ORIGINAL RESEARCH

Different Determinants of Ventilatory Inefficiency at Different Stages of Reduced Ejection Fraction Chronic Heart Failure Natural History

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***Background*—**It is not known whether determinants of ventilation (VE)/volume of exhaled carbon dioxide (VCO_2) slope during incremental exercise may differ at different stages of reduced ejection fraction chronic heart failure natural history.

***Methods and Results*—**VE/VCO_2 slope was fitted up to lowest VE/VCO_2 ratio, that is, a proxy of the VE/perfusion ratio devoid of nonmetabolic stimuli to ventilatory drive. VE/VCO_2 slope tertiles were generated from our database (<27.5 [tertile 1], ≥27.5 to <32.0 [tertile 2], and ≥32.0 [tertile 3]), and 147 chronic heart failure patients with repeated tests yielding VE/VCO_2 slopes in 2 different tertiles were selected. Determinants of VE/VCO_2 slope changes across tertile pairs 1 versus 2, 2 versus 3, and 1 versus 3 were assessed by exploring changes in VE and VCO_2 at lowest VE/VCO_2 and those in VE/work rate (W) and VCO_2/W slope. Resting and peak cardiac output (CO) were calculated as VO_2/estimated arteriovenous O_2 difference and the CO/W slope analyzed. Notwithstanding a progressively lower W with increasing tertile, VE at lowest VE/VCO_2 and VE/W slope were significantly higher in tertiles 2 and 3 versus tertile 1. Conversely, VCO_2 at lowest VE/VCO_2 and CO/W slope significantly decreased across tertiles, whereas VCO_2/W slope did not. Difference (Δ) in VE/W slope between tertiles accounted for 71% of $\Delta VE/VCO_2$ slope variance, with ΔVCO_2/W slope explaining an additional 26% (model r=0.99; r^2=0.97; P<0.0001). Similar results were obtained substituting ΔVCO_2/W slope with ΔCO/W slope.

***Conclusions*—**Ventilatory overactivation is the predominant cause of VE/VCO_2 slope increase at initial stages of chronic heart failure, whereas hemodynamic impairment plays an additional role at more-advanced pathophysiological stages. **(*J Am Heart Assoc*. 2017;6:e005278. DOI: 10.1161/JAHA.116.005278.)**

Key Words: cardiac output • chronic heart failure • exercise • exercise gas exchanges • ventilatory efficiency

Ventilatory inefficiency, that is, increased slope of the ventilation (VE) versus volume of exhaled carbon dioxide (VCO_2) relationship, as evaluated by incremental cardiopulmonary exercise testing (CPET), is a hallmark of exercise pathophysiology and an acknowledged risk marker in reduced ejection fraction chronic heart failure (CHF).[1,2] Both ventilatory and hemodynamic factors have been proposed as primarily responsible for the progressive VE/VCO_2 slope increase observed with increasing severity of CHF.[1–7] However, which of the 2 is the main cause of increased VE/VCO_2 slope in CHF has not been established as yet. In this regard, a crucial methodological issue is that all available studies dealing with VE/VCO_2 slope determinants have had a cross-sectional design, ruling out the possibility of exploiting the informative content of VE and VCO_2 changes in individual patients at different points in time during the course of their disease. To the best of our knowledge, no such data are currently available.

VE/VCO_2 slope or ratio equals $863/pCO_2 \times (1 - Vd/Vt)$, where pCO_2 is the arterial CO_2 partial pressure and Vd/Vt is the physiological dead space/tidal volume ratio.[8] Accordingly, an increase of VE/VCO_2 slope may be attributed to increased physiological dead space (high VE/perfusion ratio, normocapnia) or enhanced ventilatory reflex sensitivity (no high VE/perfusion ratio, hypocapnia) or a combination of the 2. Based on the above, to explore the determinants of VE/VCO_2 slope modifications over time, VE should be matched as closely as possible to metabolic CO_2 production in the absence of nonmetabolic stimuli (ie, anxiety and/or lactic-acid–generated H^+) to ventilatory drive possibly reducing pCO_2. In fact, in this physiological context, (1) no acute hyperventilation occurs and stability of body CO_2 stores is expected, (2) changes in VCO_2 are more closely linked to those in cardiac output by Fick's principle, and (3) the lowest VE/VCO_2 ratio represents

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the point in time when VE is best matched to perfusion relative to VCO_2 and can be used as a proxy of the VE/perfusion ratio.[9–12]

The aim of this study was to evaluate the relative contribution of VE and VCO_2 to changes in VE/VCO_2 slope over time in individual CHF patients. VE and VCO_2 were evaluated as: (1) absolute values at lowest VE/VCO_2; (2) change in VE and VCO_2 per unit increase of a "third-party" performance parameter, that is, work rate, using the same incremental ramp protocol steepness in all evaluated CPETs. Resting and peak cardiac output, calculated as VO_2/estimated arteriovenous O_2 difference, were also evaluated to enable more-reliable inferences about the relationship between VE/VCO_2 slope and hemodynamics changes. All parameters were compared between different VE/VCO_2 slope categories of increasing average value, as reached by individual patients at different points in time over the natural history of their disease.

Methods

Study Population

We retrospectively evaluated 4820 CPETs carried out in the Exercise Pathophysiology Laboratory of our Institute between January 1, 1995 and December 31, 2013. The process of study population selection is shown in Figure 1. Preliminary inclusion criteria were: (1) history of CHF from ischemic or idiopathic dilated cardiomyopathy and clinical/pharmacological stability for ≥3 months at the time of CPET; (2) echocardiographic left ventricular ejection fraction ≤40%; (3) CPET stopped for fatigue and/or dyspnea with peak respiratory exchange ratio of ≥1.05; and (4) availability of at least 2 tests in the same patient over the evaluated time period. Accordingly, 1662 tests (carried out in 464 patients) were eligible for the study and divided into 3 groups based on tertiles of VE/VCO_2 slope, namely, <27.5 (tertile 1), ≥27.5 to <32.0 (tertile 2), and ≥32.0 (tertile 3).

