A Non Invasive Estimate of Dead Space Ventilation from Exercise Measurements

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Abstract

Rationale: During exercise, heart failure patients (HF) show an out-of-proportion ventilation increase, which in patients with COPD is blunted. When HF and COPD coexist, the ventilatory response to exercise is unpredictable.

Objectives: We evaluated a human model of respiratory impairment in 10 COPD-free HF patients and in 10 healthy subjects, tested with a progressive workload exercise with different added dead space. We hypothesized that increased serial dead space upshifts the VE vs. VCO2 relationship and that the VE-axis intercept might be an index of dead space ventilation.

Measurements: All participants performed a cardiopulmonary exercise test with 0, 250 and 500 mL of additional dead space. Since DS does not contribute to gas exchange, ventilation relative to dead space is ventilation at VCO2 = 0, i.e. VE-axis intercept. We compared dead space volume, estimated dividing VE-axis intercept by the intercept on respiratory rate axis of the respiratory rate vs. VCO2 relationship with standard method measured DS.

Main results: In HF, adding dead space increased VE-axis intercept (+0 mL = 4.98±1.63 L; +250 mL = 9.69±2.91 L; +500 mL = 13.26±3.18 L; p<0.001) and upshifted the VE vs.VCO2 relationship, with a minor slope rise (+0 mL = 27±4 L; +250 = 28±5; +500 = 29±4; p<0.05). In healthy, adding dead space increased VE-axis intercept (+0 mL = 4.9±1.4 L; +250 mL = 9.3±2.4; +500 mL = 13.1±3.04; p<0.001) without slope changes. Measured and estimated dead space volumes were similar both in HF and healthy subjects.

Conclusions: VE-axis intercept is related to dead space ventilation and dead space volume can be non-invasively estimated.

Introduction

The behaviour of ventilation during exercise in heart failure (HF) and in chronic obstructive pulmonary disease (COPD) patients may differ, being characterized in the former by an out-of-proportion increase of ventilation (VE), which is greater the greater the HF severity [1] and, in the latter, by a normal or excessive increase of ventilation in mild or moderate COPD and a blunted ventilation increase in severe COPD patients [2–4]. The elevated ventilatory response in HF patients seen before lactic acidosis ensues and the carbon dioxide (CO2) [5] generated by the lactate is trivial relative to the rate of metabolic CO2 production (VCO2) [6,7]. The relationship between VE and VCO2 is used to evaluate ventilatory efficiency [8]; in HF, as well as in pulmonary arterial hypertension, an increase of the slope of the VE vs. VCO2 relationship is associated with a poor prognosis [9–16]. In COPD, ventilatory limitation to exercise is defined either as a reduction of ventilatory reserve or as a lowering of inspiratory capacity [17]. In case of severe COPD, the rise of ventilation during exercise is blunted, and consequently the slope of VE vs. VCO2 relationship is normal or low, being the slope lower the more pronounced the emphysema profile [2].

HF and COPD often coexist with a reported prevalence of COPD in HF patients ranging between 23 and 30% [18] and with a relevant impact on mortality and hospitalization rates [19]. In patients with COPD and HF, the ventilatory response to exercise is poorly predictable. Indeed, HF hyperventilation can be counteracted by the incapacity of increasing tidal volume (VT) and alveolar ventilation, both being distinctive features of VE during exercise in COPD patients [17]. As a result, the slope of VE vs.VCO2 relationship might be elevated, normal or even low in patients with COPD and HF, regardless of the presence and of the severity of ventilatory inefficiency. Up to now, only few studies have evaluated the ventilatory behaviour during exercise in

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patients with coexisting HF and COPD, being patients with comorbidities usually excluded from research trials dedicated to HF or COPD [20].

In the present study, we evaluated HF patients and healthy individuals through a progressive workload exercise with different added DS, hoping to mimic at least in part the effects of COPD on ventilation behaviour during exercise. We hypothesized that increased serial DS upshifts the VE vs. $V_{CO_2}$ relationship and that the VE-axis intercept ($V_{EY_{int}}$) might be an index of DS ventilation. Indeed, since DS does not contribute to gas exchange, VE relative to DS is VE at $V_{CO_2} = 0$, i.e., $V_{EY_{int}}$ on the VE vs. $V_{CO_2}$ relationship.

Methods

Subjects
Ten HF patients and 10 healthy subjects were enrolled in the present study.

HF patients were regularly followed-up at our HF unit. Study inclusion criteria for HF patients were New York Heart Association functional classes (NYHA) I to III, echocardiographic evidence of reduced left ventricular systolic function (left ventricular ejection fraction $\leq 40\%$), optimized and individually tailored drug treatment, stable clinical conditions for at least 2 months, capability/willingness to perform a maximal or near maximal cardiopulmonary exercise test (CPET). Patients were excluded if they had obstructive and/or restrictive lung disease (forced expiratory volume in first second/forced vital capacity ratio $(FEV_1/FVC) < 0.70$, and/or lung vital capacity $(VC) < 80\%$ of predicted value [21]), clinical history and/or documentation of pulmonary embolism, primary valvular heart disease, pulmonary artery hypertension, pericardial disease, exercise-induced angina, ST changes, severe arrhythmias and significant cerebrovascular, renal, hepatic and haematological disease.

