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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. VCO_2 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 $VCO_2 = 0$, 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. VCO_2 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.VCO_2 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 = 9.3±2.4; +500 = 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.

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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 (CO_2) [5] generated by the lactate is trivial relative to the rate of metabolic CO_2 production (VCO_2) [6,7]. The relationship between VE and VCO_2 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. VCO_2 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. VCO_2 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.VCO_2 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

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. VCO_2 relationship and that the VE-axis intercept (VE_{Yinter}) might be an index of DS ventilation. Indeed, since DS does not contribute to gas exchange, VE relative to DS is VE at $VCO_2 = 0$, i.e., VE_{Yint} on the VE vs. VCO_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$\pm$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), VCO_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 VCO_2 is characterized by a linear relationship ($VE = aVCO_2 + b$), with ''a'' as the slope and ''b'' as the intercept on the VE axis (VE_{Yint}) [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 $VCO_2 = 0$, which is the Y intercept of VE vs. VCO_2 relationship. To calculate DS volume (VD) from VE_{Yint} (VD_{Yint}), we need to identify the corresponding respiratory rate (RR). This was obtained as the intercept of the RR vs. VCO_2 relationship on the RR axis (RR_{Yint}). Specifically, the RR vs. VCO_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 VE_{Yint} and RR_{Yint} is reported in figure 1.

We compared estimated VD values (VD_{Yint}) 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}) is obtained by the following equation:

$$VD = VT * [1 - -(863 * VCO2)/(VE * PaCO2)]$$

with 863 as a constant and P_aCO_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. VCO_2 relationship and/or it simply upshifts it.

Statistical analysis

Data are mean $\pm$ 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,

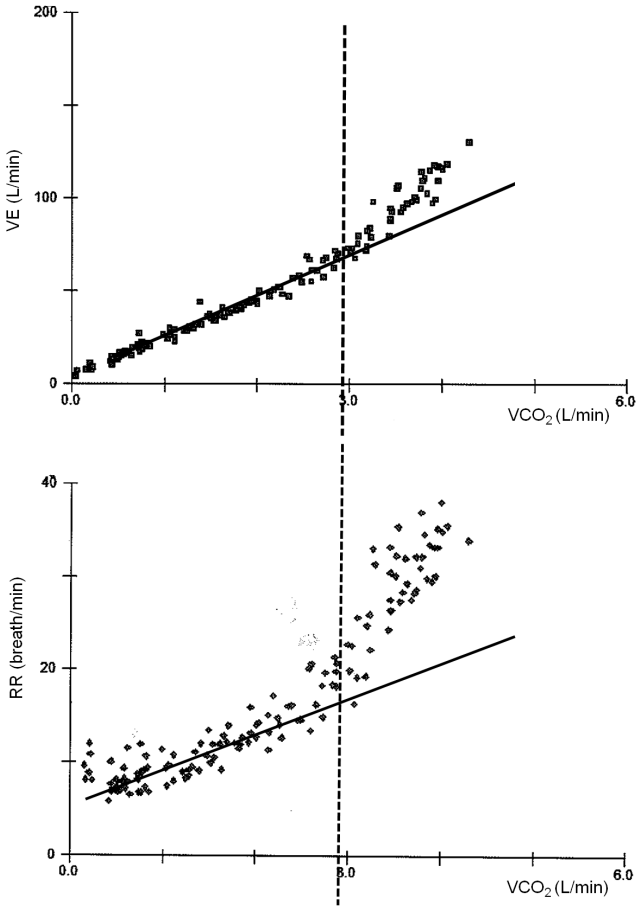

Figure 1. VE vs. VCO_2 relationship in a patient. The relationship is linear up to the respiratory compensation point (end of the isocapnic buffering period) (Upper panel). RR vs. VCO2 relationship. The relationship is calculated as for VE vs. VCO_2 (Lower panel).
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analysis 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 VD_{Yint} values and VD_{meas} 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 β-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, $P_{ET}CO_2$ and P_aCO_2 during exercise are reported with 0, 250 and 500 mL of added DS.