Subsequently, a further selection was made looking for availability of test pairs in different VE/VCO_2 slope tertiles in the same patient, that is, in tertiles 1 and 2 (1 versus 2), 2 and 3 (2 versus 3), and 1 and 3 (1 versus 3). In the case of availability of more than 2 tests in the same tertile in a given patient, only the first test in chronological order was chosen. The test pairs were selected independently of the direction of VE/VCO_2 slope change between tertiles, that is, increase versus decrease, assuming each tertile as a descriptor of a homogeneous pathophysiological setting irrespective of previous clinical history. As a result, 147 test and tertile pairs, carried out in as many patients, were included in the study, of which 55, 48, and 44 were in the 1 versus 2, 2 versus 3, and 1 versus 3 groups, respectively (Figure 1). Of note, the tertile 1 and 2 upper limits of the final study population did not differ from those set after the preliminary selection (27.3 vs 27.5 and 31.8 vs 32.0, respectively), that were thus maintained.

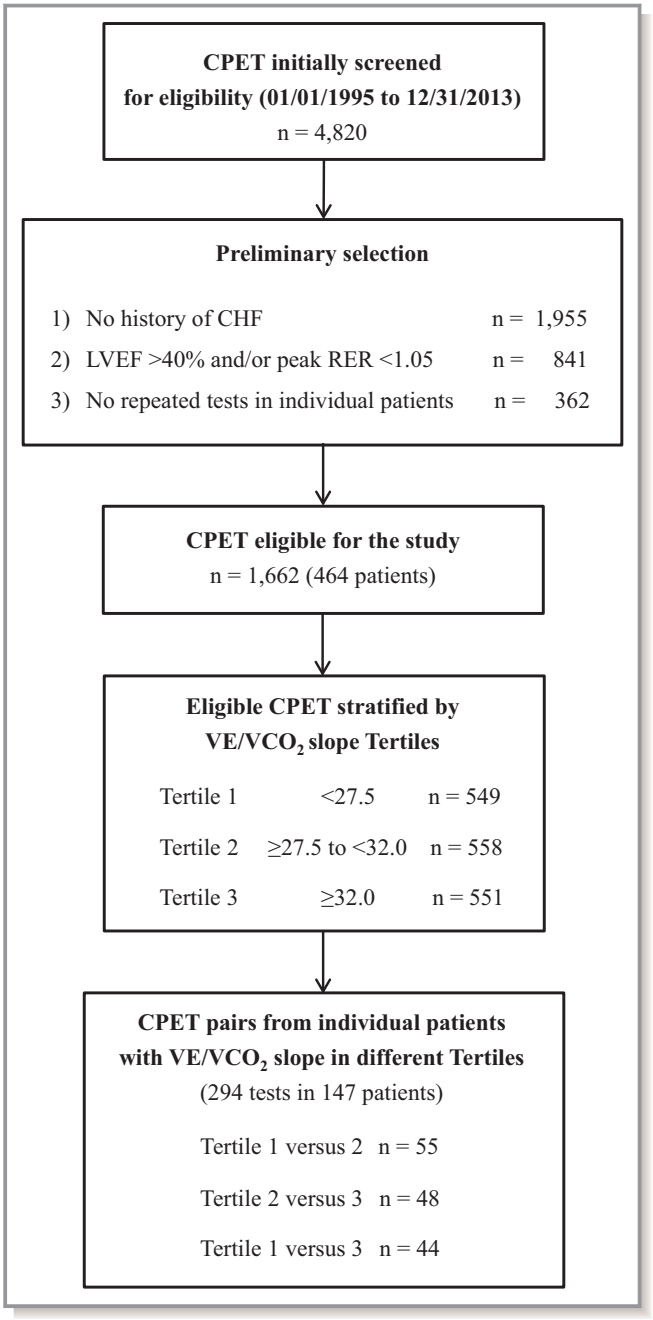

Figure 1. Flow chart showing study population selection. CHF indicates reduced ejection fraction chronic heart failure; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; RER, respiratory exchange ratio; VCO_2, volume of exhaled carbon dioxide; VE, ventilation.

Daily β-blocker carvedilol-equivalent dose was calculated for patients on bisoprolol and nebivolol as dose×5 and as dose/4 for those on metoprolol.[13]

The protocol was approved by the Central Ethics Committee of the Salvatore Maugeri Foundation, IRCCS, and written informed consent was obtained from all participants.

Cardiopulmonary Exercise Testing

Respiratory gas exchange measurements were obtained breath by breath using a computerized metabolic cart (Vmax29; Sensormedics, Yorba Linda, CA). Pre-exercise resting data were recorded for 2 minutes with the patient sitting still on the cycle ergometer (Ergo-metrics 800S; Sensormedics), and resting VE, VCO_2, and VO_2 were the average of values collected during the whole resting phase. Subsequently, a 1-minute unloaded cycling warmup was started followed by a ramp incremental protocol of 10 W/min, and participants were encouraged to exercise until exhaustion. Peak VO_2 was recorded as the mean of values observed during the last 30 seconds of the exercise phase and the first ventilatory threshold (1^{st}VT) estimated by the V-slope and/or respiratory equivalents methods.[11,12] Predicted VO_{2max} and VE/VCO_2 slope values were determined according to formulae outlined by Wasserman et al[12] and Sun et al,[10] respectively.