A group of age matched healthy subjects was recruited among the hospital staff and from the local community through personal contacts. Inclusion criteria were absence of history and/or clinical evidence of any cardiovascular or pulmonary or systemic disease contraindicating the test or modifying the functional response to exercise, any condition requiring daily medications, and the inability to adequately perform the procedures required by the protocol. No subjects were involved in physical activities other than recreational.

The investigation was approved by the local ethics committee (“Ethics committee Centro Cardiologico Fondazione Monzino”, Institutional Review Board no. S186/311) and all participants signed a written informed consent before enrolling in the study.

Study protocol

At enrolment, demographical and clinical data were collected, lung function measurements and echocardiographic evaluation were performed to verify that the subjects screened met the study inclusion/exclusion criteria, and the informed consent was obtained.

Spirometry (Vmax 29C, SensorMedics, Yorba Linda, CA, US) was performed by all participants in accordance with the recommended technique [22], and measurements were standardized as percentages of predicted normal values [23].

To become familiar with the procedure, both HF patients and healthy subjects had been previously trained to perform an exercise test in our laboratory [24]. Thereafter, on different days, following a random order, exercise testing was done with additional DS equal to 0 mL, 250 mL and 500 mL.

All participants underwent incremental CPET on an electronically braked cycle-ergometer (Ergometrics-800, SensorMedics, Yorba Linda, CA, US) using a personalized ramp protocol that was chosen aiming at a test duration of 10–2 minutes. The exercise was preceded by 5 minutes of rest gas exchange monitoring and by a 3-minute unloaded warm-up. A 12-lead ECG, blood pressure and heart rate were also recorded, and arterial oxygen saturation was monitored through a pulse oxymeter. The participants wore a nose clip and breathed through a mouthpiece connected to a mass flowmeter (Vmax 29C, SensorMedics, Yorba Linda, CA, US). Subjects were asked to cycle at a pedalling rate of 60-70 rpm, and CPET were self-terminated by the subjects when they claimed that maximal effort had been achieved. Oxygen consumption ($VO_2$), $V_{CO_2}$ and VE were measured breath by breath with flowmeter and respiratory gas sampling lines at the end of the added DS. They were averaged every 20 seconds. Anaerobic threshold (AT) was calculated with the standard technique [25]. All tests were executed and evaluated by 2 expert readers.

In the absence of psychogenic hyperventilation, below the respiratory compensation point [26], the relation between VE and $V_{CO_2}$ is characterized by a linear relationship ($VE = aV_{CO_2} + b$), with “$a$” as the slope and “$b$” as the intercept on the VE axis ($V_{EY_{int}}$) [8]. Since DS does not contribute to gas exchange, it is possible to hypothesize that the ventilation relative to DS is similar or related to the VE at $V_{CO_2} = 0$, which is the Y intercept of VE vs. $V_{CO_2}$ relationship. To calculate DS volume ($VD$) from $V_{EY_{int}}$ ($VD_{Y_{int}}$), we need to identify the corresponding respiratory rate (RR). This was obtained as the intercept of the RR vs. $V_{CO_2}$ relationship on the RR axis ($RR_{Y_{int}}$). Specifically, the RR vs. $V_{CO_2}$ relationship was calculated through its linear portion that starts from the beginning of exercise and ends when RR increases more steeply, which corresponds to the tidal volume inflection/plateau [27,28]. An example on how we calculate $V_{EY_{int}}$ and $RR_{Y_{int}}$ is reported in figure 1.

We compared estimated $VD$ values ($VD_{Y_{int}}$) with resting and exercise values of $VD$, measured with standard method [8] ($VD_{meas}$), in the 3 experimental conditions, with 0 mL, 250 mL and 500 mL of added DS. The volume of mouthpiece and flowmeter (50 mL) was subtracted from $VD$. The standard calculation of $VD$ [8] ($VD_{meas,0}$) is obtained by the following equation:

$$VD = VT*(1 - -(863 * VCO_2) / (VE * PaCO_2))$$

with 863 as a constant and $PaCO_2$ as pressure for arterial CO$_2$.

In healthy individuals [29], but not in HF patients [30], $P_{aCO_2}$ can be reliably estimated from end-tidal expiratory pressure for CO$_2$ ($P_{ET}CO_2$). Therefore, we measured $P_{aCO_2}$ from arterial gas sampling in HF patients, and we estimated $P_{aCO_2}$ from $P_{ET}CO_2$ in healthy subjects. Thus, only in HF patients, a small catheter was introduced into a radial artery, blood samples were obtained at rest and every 2 minutes during exercise, and $P_{aCO_2}$ was determined with a pH/blood gas analyzer (GEM 4000, Instrumentation Laboratory, Bedford, MA, US).