Values of VE_{Yint}, RR_{Yint}, VD_{Yint}, VD_{meas} 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 VE_{Yint} increased significantly, whereas RR_{Yint} showed a limited increase. Adding DS upshifted the VE vs. VCO_2 relationship with a minor slope increase (figure 2).

The calculated VD_{Yint} rose as added DS increased; mean VD_{Yint} increase with 250 and 500 mL of added space was 226±127 mL and 446±123 mL. VD_{meas} 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 VD_{Yint} vs. VD_{meas} at rest for HF patients in the 3 exercise conditions. As an average, a good agreement was observed when VD was calculated either by VE_{Yint}, or VD_{meas}, 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 RR_{Yint} did not change, whereas only the VE_{Yint} increased significantly (table 4) with an upshift of the relationship (figure 4). Similarly to HF patients, VD_{Yint} 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, VD_{meas} 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_aCO_2 by $P_{ET}CO_2$ with added DS (table 5).

Figure 5 reports the Bland and Altman plot of VD_{Yint} vs. VD_{meas} 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 VE_{Yint} increase both in healthy individuals and in HF patients. Therefore, VE_{Yint} is related to DS ventilation. Moreover, we showed that the value of DS can be non-invasively estimated as the ratio of VE_{Yint}/RR_{Yint}.

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

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/m^2)	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
FEV_1 (L)	2.56±0.58	3.57±0.84	<0.001
FEV_1 (% predicted)	79±14	107±17	<0.001
FEV_1/FVC	73±4	76±5	NS

Data are presented as number or mean ± SD. **BMI** = body mass index; **NS** = not significant; **FEV_1** = forced expiratory volume in 1 s; **FVC** = forced vital capacity; **VC** = vital capacity.

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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 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.

HEART FAILURE PATIENTS	ADDED DEAD SPACE			ANOVA p value
	+0 mL	+250 mL	+500 mL	
Peak workload (W)	109±41*	103±47	96±41	0.006
Peak VO_2 (mL/min/Kg)	19.9±5.8	19.3±5.6	19.6±5	NS
VO_2 at AT (mL/min/Kg)	13±3	14.1±4	12.7±5.8	NS
Peak O_2 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±0.49$^{\$}$	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 PaO_2 (mmHg)	107±12	104±16	100±20	NS
Peak SaO_2 (L/min)	98.4±1.2	97.5±1.9	97.7±1.7	NS
HEALTHY SUBJECTS				
Peak workload (W)	200±51	195±51	189±45	NS
Peak VO_2 (mL/min/Kg)	36.1±8.4	35.6±7.2	35.8±7.5	NS
VO_2 at AT (mL/min/Kg)	21.7±5.7	23.6±3.7	25.3±6.6	NS
Peak O_2 pulse (mL/beat)	17.5±4.2	17±2.9	18.4±3.4	NS
Peak HR (beat/min)	156±18	157±18	156±18	NS
Peak VT (L)	2.71±0.6	2.57±0.9	2.95±0.5	NS
Peak VE (L/min)	88.6±21.9	87.2±16.2	88.6±17.1	NS
Peak RR (bpm)	32±4	32±6	30±5	NS

Data are presented as means ± SD; **AT** = anaerobic threshold; **bpm** = breaths per minute; **HR** = heart rate; **NS** = not significant; **P_aO_2** = arterial oxygen pressure; **RR** = respiratory rate; S_aO_2 = arterial oxygen saturation; **RR** = respiratory rate; **VO_2** = oxygen consumption; **VE** = ventilation; **VT** = tidal volume; **W** = watt.

$^{\$}p<0.05$ versus +500 mL; * $p<0.01$ versus +500 mL.

