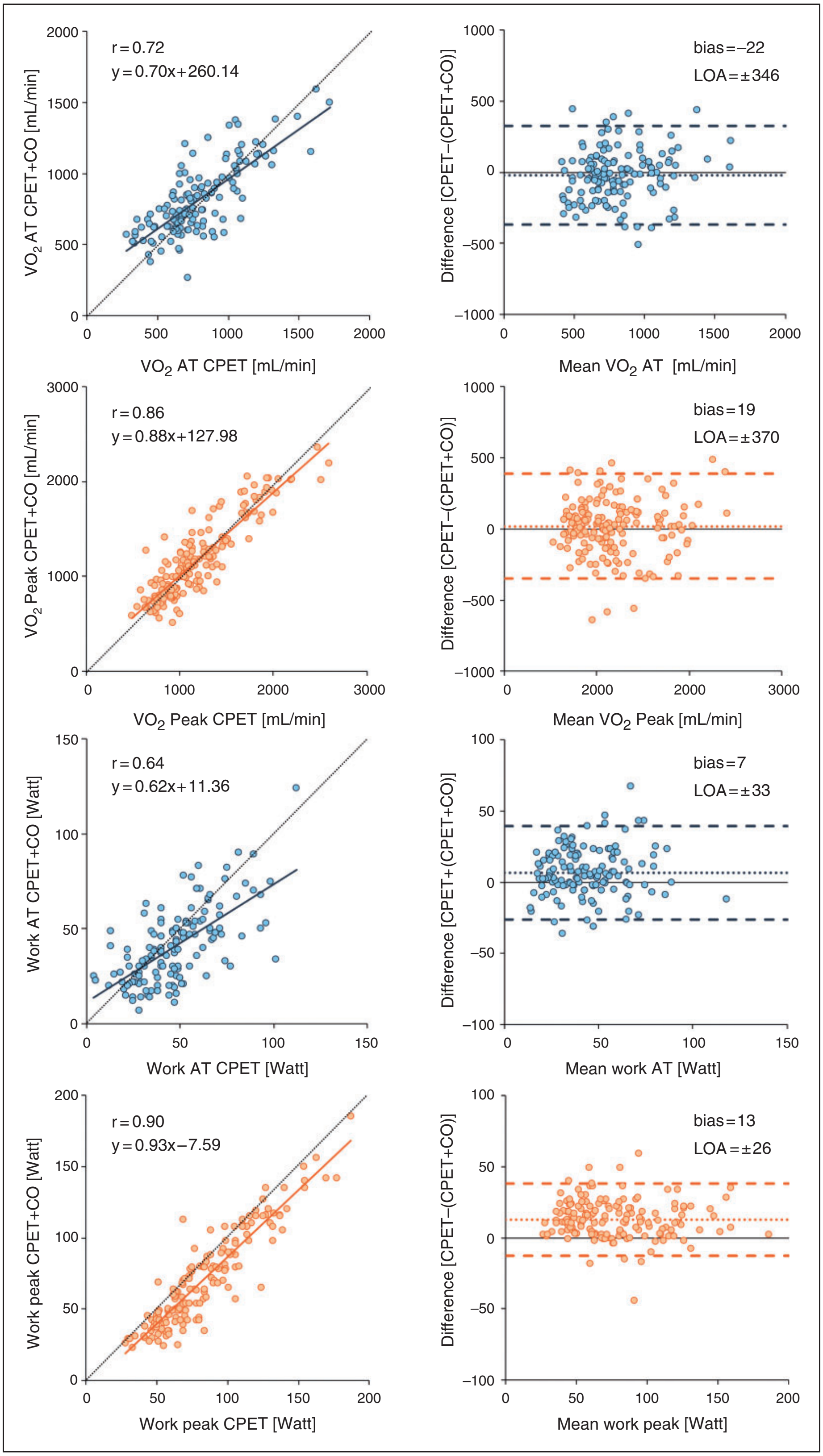

Figure 1. Linear regression and Bland-Altman analysis of the oxygen output (VO_2) and workload measurements performed by cardiopulmonary exercise test (CPET) and CPET+cardiac output (CO) tests at the anaerobic threshold and at peak exercise.