We calculated possible $VD$ changes during exercise, and we evaluated whether an added DS modifies the slope of the VE vs. $V_{CO_2}$ relationship and/or it simply upshifts it.

Statistical analysis

Data are mean ± standard deviation (SD). Cardiopulmonary measurements were collected breath by breath and reported as average over 20 s. Comparisons between the two groups were done through unpaired t-test. Both in HF and in healthy subjects,
analysis of variance for repeated measures with Bonferroni post hoc test was performed to analyze the effect of the adding of different DS and to evaluate the changes of VD meas during exercise in the 3 experimental conditions. Bland and Altman relationship was calculated to compare VDYint values and VDmeas values in HF patients and in healthy individuals.

Statistical significance was set at \( p < 0.05 \). All statistics were performed with IBM SPSS statistics 20.0 for windows.

Results

We enrolled 10 HF patients (9 males; mean age 61 ± 13 years) and 10 age-matched healthy subjects (8 males; mean age 59 ± 10 years). The main anthropometric data were not significantly different between the two groups. Patients with HF and healthy subjects were free from obstructive defects; although within the predicted normal limits, lung volumes tended to be smaller in HF patients than in normal subjects (table 1).

HF patients

Mean left ventricle ejection fraction was 33 ± 5%. The cause of HF was ischemic dilated cardiomyopathy in 4 cases and primary dilated cardiomyopathy in 6 cases. Three patients had an implantable cardioverter defibrillator; 9 were in sinus rhythm and 1 was in permanent atrial fibrillation. Four patients were in NYHA class I, 5 in NYHA class II and 1 in NYHA class III. All HF patients were on \( \beta \)-blockers, 9 with angiotensin-converting enzyme inhibitors, 4 with aldosterone receptor antagonists, 5 with diuretics and 3 with amiodarone.

All HF patients performed CPET without added DS and with 250 mL and 500 mL of additional DS without complications. In the HF group, peak VO\(_2\) was slightly reduced compared to healthy subjects. With the exception of reduced peak workload and of an increased VT, the adding of different DS did not significantly impact on CPET data at peak of exercise and on VO\(_2\) at AT (table 2). In table 3 VE, RR, VT, VD/VT, VCO\(_2\), P\(_{\text{ET}}\)CO\(_2\) and P\(_{\text{ET}}\)CO\(_2\) during exercise are reported with 0, 250 and 500 mL of added DS.

Values of VEYint, RRYint, VDYint, VDmeas and the slope of VE vs VCO\(_2\) relationship in HF patients with 0 mL, 250 mL and 500 mL of additional DS are reported in table 4.

With the adding of DS, the VEYint increased significantly, whereas RRYint showed a limited increase. Adding DS upshifted the VE vs. VCO\(_2\) relationship with a minor slope increase (figure 2).

The calculated VDYint rose as added DS increased; mean VDYint increase with 250 and 500 mL of added space was 226 ± 127 mL and 446 ± 123 mL. VDmeas increased during exercise in the 3 conditions albeit only as a trend when DS was not added (table 5).

Figure 3 reports the Bland and Altman plot of VDYint vs. VDmeas at rest for HF patients in the 3 exercise conditions. As an average, a good agreement was observed when VD was calculated either by VEYint or VDmeas, with or without additional DS.

Healthy subjects

Healthy subjects performed all CPET without complications. Peak exercise data and VO\(_2\) at AT were not significantly affected by the adding of DS (table 2).

When DS was added, the value of the slope of VE vs VCO\(_2\) relationship and RRYint did not change, whereas only the VEYint increased significantly (table 4) with an upshift of the relationship (figure 4). Similarly to HF patients, VDYint increased with added DS in the three experimental conditions, specifically by 300 ± 150 mL and by 570 ± 160 mL with 250 and 500 mL, respectively.

During exercise, VDmeas remained constant without additional DS, whereas it significantly decreased during exercise with added DS, but this finding is likely due to the underestimation of P\(_{\text{ET}}\)CO\(_2\) with added DS (table 5).

Figure 5 reports the Bland and Altman plot of VDYint vs. VDmeas at rest for healthy subjects and showed a good correlation between the two methods both with and without additional DS.

Discussion

In the present study, we evaluated a human model of increased dead space in HF patients and in healthy subjects, applying a progressive workload exercise with different added DS. We documented that a rise in serial DS, mimicking a rise in anatomical DS, was parallel to the VEYint increase both in healthy individuals and in HF patients. Therefore, VEYint is related to DS ventilation. Moreover, we showed that the value of DS can be non-invasively estimated as the ratio of VEYint/RRYint.