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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$^{\$\mu}$	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
VCO_2 (L/min)	0.25 ± 0.06	0.29 ± 0.13	0.29 ± 0.14	NS
$P_{ET}CO_2$ (mmHg)	33.4 ± 1.6	33.0 ± 2.5	33.1 ± 4.2	NS
P_aCO_2 (mmHg)	35.8 ± 2.2$^{\$\mu}$	38.6 ± 1.9	39.9 ± 2.02	<0.001
4 min exercise				
VE (L/min)	21.6 ± 3.8$\mu^{\#}$	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$^{\$\mu}$	0.45 ± 0.06	0.54 ± 0.10	<0.001
VCO_2 (L/min)	0.64 ± 0.15	0.74 ± 0.17	0.73 ± 0.21	NS
$P_{ET}CO_2$ (mmHg)	37.2 ± 2.9	35.7 ± 3.6	37.4 ± 4.2	NS
P_aCO_2 (mmHg)	38.4 ± 2.8	38.8 ± 3.4	41.2 ± 3.9	NS
8 min exercise				
VE (L/min)	39.9 ± 5.9$^{\mu}$	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$^{\mu\#}$	0.41 ± 0.07	0.46 ± 0.09	<0.001
VCO_2 (L/min)	1.28 ± 0.35	1.27 ± 0.29	1.34 ± 0.35	NS
$P_{ET}CO_2$ (mmHg)	37.2 ± 4.3	36.8 ± 4.6	38.5 ± 4.2	NS
P_aCO_2 (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*$^{\mu}$	0.39 ± 0.10	0.45 ± 0.11	<0.001
VCO_2 (L/min)	1.81 ± 0.67	1.72 ± 0.68	1.58 ± 0.55	NS
$P_{ET}CO_2$ (mmHg)	35.4 ± 4.5	35.64 ± 4.8	39.0 ± 4.9	NS
P_aCO_2 (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; **VCO_2** = carbon dioxide production; **P_aCO_2** = arterial carbon dioxide pressure; **$P_{ET}CO_2$** = End-tidal carbon dioxide pressure; **bpm** = breaths per minute;
$^{\$}$: p<0.05 vs. 250 mL; $^{\mu}$: p<0.001 vs. 500 mL; *: p<0.001 vs. 250 mL; $^{\&}$: p<0.01 vs.500 mL; $^{\#}$<0.01 vs. 250 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 setting, we were able to change DS only by adding an external (anatomical equivalent) DS, so that we do not know if changes in physiological DS similarly influence the VE_{Yint}. Fourthly, VE changes during exercise are due to VCO_2, VD/VT and P_aCO_2 changes, and all may influence the VE vs. VCO_2 relationship. In the present study, we added external DS, which at each step of exercise, was associated to an increase of VD/VT and P_aCO_2 (the latter in 2 steps only as a trend) resembling what happens during exercise in COPD patients (table 3). Therefore both P_aCO_2 and VD/VT changes have likely a role in the VE vs. VCO_2 relationship changes we observed after adding DS. It is recognized that P_aCO_2 measurements were done only in HF patients and not in healthy subjects, but a different behaviour in healthy subjects is unlikely. Fifthly, the condition of VE at CO_2 production equal 0, as such at the VE_{Yint} of the VE vs. VCO_2 relationship, is a mathematical extrapolation with no physiological meaning. Moreover, absolute DS changes during exercise, so that also the VE_{Yint} value is likely close but different from the rest value. Indeed, we showed that VD tended to increase in HF patients and to reduce in healthy subjects during exercise without added DS. However, we suggest using VE_{Yint} as a tool to evaluate the presence of an increased DS, regardless of its physiological meaning with respect to rest and exercise. The adding of DS significantly reduced the external work produced in HF patients, while a not significant reduction was observed in normal subjects. Peak VO_2 remained unchanged in both groups after adding DS; this finding suggests that added DS was associated to an increased work of breathing which, as a percentage of total work, seems to be greater in HF patients than in normal subjects.

Table 4. Values of the slope of VE vs VCO_2 relationship, VE_{Yint}, RR_{Yint} 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/VCO_2 slope	27±4	28±5	29±4	0.037
VE_{Yint} (L/min)	4.98±1.63†§	9.69±2.91*	13.26±3.18	0.000
RR_{Yint} (bpm)	13±4$^{\&\$}$	15±3	16±3	0.032
VD_{Yint} (L)	0.39±0.07$^{©\S}$	0.61±0.12§	0.83±0.11	0.000
VD_{meas} (L)	0.38±0.08$^{©\S}$	0.61±0.12§	0.80±0.09	0.000
HEALTHY SUBJECTS				
VE/VCO_2 slope	23±3	24±4	24±4	NS
VE_{Yint} (L/min)	4.9±1.4†§	9.3±2.4§	13.1±3.04	0.000
RR_{Yint} (bpm)	14±4	14±4	14±3	NS
VD_{Yint} (L)	0.37±0.11$^{©\S}$	0.68±0.15§	0.95±0.14	0.000
VD_{meas} (L)	0.37±0.06$^{©\S}$	0.68±0.11*	0.94±0.1	0.000