Cardiac Output Evaluation

According to Fick's principle, cardiac output (CO) at rest and peak exercise was calculated using measured VO_2 and estimated arteriovenous O_2 difference values as CO (L/min) $=VO_2$ (mL/min)/arteriovenous O_2 difference (mL/L).[14,15] Resting and peak arterial O_2 content (CaO_2) were calculated as CaO_2 (mL/dL)=Hb (g/dL)$\times$1.34 (mL O_2/g Hb)$\times SaO_2$, where Hb is hemoglobin concentration, 1.34 is hemoglobin O_2 binding capacity, and SaO_2 is arterial hemoglobin O_2 saturation. Because of exercise-induced hemoconcentration, a value of Hb increased by 5% with respect to baseline was used to calculate peak CaO_2[12,15] and, based on data from previous work[15–17] and our laboratory, resting and peak SaO_2 were assumed to be equal to 0.97. According to available data, the resting and peak O_2 extraction in CHF patients of different severities are, on average, 40% and 80%, respectively.[12,15–18] These values were thus adopted to estimate resting and peak arteriovenous O_2 difference, as follows:

$$\text{Resting arterio} - \textit{venous}\ O_2\ \text{difference} = (\text{Hb} \times 1.34 \times 0.97) - [(\text{Hb} \times 1.34 \times 0.97) \times 0.6]$$

$$\text{Peak arterio} - \textit{venous}\ O_2\ \text{difference} = (\text{Hb} \times 1.34 \times 0.97) - [(\text{Hb} \times 1.34 \times 0.97) \times 0.2]$$

Table 1 shows the variability of peak CO estimate when using the above-mentioned method, according to different peak O_2 extraction and peak SaO_2 combinations in a hypothetical patient with peak VO_2 of 1000 mL/min and peak hemoglobin of 14.0 g/dL. For the peak O_2 extraction value used in the present study (ie, 80%), a $\pm$0.01 change in peak SaO_2 would result in a $\pm$1% change in peak CO. Conversely, for the peak SaO_2 value used in the present study (ie, 0.97), a $\pm$5% change in peak O_2 extraction would result in a $\pm$6% change in peak CO.

Table 1. Peak Cardiac Output Estimate Changes According to Different Peak O_2 Extraction and Peak Arterial Hemoglobin O_2 Saturation Estimate Combinations

		Peak O_2 Extraction Estimate			
		70%	75%	80%	85%
Peak SaO_2 estimate	0.95	8.02	7.48	7.01	6.60
	0.96	7.93	7.41	6.94	6.53
	0.97	7.85	7.33	6.87	6.46
	0.98	7.78	7.26	6.80	6.40
	0.99	7.69	7.18	6.73	6.34
	1.00	7.61	7.11	6.66	6.27

The table reports peak cardiac output estimates using Fick's principle according to different peak O_2 extraction and peak arterial hemoglobin O_2 saturation combinations. For descriptive purposes, peak cardiac output (L/min) is calculated using a peak VO_2 value of 1000 mL/min and a peak hemoglobin value of 14.0 g/dL. The gray cell corresponds to the peak O_2 extraction and peak hemoglobin O_2 saturation estimate combination used in the present study. See text for further details. Peak SaO_2=peak arterial hemoglobin oxygen saturation.

Descriptors of Ventilatory and Hemodynamic Efficiency

Lowest VE/VCO_2 and VE/VCO_2 slope

For VE/VCO_2 slope or ratio to mirror as reliably as possible the VE/perfusion relationship, ventilatory drive should not be affected by so-called "nonmetabolic" stimuli, that is, anxiety- and/or lactic-acid–generated H^+, possibly inducing hyperventilation and acutely reducing pCO_2.[10–12] Anxiety-induced hyperventilation is quite common at rest before the start of exercise, but when the subject starts pedaling anxiety usually recedes making matching of VE to perfusion improve. As ramp incremental exercise proceeds, there are 2 possible scenarios: (1) Hyperventilation occurs again if the second ventilatory threshold, that is, lowest VE/VCO_2 or respiratory compensation point,[11,12] is overcome before exercise end, making VE/VCO_2 slope increase more steeply because of the stimulus to ventilatory drive induced by lactic-acid–derived H^+ ions, or (2) lowest VE/VCO_2 coincides with exercise phase end and no breakpoint of the VE versus VCO_2 relationship is detected, thus excluding acute hyperventilation during exercise. Lowest VE/VCO_2 was visually identified by 2 experienced operators (A.M. and K.K.), who examined the VE/VCO_2 versus time relationship plotted in 10-second–averaged values after deleting errant breath-by-breath data lying >4 SD away from

the local mean. Lowest VE/VCO_2 was determined by averaging the 3 lowest consecutive 10-second–averaged data points. In case of disagreement, the opinion of a third operator (U.C.) was requested. The VE/VCO_2 slope fitting window was delimited excluding resting data and, when present, data following the lowest VE/VCO_2.

VE/work rate, VCO_2/work rate, and CO/work rate slopes

The VE/work rate and VCO_2/work rate slopes (VE/W slope and VCO_2/W slope, respectively) were calculated as the difference in VE and VCO_2 from 1 minute after the work rate started to increase to the point of lowest VE/VCO_2, divided by work rate at lowest VE/VCO_2. The delay of 1 minute after the start of the ramp increase in work rate was used to take into account the time constant for VE and VCO_2.[7] Of note, even in the absence of acute hyperventilation, VE/W slope and VCO_2/W slope steepness does increase above 1^{st}VT because of the "excess VCO_2" generated by anaerobic metabolism activation and lactic acid buffering.[12] Accordingly, VE/W slope and VCO_2/W slope were also calculated using 1^{st}VT as the upper limit of the fitting window (1^{st}VT VE/W slope and 1^{st}VT VCO_2/W slope, respectively).

The CO/work rate slope (CO/W slope) was the difference in CO from rest to peak exercise divided by peak work rate.

Statistical Analysis

One-way ANOVA with Fisher's protected least significant difference post-hoc tests, paired *t* tests, and Fisher's exact test were used to compare quantitative and qualitative variables, as appropriate. Regression and Pearson product moment coefficients were used to determine the correlation between measured variables. Step-wise regression was used to determine the relative contribution of change (Δ) in VE/W slope, VCO_2/W slope, time elapsed between CPETs, and carvedilol-equivalent β-blocker dose to that in VE/VCO_2 slope when moving from a lower to a higher tertile. Level of statistical significance was set at a 2-tailed *P* value of $\leq$0.05. The StatView software package (version 5.0.1; SAS Institute, Inc., Cary, NC) was used for statistical calculations.

Results

Study Population Clinical-Instrumental Characteristics

Demographic and clinical-instrumental characteristics for the 3 tertiles and the whole study population are reported in Table 2.