Few study limitations should be discussed at first. Firstly, our research was undertaken to analyze the role on ventilation behaviour during exercise of a respiratory comorbidity, COPD, in HF patients. We built a COPD model by adding an external dead space. We recognize that our model is only a partial COPD.
model because we have not considered any of the systemic consequences of COPD and we have limited our attention to DS changes. Our model was over-simplistic also as regards lung mechanics because an artificial dead space increase does not generate air trapping which is one of the most characteristic features of COPD during exercise. Secondly, our model was short lasting, so that chronic ventilatory and chemoreceptor adaptations to increased DS were not evaluated as were not evaluated

Table 1. Main anthropometric characteristics, demographical and pulmonary function data of heart failure patients and healthy subjects enrolled in the study.

|                           | HEART FAILURE PATIENTS | HEALTHY SUBJECTS | p value |
|---------------------------|------------------------|------------------|---------|
| Number                    | 10                     | 10               | NS      |
| Male/female               | 9/1                    | 8/2              | NS      |
| Age (yr)                  | 61 ± 12                | 59 ± 7           | NS      |
| Height (cm)               | 172 ± 9                | 173 ± 6          | NS      |
| Weight (Kg)               | 85 ± 15                | 77 ± 11          | NS      |
| BMI (Kg/m²)               | 28.6 ± 3.8             | 25.4 ± 3.2       | NS      |
| VC (L)                    | 3.58 ± 0.75            | 4.72 ± 1.03      | <0.01   |
| VC (% predicted)          | 91 ± 14                | 112 ± 13         | <0.01   |
| FVC (L)                   | 3.47 ± 0.67            | 4.63 ± 1.10      | <0.01   |
| FVC (% predicted)         | 90 ± 12                | 112 ± 14         | <0.01   |
| FEV₁ (L)                  | 2.56 ± 0.58            | 3.57 ± 0.84      | <0.001  |
| FEV₁ (% predicted)        | 79 ± 14                | 107 ± 17         | <0.001  |
| FEV₁/FVC                  | 73 ± 4                 | 76 ± 5           | NS      |

Data are presented as number or mean ± SD. BMI = body mass index; NS = not significant; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; VC = vital capacity.

Table 2. Cardiopulmonary exercise testing data in heart failure patients (upper panel) and healthy subjects (lower panel) with 0 mL, 250 mL and 500 mL of additional dead space.

|                           | ADDED DEAD SPACE | ANOVA p value |
|---------------------------|-----------------|---------------|
|                           | +0 mL           | +250 mL       | +500 mL     |
| Peak workload (W)         | 109 ± 41*       | 103 ± 47      | 96 ± 41     | 0.006    |
| Peak VO₂ (ml/min/Kg)      | 19.9 ± 5.8      | 19.3 ± 5.6    | 19.6 ± 5    | NS       |
| VO₂ at AT (ml/min/Kg)     | 13 ± 3          | 14 ± 1        | 12.7 ± 5.8  | NS       |
| Peak O₂ pulse (ml/beat)   | 15.8 ± 5.7      | 15.4 ± 5.2    | 15.7 ± 4.8  | NS       |
| Peak HR (beat/min)        | 111 ± 26        | 110 ± 28      | 104 ± 20    | NS       |
| Peak VT (L)               | 1.9 ± 0.49      | 1.93 ± 0.49⁵  | 2.09 ± 0.59 | 0.047    |
| Peak VE (L/min)           | 55.6 ± 14       | 59.8 ± 14     | 58.8 ± 11   | NS       |
| Peak RR (bpm)             | 30 ± 4          | 31 ± 5        | 30 ± 5      | NS       |
| Peak PaO₂ (mmHg)          | 107 ± 12        | 104 ± 16      | 100 ± 20    | NS       |
| Peak SaO₂ (L/min)         | 98.4 ± 1.2      | 97.5 ± 1.9    | 97.7 ± 1.7  | NS       |

Data are presented as means ± SD; AT = anaerobic threshold; bpm = breaths per minute; HR = heart rate; NS = not significant; PaO₂ = arterial oxygen pressure; RR = respiratory rate; SₐO₂ = arterial oxygen saturation; VE = ventilation; VT = tidal volume; W = watt.

¹p < 0.05 versus +500 mL; ⁵p = 0.01 versus +500 mL.

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primitive chemoreceptor abnormalities as drivers of the alveolar hypoventilation observed in COPD patients. Thirdly, with the Y-intercept we analyze an index of overall DS. However, in the present study, we were able to change DS only by adding an external (anatomical equivalent) DS, so that we do not know if added DS signifi- cantly reduced the external work produced in HF patients; while a not significant reduction was observed in normal subjects.

Table 3. Ventilatory parameters in heart failure patients with 0, 250 and 500 mL of additional dead space.