Data are presented as means ± SD; **RR_{Yint}** = respiratory rate calculated as Y intercept of RR vs VCO_2 relationship; **VCO_2** = carbon dioxide production; **VD_{Yint}** = dead space volume calculated as VE_{Yint}/RR_{Yint}; **VD_{meas}** = dead space volume measured by P_aCO_2 in heart failure patients and estimated by $P_{ET}CO_2$ in healthy subjects; **VE** = ventilation; **VE_{Yint}** = ventilation at $VCO_2 = 0$, calculated as Y intercept of VE vs VCO_2 relationship.
$^{\dagger}p<0.001$ versus +250 mL;
$^{\S}p<0.001$ versus +500 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.
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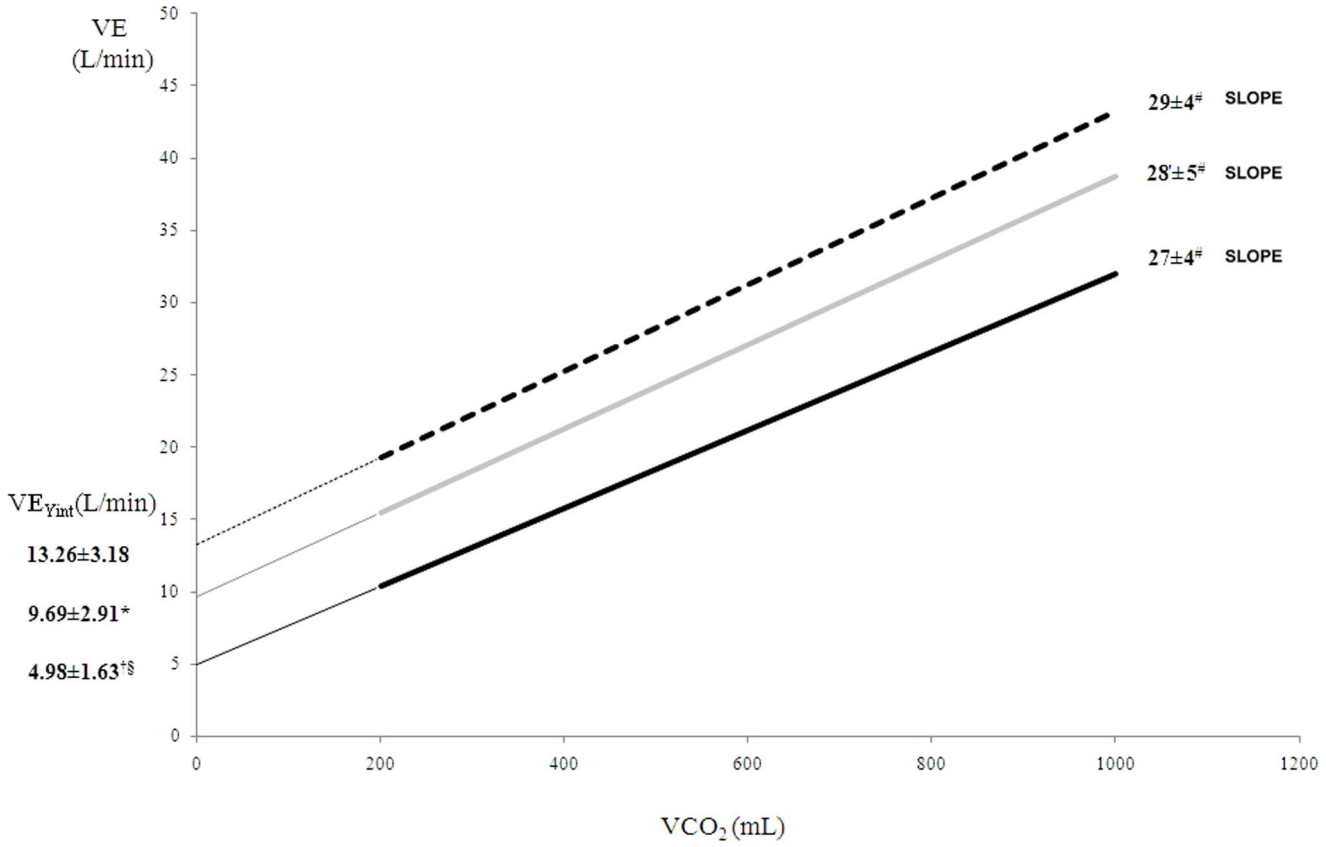