Tertiles were well matched regarding sex and body mass index (BMI), but patients in tertiles 2 and 3 were slightly older than those in tertile 1. New York Heart Association (NYHA) class and loop diuretic dose increased significantly across tertiles, testifying to a progressively more-advanced CHF clinical picture with increasing VE/VCO_2 slope. The percentage of patients on and the carvedilol-equivalent dose of β-blockers did not differ between tertiles. No significant changes in study results were detected after exclusion of non-β-blocked patients from the data set.

Ergospirometry and Hemodynamic Parameters

Ergospirometry and hemodynamic parameters for the 3 tertiles and the whole study population are reported in Table 3.

Peak VO_2 values significantly and progressively decreased across tertiles, whereas peak heart rate (HR) and peak O_2 pulse were significantly lower in tertile 3 than in tertiles 1 and 2. Of note, peak VE did not differ between tertiles, notwithstanding a progressive and significant decrease of peak work rate. Peak respiratory exchange ratio was, on average, higher than 1.10 in the whole study population, attesting maximal or near-maximal effort attainment. Peak CO progressively and significantly decreased with increasing tertile, with a 7% and 22% reduction, respectively, in tertiles 2 and 3 as compared to tertile 1.

By design, VE/VCO_2 slope increased stepwise and significantly from tertile 1 through 2 to 3 when expressed as both absolute value and percentage of predicted value. In the whole study population, VE/VCO_2 slope was inversely correlated with peak VO_2 (r=0.50; P<0.0001). A progressive and significant increase of lowest VE/VCO_2 with increasing tertile paralleled that of VE/VCO_2 slope. In the whole study population, lowest VE/VCO_2 was reached at 71±13%, 67±14% and 72±14% of peak work rate, peak VE, and peak VCO_2, respectively. The number of patients reaching lowest VE/VCO_2 at peak exercise in tertiles 1, 2, and 3 was 5 (5%), 11 (11%), and 11 (12%), respectively (P=0.16), and study results were not modified by their exclusion from analysis.

Comparisons Between Different Tertile Pairs

The average time elapsed between CPETs in the 147 test pairs included in the study was 41±39 months (range, 6–205). Of note, time was significantly longer in the 1 versus 3 group than in 1 versus 2 and 2 versus 3 groups (56±46 vs 37±34 and 31±35 months, respectively; both P<0.01). However, removing the 1 versus 3 group from the data set did not affect significantly the results of the study.

Changes over time in VE and VCO_2 at lowest VE/VCO_2 in the 1 versus 2, 2 versus 3, and 1 versus 3 groups are shown in Figure 2. VE at lowest VE/VCO_2 was found to significantly increase with increasing tertile in groups 1 versus 2 and 1 versus 3, and not to change in the 2 versus 3 group. Of note, this was counterintuitive with the significant and expected

Table 2. Demographic and Clinical-Instrumental Characteristics

	Total Population	Tertile 1 (<27.5)	Tertile 2 (≥27.5 to <32.0)	Tertile 3 (≥32.0)	*P* Value
n	294	99	103	92	…
Males, n (%)	284 (97)	95 (96)	99 (96)	90 (98)	0.71
Age, y	58±10	55±10	58±10*	61±10*	0.0011
BMI, kg/m^2	26.28±4.56	26.37±4.87	26.08±4.24	26.41±4.60	0.85
Hb, g/dL	13.5±1.4	13.9±1.3	13.4±1.4*	13.2±1.5*	0.0068
NYHA class	2.1±0.6	1.9±0.6	2.1±0.6*	2.3±0.6†	0.0002
LVEF, %	26±7	26±8	26±7	24±7	0.11
FVC, % predicted	89±16	91±17	89±17	86±14	0.34
FEV1, % predicted	85±18	88±18	84±18	82±16	0.15
β-blocker type, n (%)					
BIS	46 (16)	12 (12)	17 (16)	17 (18)	0.54
CAR	158 (54)	54 (55)	56 (55)	48 (52)	
NEB	2 (1)	0 (0)	1 (1)	1 (1)	
MET	9 (3)	5 (5)	1 (1)	3 (3)	
No β-b	79 (26)	28 (28)	28 (27)	23 (26)	
Carvedilol-equivalent β-blocker dose, mg/day	19.5±13.5	20.6±13.4	19.6±13.3	18.4±13.7	0.62
ACE-I, n (%)	272 (92)	94 (94)	103 (100)	82 (89)	0.31
Loop diuretic, n (%)	269 (91)	88 (89)	96 (93)	85 (92)	0.52
Loop diuretic dose, mg/day	81.1±83.9	62.7±45.6	71.5±82.1	110.9±106.5 †	0.0002

ACE-I indicates angiotensin-converting enzyme inhibitor; BIS, bisoprolol; BMI, body mass index; CAR, carvedilol; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MET, metoprolol; NEB, nebivolol; NYHA, New York Heart Association.
*P<0.05 versus tertile 1.
†P<0.05 versus tertiles 1 and 2.

decrease of work rate in the transition from a lower to a higher tertile in all tertile pairs. In contrast, VCO_2 at lowest VE/VCO_2 significantly and expectedly decreased with decreasing work rate in all groups. Such a contrasting behavior of VE and VCO_2 at lowest VE/VCO_2 was mirrored by that of VE/W and VCO_2/W slopes, shown in Table 4. In fact, both VE/W slope and 1stVT VE/W slope significantly increased when going from a lower to a higher tertile in all groups, whereas VCO_2/W slope did not change. Notably, however, CO/W slope was significantly lower in tertile 3 than in tertiles 1 and 2, and the same was true regarding 1stVT VCO_2/W slope. These results are summarized in Figure 3.

In addition, in the whole study population, $\Delta VE/VCO_2$ slope when moving from a lower to a higher tertile was significantly related to ΔVE/W slope (Figure 4), ΔCO/W slope (Figure 4), and time elapsed between CPETs (r=0.42; P<0.0001), whereas no relationship was found with ΔVCO_2/W slope (Figure 4) or Δcarvedilol-equivalent β-blocker dose (r=0.02; P=0.83). A step-wise regression model, including ΔVE/W slope, ΔVCO_2/W slope, time elapsed between CPETs, and Δcarvedilol-equivalent β-blocker dose as independent variables, selected ΔVE/W slope as the most powerful predictor of $\Delta VE/VCO_2$ slope, accounting for 71% of the dependent variable variance, with ΔVCO_2/W slope explaining an additional 26% (model r=0.99, r^2=0.97; P<0.0001); time elapsed between CPETs and Δcarvedilol-equivalent β-blocker dose were not included in the model. Similar results were obtained substituting ΔVCO_2/W slope with ΔCO/W slope (model r=0.90, r^2=0.81; P<0.0001), that accounted for 10% of $\Delta VE/VCO_2$ slope variance in addition to the 71% explained by ΔVE/W slope.