| HF PATIENTS | +0 mL | +250 mL | +500 mL | ANOVA p value |
|-------------|-------|---------|---------|---------------|
| **Rest**    |       |         |         |               |
| VE (L/min)  | 11.8 ± 1.7 | 16.2 ± 3.5 | 20.0 ± 4.2 | <0.001 |
| RR (bpm)    | 14.2 ± 2.0 | 16.4 ± 4.1 | 16.8 ± 3.1 | NS |
| VT (L)      | 0.8 ± 0.2 | 1.0 ± 0.2 | 1.2 ± 0.1 | <0.001 |
| VD/VT       | 0.47 ± 0.15 | 0.61 ± 0.10 | 0.67 ± 0.11 | <0.001 |
| VCO2 (L/min)| 0.25 ± 0.06 | 0.29 ± 0.13 | 0.29 ± 0.14 | NS |
| P2CO2 (mmHg)| 33.4 ± 1.6 | 33.0 ± 2.5 | 33.1 ± 4.2 | NS |
| P5CO2 (mmHg)| 35.8 ± 2.2 | 38.6 ± 1.9 | 39.9 ± 2.02 | <0.001 |
| **4 min exercise** | | | | |
| VE (L/min)  | 21.6 ± 3.8 | 30.2 ± 5.0 | 34.8 ± 4.3 | <0.001 |
| RR (bpm)    | 18.7 ± 2.7 | 20.4 ± 4.3 | 20.7 ± 4.1 | NS |
| VT (L)      | 1.2 ± 0.2 | 1.5 ± 0.3 | 1.7 ± 0.3 | <0.001 |
| VD/VT       | 0.33 ± 0.09 | 0.45 ± 0.06 | 0.54 ± 0.10 | <0.001 |
| VCO2 (L/min)| 0.64 ± 0.15 | 0.74 ± 0.17 | 0.73 ± 0.21 | NS |
| P2CO2 (mmHg)| 37.2 ± 2.9 | 35.7 ± 3.6 | 37.4 ± 4.2 | NS |
| P5CO2 (mmHg)| 38.4 ± 2.8 | 38.8 ± 3.4 | 41.2 ± 3.9 | NS |
| **8 min exercise** | | | | |
| VE (L/min)  | 39.9 ± 5.9 | 44.5 ± 4.8 | 52.4 ± 8.4 | <0.001 |
| RR (bpm)    | 25.1 ± 3.2 | 25.3 ± 5.2 | 26.8 ± 4.6 | NS |
| VT (L)      | 1.6 ± 0.3 | 1.8 ± 0.4 | 2.0 ± 0.5 | NS |
| VD/VT       | 0.28 ± 0.06 | 0.41 ± 0.07 | 0.46 ± 0.09 | <0.001 |
| VCO2 (L/min)| 1.28 ± 0.35 | 1.27 ± 0.29 | 1.34 ± 0.35 | NS |
| P2CO2 (mmHg)| 37.2 ± 4.3 | 36.8 ± 4.6 | 38.5 ± 4.2 | NS |
| P5CO2 (mmHg)| 38.0 ± 3.7 | 39.4 ± 4.2 | 41.4 ± 4.6 | NS |
| **peak exercise** | | | | |
| VE (L/min)  | 55.7 ± 14.0 | 59.9 ± 14.6 | 58.9 ± 11.3 | NS |
| RR (bpm)    | 30.3 ± 4.7 | 31.4 ± 4.0 | 29.8 ± 5.0 | NS |
| VT (L)      | 1.9 ± 0.5 | 1.9 ± 0.5 | 2.1 ± 0.6 | NS |
| VD/VT       | 0.26 ± 0.11 | 0.39 ± 0.10 | 0.45 ± 0.11 | <0.001 |
| VCO2 (L/min)| 1.81 ± 0.67 | 1.72 ± 0.68 | 1.58 ± 0.55 | NS |
| P2CO2 (mmHg)| 35.4 ± 4.5 | 35.64 ± 4.8 | 39.0 ± 4.9 | NS |
| P5CO2 (mmHg)| 35.8 ± 3.8 | 38.0 ± 4.2 | 41.3 ± 5.5 | 0.049 |

Data are presented as means ± SD; VE = ventilation; RR = respiratory rate; VT = tidal volume; VD = dead space volume; VCO2 = carbon dioxide production; P2CO2 = arterial carbon dioxide pressure; P5CO2 = End-tidal carbon dioxide pressure; bpm = breaths per minute;

f: p<0.05 vs. 250 mL; g: p<0.001 vs. 500 mL; h: p<0.001 vs. 250 mL; i: p<0.01 vs. 250 mL; j: p<0.01 vs. 250 mL.

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Estimation of Dead Space Ventilation
Table 4. Values of the slope of VE vs VCO₂ relationship, VE_{int}, RR_{int} and volume of dead space in heart failure patients (upper panel) and healthy subjects (lower panel) with 0 mL, 250 mL and 500 mL of additional dead space.

|                | HEART FAILURE PATIENTS | ADDED DEAD SPACE | ANOVA p value |
|----------------|------------------------|------------------|---------------|
|                | +0 mL | +250 mL | +500 mL |
| VE/VCO₂ slope | 27±6  | 28±5   | 29±6   | 0.037 |
| VE_{int} (L/min) | 1.63±*   | 9.69±2.91* | 13.26±3.18 | 0.000 |
| RR_{int} (bpm) | 13±6   | 15±3   | 16±3   | 0.032 |
| VD_{int} (L)   | 0.39±0.07* | 0.61±0.12* | 0.83±0.11 | 0.000 |
| VD_{max} (L)   | 0.38±0.08* | 0.61±0.12* | 0.80±0.09 | 0.000 |