(defined as 1.96 standard deviation (SD) around the mean difference). All results were considered significant with p values < 0.05. Statistical analysis was performed using SPSS 24 (SPSS Inc, Chicago, Illinois, USA).

Results

Baseline clinical characteristics of the study population are reported in Table 1. HF aetiology was: ischaemic heart disease (46 patients), idiopathic cardiomyopathy (114 patients), and valvular heart disease (21 patients). The majority of patients were reported to be in NYHA Class I and II (79%), with left ventricular ejection fraction (LVEF) = 31 ± 10%, normal respiratory function tests, and on optimal medical therapy. All patients performed both CPET and CPET+CO, without unexpected events. CPET data of both tests are reported in Table 2. Average peak respiratory quotient (RQ) was > 1.05 in both tests but higher during the CPET. No difference was found in peak VO_2, and VO_2 at the anaerobic threshold between groups. Heart rate (HR) at the anaerobic threshold and at peak was higher at the CPET than at CPET+CO test, along with a lower O_2 pulse (VO_2/HR) at the CPET. Similarly, workload at the anaerobic threshold and peak workload were higher at the CPET. Mean VE/VCO_2 slope was significantly higher at CPET+CO. All ventilatory parameters, with the exception of tidal volume, were significantly higher at the CPET than at CPET+CO.

Inter-technique comparisons between CPET and CPET+CO measurements are reported in Table 3. The results of linear regression and Bland-Altman analysis show a good agreement between the VO_2 measurements performed by CPET and CPET+CO tests both at the anaerobic threshold and at peak of exercise, while the workload reached at the anaerobic threshold and at peak exercise was lower at CPET+CO than at CPET (Figure 1). Correlation and Bland-Altman analysis between CPET and CPET+CO measurements for VE/VCO_2 slope are depicted in Figure 2. Despite a slightly wide limit of agreement (LOA), non-relevant bias was found between CPET and CPET + CO.

Discussion

Non-invasive measurement of CO during exercise can be achieved through different techniques, such as impedance cardiography, thoracic bioreactance, transthoracic echocardiography, and IGR. Measurement of CO represents an added value to a standard CPET. Since VO_2 equals CO times the arteriovenous oxygen content difference ($C(a–v)O_2$) by Fick's law, a reduction in VO_2, as determined by a standard CPET, cannot differentiate low CO (i.e. HF) from impaired ($C(a–v)O_2$) (i.e. deconditioning or myopathy).[3,16] In addition to this, a CPET+CO test enables us to better understand the specific contribution that CO and ($C(a–v)O_2$) offer to an observed reduced VO_2.

In the present study, the same cohort of patients underwent both a maximal CPET and a CPET+CO within a time frame of two months. Differences were found in cardiopulmonary parameters, despite similar values of peak VO_2. In particular, patients achieved a higher peak HR, a lower O_2 pulse, a higher workload,