Discussion

The results of the present study provide new insights into CHF exercise pathophysiology. Our major finding is that changes in VE/VCO_2 slope observed over time in individual CHF patients can be attributed to different determinants according to the pathophysiological stage of the disease. Namely, when moving from a normal to a slightly increased VE/VCO_2 slope, such a change is related to ventilatory drive overactivation not accompanied by ergospirometry signs of reduced systemic perfusion. On the other hand, in the transition to moderately/

Table 3. Ergospirometry and Hemodynamic Parameters

	Total Population	Tertile 1 (<27.5)	Tertile 2 (≥27.5 to <32.0)	Tertile 3 (≥32.0)	*P* Value
Resting VO_2, L/min	0.254±0.063	0.268±0.072	0.249±0.057*	0.244±0.58*	0.020
Resting VCO_2, L/min	0.231±0.69	0.249±0.081	0.228±0.061*	0.213±0.058*	<0.002
Resting VE, L/min	10.9±2.9	10.9±2.9	10.9±2.6	11.2±2.5	0.70
Peak VO_2, mL/kg/min	15.2±3.7	17.1±3.8	15.5±2.9*	13.0±2.9†	<0.0001
Peak VO_2, L/min	1.131±0.319	1.277±0.342	1.143±0.290*	0.961±0.233†	<0.0001
Peak VO_2, % predicted	54±13	59±14	56±11*	48±12†	<0.0001
Peak VCO_2, L/min	1.295±0.347	1.460±0.366	1.309±0.308*	1.102±0.261†	<0.0001
Peak VE, L/min	48±11	47.4±11.3	48.4±10.9	47.8±10.9	0.81
Peak RER	1.14±0.08	1.14±0.07	1.14±0.06	1.15±0.09	0.90
Peak HR, beats/min	125±21	131±19	126±22	120±23†	0.001
Peak O_2 pulse, mL/beat	9.0±2.5	9.7±2.7	9.1±2.4	8.0±2.2†	<0.0001
Peak CO, L/min	8.2±2.2	9.0±2.6	8.4±2.0*	7.1±1.9†	<0.0001
Peak work rate, W	90±23	100±24	91±22*	77±16†	<0.0001
1^{st}VT, yes, n (%)	244 (83)	84 (85)	92 (89)	68 (74)†	0.014
1^{st}VT VO_2, mL/kg per min	10.0±208	10.9±3.1	9.0±2.0*	7.8±2.0†	<0.01
1^{st}VT RER	0.92±0.05	0.94±0.03	0.92±0.07	0.93±0.07	0.54
VE/VCO_2 slope	30.2±5.6	24.5±2.4	29.7±1.4*	36.7±3.7†	<0.0001
VE/VCO_2 slope, % predicted	112±21	92±10	114±6*	136±16†	<0.0001
Lowest VE/VCO_2	34.9±5.7	29.7±3.1	34.5±2.9*	41.0±4.2†	<0.0001

1^{st}VT indicates first ventilatory threshold; CO, cardiac output; HR, heart rate; RER, respiratory exchange ratio; VCO_2, volume of exhaled carbon dioxide; VE, ventilation.
*P<0.01 versus tertile 1.
†P<0.01 versus tertiles 1 and 2.

severely increased VE/VCO_2 slope, a contribution of hemodynamic impairment is evident as well, which supports the concept of increased physiological dead space as an additional determinant of increased VE/VCO_2 slope in the more-advanced CHF stages.

Studies investigating the pathophysiological basis for an increased VE/VCO_2 slope in CHF have reported conflicting results. Enhanced ventilatory reflex sensitivity because of autonomic imbalance, early exercise-induced metabolic acidosis, lowered chemoceptive pCO_2 set point, and restrictive respiratory pattern with increased respiratory rate [1,3,4,7,19–21] have been proposed as causes of the reduced ventilatory efficiency in CHF patients. Alternatively, other studies have suggested increased Vd/Vt and VE/perfusion mismatch from inadequate perfusion of normally ventilated alveoli as hemodynamic determinants of a high VE/VCO_2 slope.[5–7] However, it is not clear whether relative hyperventilation or VE/perfusion mismatch plays the major role in increasing VE/VCO_2 slope in CHF, nor is it known whether the relative contribution of these 2 factors may differ at different pathophysiological stages of the disease. Even if some researchers have described the coexistence of ventilatory and hemodynamic determinants of increased VE/VCO_2 slope in CHF,[8,21] no stratification of data by increasing VE/VCO_2 slope values has ever been carried out. This is the first protocol to systematically evaluate dynamic changes in VE and VCO_2 as related to those in VE/VCO_2 slope over the natural course of CHF, thus enabling modifications in VE/VCO_2 slope to be viewed in the perspective of both their ventilatory and hemodynamic determinants.