Figure 2. VE vs. VCO_2 relationship in heart failure patients with 0 mL (black line), 250 mL (grey line) and 500 mL (dotted line) of additional dead space (DS). The adding of DS uplifts the VE vs. VCO_2 relationship with a minor slope increase. † $p<0.001$ versus +250 mL; § $p<0.001$ versus +500 mL; * $p<0.01$ versus +500 mL; # $p<0.05$ versus other all.
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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**	**HF**	**H**
VD_{meas} rest (L)	0.38 ± 0.08	0.37 ± 0.06	0.61$^{\alpha}$ ± 0.12	0.68$^{¥\ \mu\circledR}$ ± 0.11	0.80$^{\Omega}$ ± 0.09	0.94$^{\rho\infty\in\pounds\copyright}$ ± 0.10
VD_{meas} 2′ (L)	0.38 ± 0.11	0.36 ± 0.04	0.63 $^{\alpha}$ ± 0.07	0.57 ± 0.13	0.87 ± 0.08	0.70 ± 0.17
VD_{meas} 4′ (L)	0.39 ± 0.08	0.34 ± 0.05	0.68 $^{\alpha}$ ± 0.11	0.56 ± 0.09	0.91 ± 0.09	0.67 ± 0.16
VD_{meas} 6′ (L)	0.43 ± 0.19	0.36 ± 0.08	0.71 ± 0.13	0.51 ± 0.09	0.92 ± 0.15	0.62 ± 0.15
VD_{meas} 8′ (L)	0.43 ± 0.09	0.32 ± 0.08	0.73 $^{\alpha}$ ± 0.11	0.48 ± 0.12	0.90 ± 0.14	0.57 ± 0.12
VD_{meas} peak (L)	0.45 ± 0.18	0.31 ± 0.11	0.71 $^{\alpha}$ ± 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_{Yint}** = dead space volume calculated as VE_{Yint}/RR_{Yint}; **VD_{meas}** = dead space volume measured by P_aCO_2 in heart failure patients and estimated by $P_{ET}CO_2$ in healthy subjects.
$^{\alpha}p<0.001$ versus VD_{meas} 6′; $^{\Omega}$ $p<0.05$ versus VD_{meas} 6′; $^{¥}$ $p<0.05$ versus VD_{meas} 6′; $^{\mu}$ $p< 0.001$ versus VD_{meas} 8′; $^{\circledR}$ $p<0.01$ versus VD_{meas} peak; $^{\rho}$ $p<0.001$ versus VD_{meas} 2′; $^{\infty}$ $p<0.001$ versus VD_{meas} 4′; $^{\in}$ $p<0.001$ versus VD_{meas} 6′; $^{£}p<0.001$ versus VD_{meas} 8′; $^{\copyright}$ $p<0.001$ versus VD_{meas} peak.
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We measured DS during exercise using a standard formula [8] in HF patients. To avoid systemic artery catheterization, we estimated P_aCO_2 from $P_{ET}CO_2$ in healthy subjects, which is a accepted method in the absence of lung disease [29]. It is recognized, however, that albeit largely used in the clinical setting, extrapolation of P_aCO_2 from $P_{ET}CO_2$ even in normal individual 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 P_aCO_2 underestimation by $P_{ET}CO_2$ when adding DS, confirming the need to directly measure P_aCO_2 during exercise for DS evaluation [30]. The low $P_{ET}CO_2$ compared to P_aCO_2 observed during exercise with added dead space (Table 3) is likely due to the rapid rise of PCO_2 during exhalation, which does not reach a plateau.