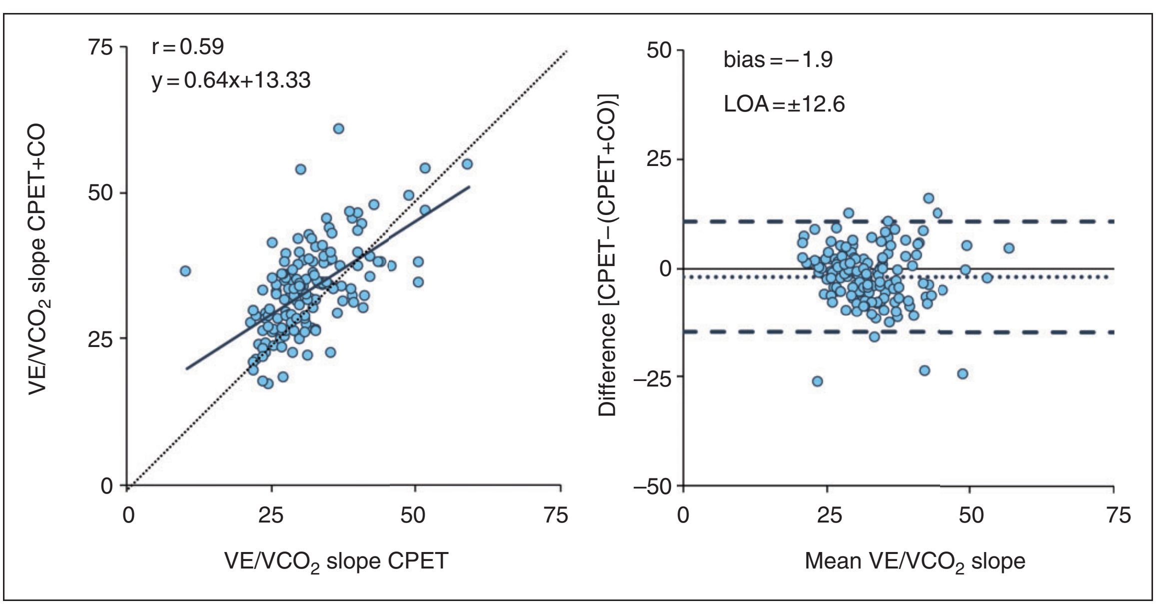

Figure 2. Linear regression and Bland-Altman analysis of the ventilation vs carbon dioxide output (VE/VCO_2) slope measured by cardiopulmonary exercise test (CPET) and CPET+cardiac output (CO) tests. LOA: limit of agreement.

and a more favourable ventilatory efficiency during CPET without respiratory manoeuvres for CO determination. The rebreathing manoeuvre affects some but not all CPET parameters. As regards HR behaviour, during CPET+CO it is possible that the inspiratory manoeuvre needed for IGR elicits vagal stimulation which interfere with HR increase during exercise. Moreover, in a CPET+CO test, the patient has to perform ventilatory manoeuvres that include rebreathing from a bag prefilled with the inert gases for a period of 10–20 s, at rest and during the test (generally, when 50% of test progress is reached), and at peak exercise for CO measurements. They normally last for a period of 10–20 s. These rebreathing manoeuvres require additional respiratory work: indeed, the comparable VO_2 at anaerobic threshold and at peak, in contrast with lower workload at anaerobic threshold and at peak with IGR, suggest a greater respiratory work that would elicit locomotor muscle vasoconstriction and compromise limb perfusion,[18] leading to a worse performance. The increased VE/VCO_2 slope and the lower peak ventilation (VE) values in IGR seem to confirm this hypothesis, i.e. a rise of respiratory work at the expense of locomotor muscles. Notably, VE/VCO_2 slope is among the cornerstones of HF prognosis by CPET,[19–21] and our data cast some doubts on its interpretation in a CPET+CO test.

In conclusion, although the IGR method is at its early phase of expansion, it represents a promising tool for better management of patients with cardiac disease, giving reliable measures of peak VO_2 similar to those obtained through the standard CPET, with the added value of the noninvasive estimation of CO. However, other relevant CPET-derived parameters, such as peak HR, workload, VE and VE/VCO_2 slope should be analysed with caution, since they are directly influenced by the IGR technique itself.

Author contribution

CV, MM and PA contributed to conception and design; GS contributed to conception and design; MM contributed to design and acquisition of data; LF and SR contributed to analysis and interpretation; BP contributed to acquisition analysis and interpretation; FDM, PPF and GS contributed to interpretation; CV and PA drafted manuscript; ES contributed to acquisition of data; MM, LF, BP, ES, FDM, PPF, SR, GS and PA critically revised the manuscript.

Declaration of conflicting interests

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