Our results favor the concept of ventilatory drive overactivation as an important factor causing changes in VE/VCO_2 slope over time across the whole spectrum of CHF severity. This point is supported by: (1) the counterintuitive finding of a significant increase of VE at lowest VE/VCO_2 in the transition from tertile 1 to 2 and 1 to 3 (+6% and +10%, respectively), notwithstanding a corresponding decrease of work rate (−9% and −20%, respectively) (Figure 2); (2) a progressive and significant increase of VE/W slope and 1^{st}VT VE/W slope with increasing tertile in 1 versus 2, 2 versus 3, and 1 versus 3 groups, resulting in very similar mean VE values among tertiles not only at lowest VE/VCO_2, but also at peak exercise (Figure 3 and Table 3); and (3) the strong direct relationship linking $\Delta VE/VCO_2$ slope and $\Delta VE/W$ slope (Figure 4), with the latter accounting for around three quarters of $\Delta VE/VCO_2$ slope variance. Notably, an increased VE/W slope was evident

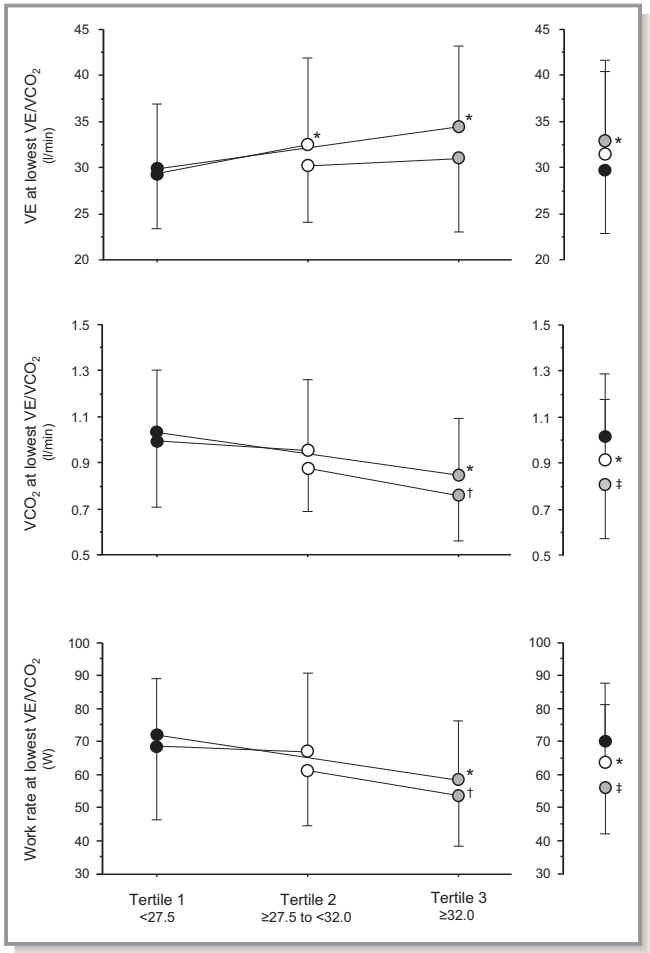

Figure 2. Changes in ventilation, VCO_2, and work rate at lowest VE/VCO_2 between different VE/VCO_2 slope tertile pairs. Tertile pairs are represented as circle pairs connected by lines. Data are expressed as mean±SD. The *x*-axis and symbols on the right side of the graphs show average values per tertile. In the presence of a step-wise work rate and VCO_2 decrease with increasing tertile in all tertile pairs, ventilation progressively and counterintuitively increased. This highlights the role played by ventilatory overactivation in determining increased VE/VCO_2 slope over a wide range of chronic heart failure pathophysiology stages. VCO_2 indicates volume of exhaled carbon dioxide; VE, ventilation. **P*<0.01 versus tertile 1; †*P*<0.01 versus tertile 2; ‡*P*<0.01 versus tertiles 1 and 2.

Table 4. Comparisons of Ventilatory and Hemodynamic Efficiency Descriptors Between Different VE/VCO_2 Slope Tertile Pairs

	Tertile 1 (<27.5)	Tertile 2 (≥27.5 to <32.0)	Tertile 3 (≥32.0)	*P* Value
VE/W slope, mL/min per watt				
1 vs 2	266±49	321±50	…	<0.0001
2 vs 3	…	316±45	374±61	<0.0001
1 vs 3	270±54	…	400±71	<0.0001
1stVT VE/W slope, mL/min per watt				
1 vs 2	227±74	286±94	…	0.0015
2 vs 3	…	294±70	323±95	0.07
1 vs 3	267±67	…	348±81	<0.0001
VCO_2/W slope, mL/min per watt				
1 vs 2	10.8±1.7	10.8±1.6	…	0.95
2 vs 3	…	10.6±1.5	10.3±1.5	0.20
1 vs 3	11.0±1.9	…	10.8±1.6	0.62
1stVT VCO_2/W slope, mL/min per watt				
1 vs 2	9.3±2.3	9.8±2.4	…	0.14
2 vs 3	…	9.7±1.9	9.0±2.9	0.16
1 vs 3	10.6±2.0	…	9.2±1.9	0.006
CO/W slope, mL/min per watt				
1 vs 2	49±16	50±14	…	0.81
2 vs 3	…	50±14	44±15	0.058
1 vs 3	56±11	…	45±14	0.0007

1stVT indicates first ventilatory threshold; 1 vs 2=tertile 1 versus tertile 2; 1 vs 3=tertile 1 versus tertile 3; 2 vs 3=tertile 2 versus tertile 3; CO, cardiac output; VCO_2, volume of exhaled carbon dioxide; VE, ventilation.

since the very beginning of exercise in all VE/VCO_2 slope tertiles. This is an important finding, testifying to an increased VE per unit increase of work rate independent of both relative exercise intensity and stage of disease pathophysiology, excluding metabolic acidosis as a possible determinant of such an augmented ventilatory drive. In the absence of significant changes in hemodynamics, an increase over time of VE at a given work rate can be attributed to an increase of excitatory inputs on VE from overactive ergoreflexes and chemoreflexes, lowering the pCO_2 set point. Even if no data have yet been reported about autonomic overactivation in CHF stratified by different VE/VCO_2 slope categories, in cross-sectional studies muscle ergoreceptor overactivity, muscle sympathetic nerve activity, and circulating norepinephrine levels have all been shown to correlate with both VE/VCO_2 slope and peak VO_2.[3,22,23] In addition, a derangement in cardiopulmonary reflex control occurs early in the course of CHF.[24,25] In this regard, Ponikowski et al have described an increased VE/VCO_2 slope even in CHF patients with preserved exercise tolerance, in whom an increased ventilatory response to exercise would not reflect an advanced stage of the disease, but rather a specific hypersensitivity of ventilatory reflex control.[26] These data are consistent with the slightly increased ventilatory drive we documented in patients with a slight increase of VE/VCO_2 slope in the presence of an unchanged CO/W slope.