HEALTHY SUBJECTS

|                | +0 mL | +250 mL | +500 mL |
|----------------|--------|---------|---------|
| VE/VCO₂ slope | 23±3   | 24±4    | 24±4    | NS     |
| VE_{int} (L/min) | 4.9±1.4* | 9.3±2.4* | 13.1±3.04 | 0.000 |
| RR_{int} (bpm) | 14±4   | 14±4    | 14±3    | NS     |
| VD_{int} (L)   | 0.37±0.11* | 0.68±0.15* | 0.95±0.14 | 0.000 |
| VD_{max} (L)   | 0.37±0.06* | 0.68±0.11* | 0.94±0.1 | 0.000 |

Data are presented as means ± SD; RR_{int} = respiratory rate calculated as Y intercept of RR vs VCO₂ relationship; VCO₂ = carbon dioxide production; VD_{int} = dead space volume calculated as VE_{int}/RR_{int}; VD_{max} = dead space volume measured by P_{a}CO₂ in heart failure patients and estimated by P_{ET}CO₂ in healthy subjects; VE = ventilation; VE_{int} = ventilation at VCO₂ = 0, calculated as Y intercept of VE vs VCO₂ relationship.

*p < 0.001 versus +250 mL;
* p < 0.01 versus +500 mL;
* p < 0.05 versus +250 mL;
* p < 0.05 versus +500 mL;
* p < 0.01 versus +250 mL.

Figure 2. VE vs. VCO₂ relationship in heart failure patients with 0 mL (black line), 250 mL (grey line) and 500 mL (dotted line) of additional dead space (DS). The adding of DS uplifts the VE vs. VCO₂ relationship with a minor slope increase. † p < 0.001 versus +250 mL; ‡ p < 0.001 versus +500 mL; * p < 0.01 versus +500 mL; † p < 0.05 versus other all.

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We measured DS during exercise using a standard formula [8] in HF patients. To avoid systemic artery catheterization, we estimated PaCO₂ from PETCO₂ in healthy subjects, which is an accepted method in the absence of lung disease [29]. It is recognized, however, that albeit largely used in the clinical setting, extrapolation of PaCO₂ from PETCO₂ even in normal individuals is approximate and likely to cause some of the variability observed (figure 5). Moreover, the values obtained in normal subjects with added DS showed a progressive and unrealistic DS reduction. This is due to a PaCO₂ underestimation by PETCO₂ when adding DS, confirming the need to directly measure PaCO₂ during exercise for DS evaluation [30]. The low PETCO₂ compared to PaCO₂ observed during exercise with added dead space (Table 3) is likely due to the rapid rise of PCO₂ during exhalation, which does not reach a plateau.

Adding DS increased the slope of VE vs. VCO₂ relationship in HF patients but not in control subjects. This is different from what happens in patients with severe COPD who show a high VE/VCO₂ ratio at the beginning of exercise but a blunted VE increase during exercise, so that the slope of VE vs. VCO₂ relationship is normal or low [2]. In our model, the DS increase was too modest to generate a ventilatory limitation to exercise, being the ventilatory reserve at peak exercise always preserved. Accordingly, in HF patients, but not in healthy subjects, we observed a minor exercise performance reduction with the adding of DS.

Table 5. Values of volume of dead space at rest and during exercise in heart failure patients and healthy subjects with no additional dead space and with 250 mL and 500 mL of additional dead space.

|               | +0 mL | +250 mL | +500 mL |
|---------------|-------|---------|---------|
|                | HF    | H       | HF      | H       |
| VD_{measure}  | rest (L) | 0.38 ± 0.08 | 0.37 ± 0.06 | 0.61* ± 0.12 | 0.68** ± 0.11 | 0.80* ± 0.09 | 0.94** ± 0.10 |
| VD_{measure}  | 2' (L) | 0.38 ± 0.07 | 0.36 ± 0.04 | 0.63* ± 0.07 | 0.57 ± 0.13 | 0.87 ± 0.08 | 0.70 ± 0.17 |
| VD_{measure}  | 4' (L) | 0.39 ± 0.08 | 0.34 ± 0.05 | 0.68* ± 0.11 | 0.56 ± 0.09 | 0.91 ± 0.09 | 0.67 ± 0.16 |
| VD_{measure}  | 6' (L) | 0.43 ± 0.09 | 0.36 ± 0.08 | 0.71 ± 0.13 | 0.51 ± 0.09 | 0.92 ± 0.15 | 0.62 ± 0.15 |
| VD_{measure}  | 8' (L) | 0.43 ± 0.09 | 0.32 ± 0.08 | 0.73* ± 0.11 | 0.48 ± 0.12 | 0.90 ± 0.14 | 0.57 ± 0.12 |
| VD_{measure}  | peak (L) | 0.45 ± 0.18 | 0.31 ± 0.11 | 0.71* ± 0.13 | 0.44 ± 0.08 | 0.90 ± 0.13 | 0.55 ± 0.12 |
| p value       | NS    | NS      | 0.001   | 0.001   | 0.05    | 0.001   |

Data are presented as means ± SD; DS = dead space; H = healthy subjects; HF = heart failure patients; NS = not significant; VD_{measure} = dead space volume calculated as VE/RR_{int}; VD_{int} = dead space volume measured by P_{a}CO₂ in heart failure patients and estimated by P_{E}CO₂ in healthy subjects. *p < 0.001 versus VD_{measure} 6; **p < 0.05 versus VD_{measure} 6; *p < 0.05 versus VD_{measure} 8; †p < 0.01 versus VD_{measure} peak; ‡p < 0.001 versus VD_{measure} 2; ‡p < 0.001 versus VD_{measure} 4; ‡p < 0.001 versus VD_{measure} 8; ‡p < 0.001 versus VD_{measure} peak.