Adding DS increased the slope of VE vs. VCO_2 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/VCO_2 ratio at the beginning of exercise but a blunted VE increase during exercise, so that the slope of VE vs. VCO_2 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.

The VE vs. VCO_2 relationship is frequently used as a prognostic tool in HF patients [9–13]. Some laboratories prefer

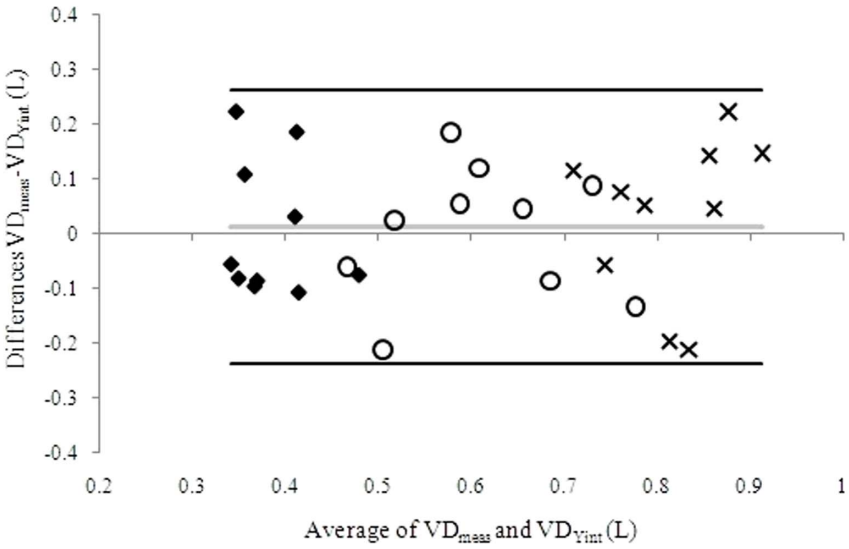

Figure 3. Bland and Altman plot of estimated dead space (DS) volume calculated as VE_{Yint}/RR_{Yint} (VD_{Yint}) and measured DS volume (VD_{meas}) at rest, calculated as (1–863/P_aCO_2(VE/VCO_2)*VT) for heart failure patients with 0 mL (diamonds), 250 mL (circles) and 500 mL (crosses) of additional DS. The grey line identifies the mean difference of VD_{meas} - $VD_{Yint;}$ the black lines identify the mean difference of VD_{meas} - and VD_{Yint} ± 1.96*standard deviation. P_aCO_2 = arterial carbon dioxide pressure; VE = ventilation; VT = tidal volume.
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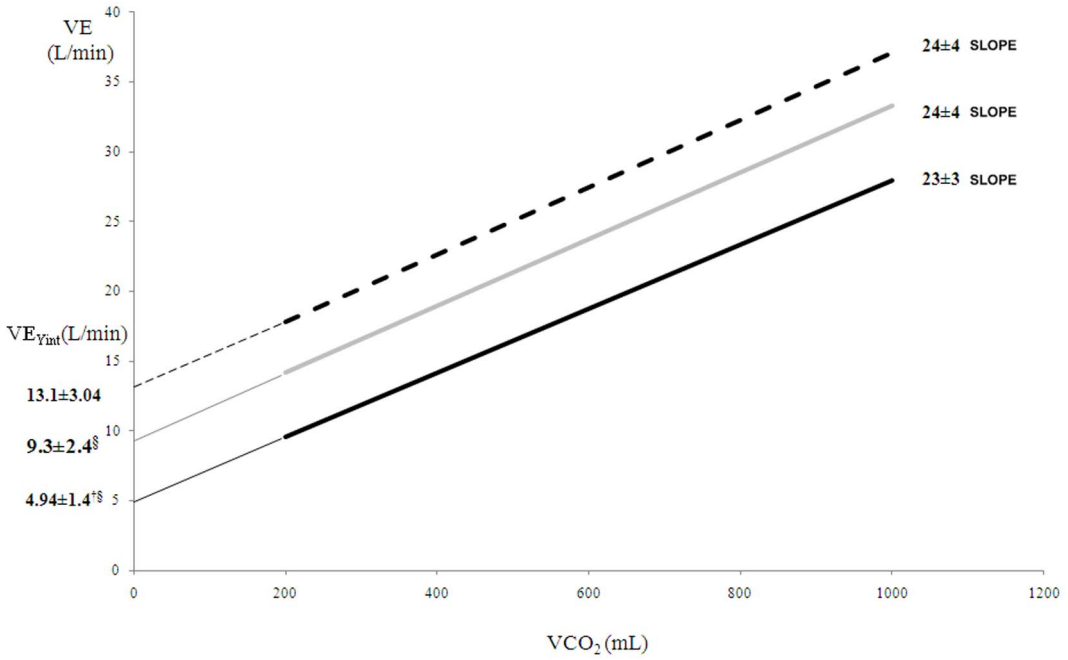