On the other hand, VCO_2 at lowest VE/VCO_2 progressively and significantly decreased with increasing VE/VCO_2 slope tertile in 1 versus 2, 2 versus 3, and 1 versus 3 groups. Such a decrease was accompanied by a very similar VCO_2/W slope among tertiles, making VCO_2 at lowest VE/VCO_2 diminish, on

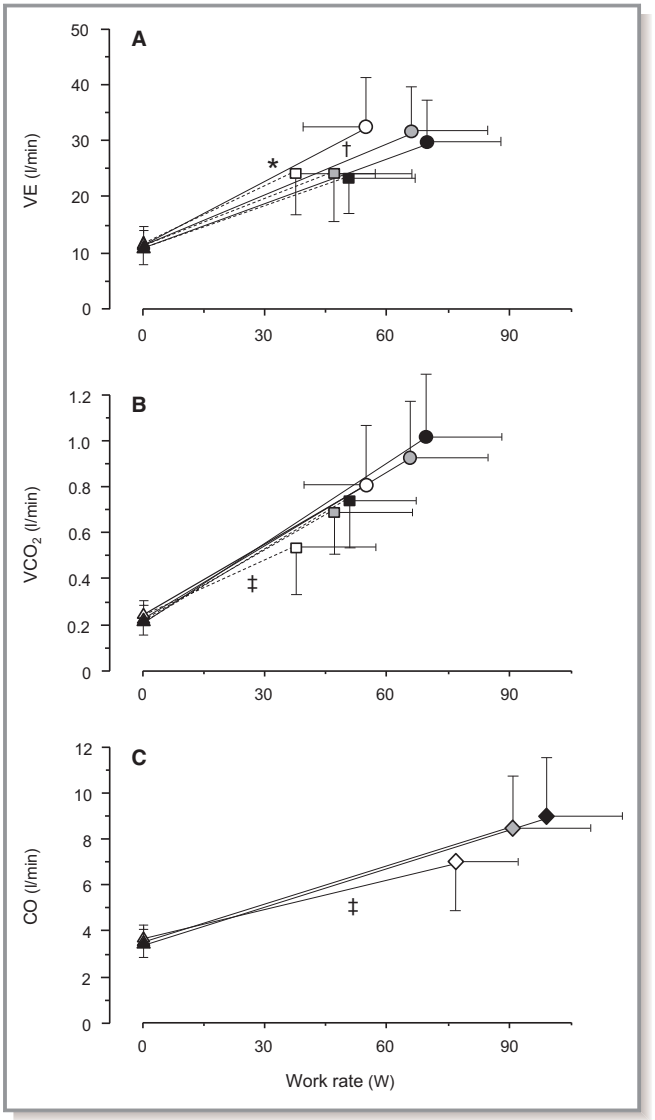

Figure 3. Ventilation, VCO_2, and cardiac output as a function of work rate in the study population. Black, gray, and white shapes represent tertiles 1, 2, and 3, respectively. Triangles, squares, circles, and diamonds represent start of exercise phase, first ventilatory threshold (1^{st}VT), lowest VE/VCO_2, and peak exercise, respectively. Data are expressed as mean±SD. The VE/W slope and 1^{st}VT VE/W slope (A) progressively increase across VE/VCO_2 slope tertiles, whereas the VCO_2/W slope does not (B). On the contrary, both 1^{st}VT VCO_2/W slope (B) and cardiac output/W slope (C) are significantly lower in tertile 3 than in tertile 1 or 2, which indicates reduced hemodynamic efficiency, in addition to ventilatory overactivation, in patients with moderately/severely increased VE/VCO_2 slope. CO indicates cardiac output; VCO_2, volume of exhaled carbon dioxide; VE, ventilation. *P<0.05 versus tertiles 2 and 3 for both VE/W and 1^{st}VT VE/W slopes; †P<0.05 versus tertile 3 for both VE/W and 1^{st}VT VE/W slopes; ‡P<0.05 versus tertile 1 and 2 for 1^{st}VT VCO_2/W slope (B) and CO/W slope (C).