Figure 3. Bland and Altman plot of estimated dead space (DS) volume calculated as VE/RR_{int} (VD_{int}) and measured DS volume (VD_{measure}) at rest, calculated as (1 – 863/P_{a}CO₂(VE/VCO₂)VT) for heart failure patients with 0 mL (diamonds), 250 mL (circles) and 500 mL (crosses) of additional DS. The grey line identifies the mean difference of VD_{measure} - VD_{int}; the black lines identify the mean difference of VD_{measure} - and VD_{int} ± 1.96*standard deviation. P_{a}CO₂ = arterial carbon dioxide pressure; VE = ventilation; VT = tidal volume.

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to analyze the ratio of the relationship [31], others the slope [32]. However, the ratio varies during exercise, so that which exercise VE/VCO₂ ratio value should be considered is still a matter of debate [31]. Moreover, while the behaviour of VE/VCO₂ ratio during exercise is well described in normal and HF individuals [31], its behaviour in COPD or in patients with HF and COPD is less characteristic and not used as a diagnostics/prognostic tool. To avoid the above-mentioned uncertainties, many authors prefer to study the VE vs. VCO₂ relationship throughout the exercise [33] or up to the respiratory compensation point [8]. To do so, the slope of the VE vs. VCO₂ relationship is calculated, but no attention is dedicated to the intercept of this relationship on the VE axis. However, the increase of the slope of VE vs. VCO₂ relationship may be blunted when COPD is associated to HF [2]. Notably, the presence of COPD in HF may be difficult to be defined because some lung impairment is typical of HF and particularly in more advanced cases regardless of COPD [5]. In the present study, we showed that a DS increase is parallel to the VE₂ increase, so that its value should be taken into account when analyzing the VE vs. VCO₂ relationship. Indeed, VE₂ increase were observed even by adding a relatively small DS (250 mL) which corresponded to 1/10 of peak VT in healthy subjects. It is recognized, however, that whilst the means of estimated and measured VD are similar, the individual values differ up to 60% in case of no added DS and up to ~20% when 500 mL DS were added. This suggests caution when analyzing specific individual data, particularly in the presence of no or modest lung disease.

In the present study, we added 250 mL and 500 mL of DS during exercise. To confirm that VE₂ increase was related to DS increase, we calculated VD. To do so, we need to divide VE by RR, but the value of RR to be chosen is an open question. We used the intercept of the RR vs. VCO₂ relationship on the RR axis because this is the RR value corresponding to VE₂. Interestingly, the changes of VE₂ values with added DS were very similar to the amount of added DS.

In conclusion, we provide the rational basis for the assessment of VE₂ during exercise as a tool to evaluate DS. Further studies are needed to confirm and to analyze the clinical meaning of the present observation.

Figure 4. VE vs. VCO₂ relationship in healthy subjects with 0 mL (black line), 250 mL (grey line) and 500 mL (dotted line) of additional dead space (DS). The adding of DS upshifts the VE vs VCO₂ relationship without significant slope changes. † p<0.001 versus +250 mL; § p<0.001 versus +500 mL. doi:10.1371/journal.pone.0087395.g004

Figure 5. Bland and Altman plot of estimated dead space (DS) volume calculated as VE₂/RR (VD) and measured DS volume (VD) at rest, calculated as (1–863/P aCO₂(V/E/VCO₂)/VT) with P aCO₂ for healthy subjects with 0 mL (diamonds), 250 mL (circles) and 500 mL (crosses) of additional DS. The grey line identifies the mean difference of VD− and VD; the black lines identify the mean difference of VD− and VD; standard deviation. P aCO₂ was estimated from PETCO₂. P aCO₂ = carbon dioxide pressure; PETCO₂ = tele-expiratory carbon dioxide pressure; VE = ventilation; VT = tidal volume. doi:10.1371/journal.pone.0087395.g005
At a Glance Commentary

The ventilation (VE) vs. VCO₂ relationship during exercise is commonly used to assess ventilatory efficiency and prognosis in heart failure patients. The slope of the VE vs. VCO₂ relationship increases as heart failure severity increases, whereas in respiratory patients the VE vs. VCO₂ slope during exercise is reduced by the greater the ventilatory limitation. However, respiratory disease often coexists in heart failure patients so that the mean of the slope of the VE vs. VCO₂ relationship in these cases is unclear. We reasoned that the VE vs. VCO₂ behavior during exercise is a linear relationship, at least up to the respiratory compensation point. Furthermore, VE vs. VCO₂ slope is characterized by a slope and a Y intercept value. The latter has been ignored, but it represents the ventilation at VCO₂ = 0 and therefore is somehow related to dead space ventilation. Accordingly, we built a human model of increased anatomical dead space, resembling what happens in chronic obstructive pulmonary disease, by adding external dead space during exercise in healthy subjects and HF patients. We demonstrated that adding dead space increases the Y intercept of the VE vs. VCO₂ relationship. The Y intercept of VE vs. VCO₂ relationship is suggested as an index of increased dead space ventilation so that the finding of a elevated Y-intercept in a heart failure patient should bring the suspicion of a coexisting respiratory disease.