Figure 4. VE vs. VCO_2 relationship in healthy subjects with 0 mL (black line), 250 mL (grey line) and 500 mL (dotted line) of additional dead space (DS). The adding of DS upshifts the VE vs VCO_2 relationship without significant slope changes. † $p<0.001$ versus +250 mL; § $p<0.001$ versus +500 mL.
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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/VCO_2 ratio value should be considered is still a matter of debate [31]. Moreover, while the behaviour of VE/VCO_2 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. VCO_2 relationship throughout the exercise [33] or up to the respiratory compensation point [8]. To do so, the slope of the VE vs. VCO_2 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. VCO_2 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 VE_{Yint} increase, so that its value should be taken into account when analyzing the VE vs. VCO_2 relationship. Indeed, VE_{Yint} differences 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.

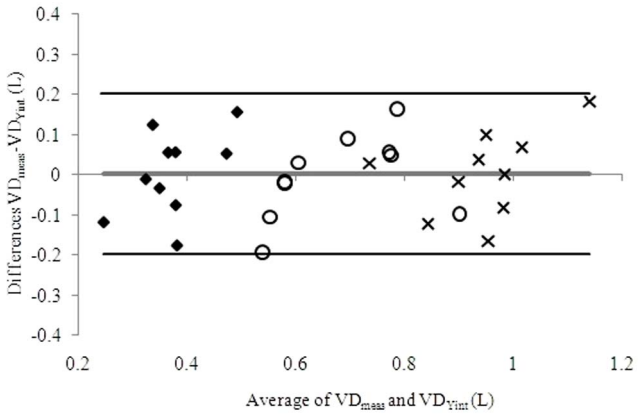

Figure 5. Bland and Altman plot of estimated dead space (DS) volume calculated as VE_{Yint}/RR_{Yint} (VD_{Yint}) and measured DS volume (VD_{meas}) at rest, calculated as (1–863/P_aCO_2(VE/VCO_2)*VT) with P_aCO_2 for healthy subjects with 0 mL (diamonds), 250 mL (circles) and 500 mL (crosses) of additional DS. The grey line identifies the mean difference of VD_{meas} - VD_{Yint}; the black lines identify the mean difference of VD_{meas} - and VD_{Yint} ± 1.96*-standard deviation. P_aCO_2 was estimated from $P_{ET}CO_2$. P_aCO_2 = carbon dioxide pressure; $P_{ET}CO_2$ = tele-expiratory carbon dioxide pressure; VE = ventilation; VT = tidal volume.
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In conclusion, we provide the rational basis for the assessment of VE_{Yint} during exercise as a tool to evaluate DS. Further studies are needed to confirm and to analyze the clinical meaning of the present observation.

At a Glance Commentary

The ventilation (VE) vs. VCO_2 relationship during exercise is commonly used to assess ventilatory efficiency and prognosis in heart failure patients. The slope of the VE vs. VCO_2 relationship increases as heart failure severity increases, whereas in respiratory patients the VE vs. VCO_2 slope during exercise is reduced 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. VCO_2 relationship in these cases is unclear.

We reasoned that the VE vs. VCO_2 behavior during exercise is a linear relationship, at least up to the respiratory compensation point, characterized by a slope and a Y intercept value. The latter has been ignored, but it represent the ventilation at $VOC_2 = 0$ and therefore it 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. VCO_2 relationship. The Y intercept of VE vs. VCO_2 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 suspicious 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.

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