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Author Contributions

Conceived and designed the experiments: PA. Performed the experiments: PG AA. Analyzed the data: PG PA. Contributed reagents/materials/analysis tools: PG AA. Wrote the paper: PG AA PPF SS PP.

References

1. Metra M, Deti Gas I. (1996) Role of exercise ventilation in the limitation of functional capacity in patients with congestive heart failure. Basic Res Cardiol 91 Suppl 1: 31–36.
2. Paoletti P, De Filippis F, Fraioli F, Cinquanta A, Vally G, et al. (2011) Cardiopulmonary exercise testing (CPET) in pulmonary emphysema. Respir Physiol Neurobiol 179: 167–175.
3. Pierce AK, Luerman D, Loutardmekl J, Blomqvist G, Johnson RL, Jr (1968) Exercise ventilatory patterns in normal subjects and patients with airway obstruction. J Appl Physiol 25: 249–254.
4. Teopompi E, Tzani P, Aiello M, Ramponi S, Visca D, et al. (2013) Ventilatory Response to Carbon Dioxide Output in Patients with Chronic Heart Failure and in Patients with Chronic Obstructive Pulmonary Disease with Comparable Exercise Capacity. Respir Care.
5. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, et al. (2007) Impairment of ventilatory efficiency in heart failure: effects of physical training. Circulation 93: 940–952.
6. Wasserman K, Hansen JE, Sue DY, Stringer WW, Siestema KF, et al. (1973) Lung function and exercise gas exchange in chronic heart failure. Circulation 49: 2221–2227.
7. Chua TP, Harrington D, Poskowksi P, Webb-Plpeck P, Pool-Wilson PA, et al. (1997) Effects of dihydroecine on chemosensitivity and exercise tolerance in patients with chronic heart failure. Am J Coll Cardiol 29: 147–152.
8. Piepoli M, Clark AK, Volterman M, Adamopoulos S, Sibbit P, et al. (1996) Contribution of muscle alacters to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. Circulation 93: 940–952.
9. Wasserman K, Hansen JE, Sue DY, Stringer WW, Siestema KF, et al. (1973) Principles of exercise testing and interpretation. 2nd ed. Lippincott Williams & Wilkins.
10. Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A, et al. (2002) Cardiopulmonary exercise testing and ventilation in patients with heart failure and chronic obstructive pulmonary disease. Med Clin North Am 86: 525–547.
11. Rutten FF, Cramer MJ, Lammers JW, Grobbe DE, Hoes AW (2006) Heart failure and chronic obstructive pulmonary disease: An ignored combination? Eur J Heart Fail 8: 706–711.
12. Hawkins NM, Wang D, Petrie MC, Pfeifer MA, Swedberg K, et al. (2010) Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. Eur J Heart Fail 12: 557–565.
13. Guazzi M, Myers J, Vicenz J, Bensimon D, Chase P, et al. (2010) Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant obstructive pulmonary disease. Am Heart J 160: 900–905.
14. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, et al. (2007) Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 147: 633–636.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburo R, et al. (2005) Standardization of spirometry. Eur Respir J 26: 319–338.
16. Quinjeh PH, Tammelung GJ, Cotes JE, Pederson OF, Pedon R, et al. (1993) Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests. European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 16: 5–40.
17. Elborn JS, Stanford CF, Nicholls DP (1996) Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test. Eur Heart J 11: 75–81.
18. Treasure WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60: 2020–2027.
19. Whipp BJ, Davis JA, Wasserman K (1989) Ventilatory control of the ‘isocapnic buffering’ region in rapidly-incremental exercise. Respir Physiol 76: 357–367.
20. Lavezziana P, O’Donnell DJ, O’Nur D, Agostoni P, Padeleti L, et al. (2009) Effect of biometric pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. J Appl Physiol 106: 1547–1553.
21. Lavezziana P, Webb KA, Ora J, Wadell K, O’Donnell DE (2011) Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. Am J Respir Crit Care Med 184: 1367–1373.
22. Robbins PA, Conway J, Cunningham DA, Khamnei S, Paterson DJ (1990) A comparison of indirect methods for continuous estimation of arterial PCO₂ in men. J Appl Physiol 68: 1271–1275.
23. Kusner DJ, Galantucci J, Nazzari M, Messini E, Visca D, et al. (2010) Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 182: 1367–1373.