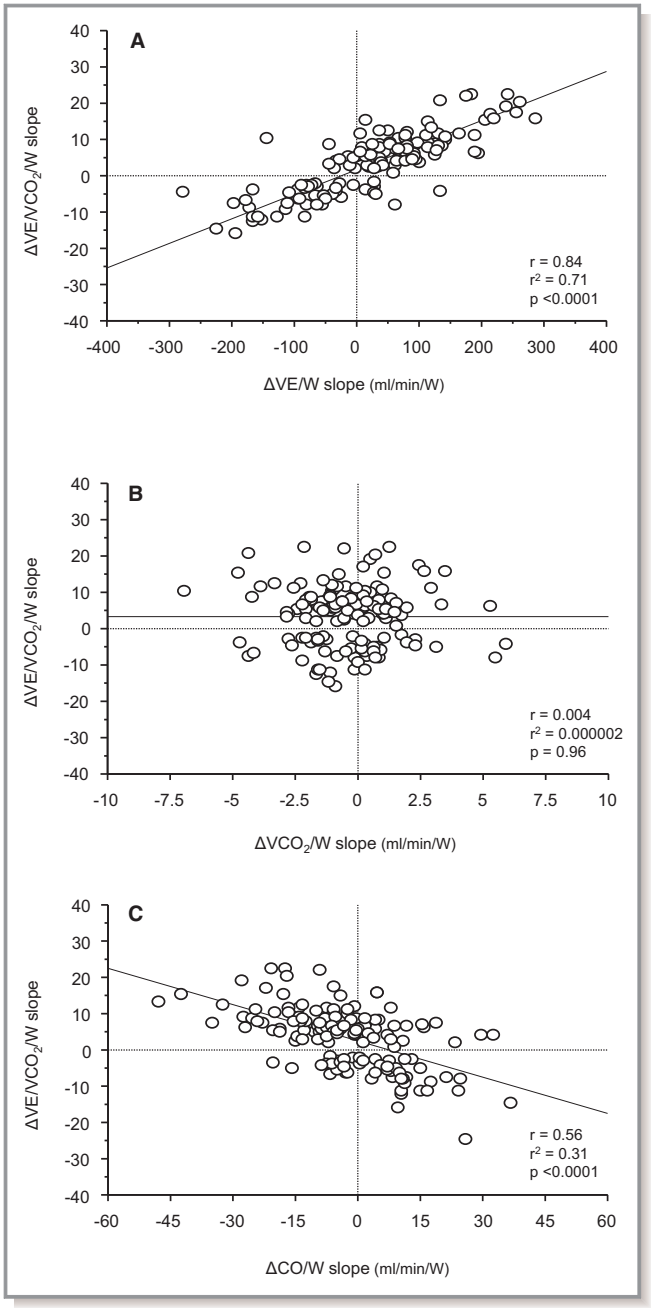

Figure 4. $\Delta VE/VCO_2$ slope as a function of $\Delta VE/W$ slope, $\Delta VCO_2/W$ slope, and $\Delta CO/W$ slope in the study population. $\Delta VE/VCO_2$ slope is directly related to $\Delta VE/W$ slope (A) and inversely to $\Delta CO/W$ slope (C). Conversely, no correlation at all is detected between $\Delta VE/VCO_2$ slope and $\Delta VCO_2/W$ slope (B). CO indicates cardiac output; VCO_2, volume of exhaled carbon dioxide; VE, ventilation; W, work rate.

average, as expected according to corresponding work rate reduction. This may lead to hypothesize an invariant hemodynamic picture across different tertiles. A similar VCO_2/W slope in CHF patients of different severities has already been described by Wasserman et al.[7] These researchers attributed their finding to a progressively increasing anaerobic metabolism-generated "excess VCO_2," which could somewhat distort the relationship between VCO_2/W slope and hemodynamic on-response. In any case, in the 2 versus 3 and 1 versus 3

groups, 1stVCO_2/W slope, that is, a parameter by definition independent of anaerobic metabolism, was found to be significantly lower in tertile 3 than in 1 or 2, supporting the concept of a reduced hemodynamic efficiency at submaximal effort in patients with highest VE/VCO_2 slope values. The finding in the same groups of a CO/W slope and peak O_2 pulse significantly lower in tertile 3 than in 1 or 2 lends further support to this point, arguing in favor of a hemodynamic impairment over the whole range of exercise intensities in more-compromised patients. This is in keeping with both the acknowledged progressive reduction of the CO versus exercise intensity slope with increasing disease severity[18,27] and the direct correlation between peak VE/VCO_2 ratio or VE/VCO_2 slope and peak Vd/Vt described in CHF patients.[7,8,21] Recent data further corroborate the relationship between VE/VCO_2 slope and hemodynamic inefficiency in CHF, showing an acute reduction of VE/VCO_2 slope in advanced CHF patients after switching on cardiac resynchronization (and thus acutely increasing cardiac output) as compared to the switched-off modality.[28] The mechanism by which hemodynamic inefficiency may lead to increased VE/perfusion ratio and Vd/Vt is a matter of debate. In this regard, a number of circulatory factors responsible for regional VE/perfusion mismatching have been advocated, among which intrinsic pulmonary vascular changes and impaired vasoregulation may play a crucial role.[29] On the other hand, modeling and animal studies have shown that an increased average VE/perfusion ratio, attributed to reduced global lung perfusion, can generate wasted VE independently of regional VE/perfusion mismatching.[30,31] Our data do not allow to distinguish between inefficient regional or global lung perfusion as a cause of increased wasted VE, nor to ascertain whether a threshold amount of global lung perfusion reduction has to be overcome to induce significant VE/perfusion mismatch.

Study Limitations

VE/VCO_2 slope and peak VO_2 are known to increase and decrease, respectively, with increasing age. In the present study, $\Delta VE/VCO_2$ slope was indeed directly related to time elapsed between CPETs in individual patients, which was reflected in the significantly older age of patients in tertiles 2 and 3 than tertile 1. However, differences in VE/VCO_2 slope and peak VO_2 between groups were maintained when expressing these parameters as a percentage of predicted value, that is, corrected for age and sex, thus allowing to exclude a significant effect of age on the results. We did not measure pCO_2 or Vd/Vt, so the relationship between VE/VCO_2 slope and ventilatory and/or hemodynamic inefficiency could not be directly evaluated. Longitudinal studies measuring exercise cardiac output, respiratory gas exchanges, and arterial blood gases in the presence of VE/VCO_2 slope changes during the clinical history of CHF or in response to a given intervention—such as aerobic exercise training[32] or beta-blocking therapy[33]—need to be designed to clarify this issue. The average VE/VCO_2 slope of the highest tertile of our population is 36.7; it is thus unknown whether our results apply also to patients with higher VE/VCO_2 slope values, in whom the relative contribution of ventilatory and hemodynamic factors may differ from that described here. Like every method used to indirectly estimate CO, also that used in the present study is open to criticism. Of note, however, we used an indirect Fick's principle calculation where only venous O_2 content and hemoglobin O_2 saturation were estimated, that is, 2 parameters with an acknowledged very low interindividual variability both at rest and peak incremental exercise not only in normal subjects, but also in CHF patients.[15–18] This should have kept the imprecision of our CO estimate (Table 1) within acceptable limits (see also Methods section). Finally, most of the study population were male, middle-aged patients; thus, applicability of our findings to female and/or elderly patients remains to be determined.

Conclusions

VE/VCO_2 slope is a major exercise-related risk marker in CHF, even more powerful than time-honored peak VO_2, and knowledge of its pathophysiological determinants is thus of paramount importance to optimize decision making in the clinical setting.[8,30] The key finding of our study is that the progressive increase of VE/VCO_2 slope observed with increasing disease severity in CHF may be attributed to different determinants according to the stage of disease pathophysiology. In patients with slightly increased VE/VCO_2 slope, an increase of ventilatory drive is the only detectable component, whereas in those with moderately/severely increased VE/VCO_2 slope an additional contribution of hemodynamic inefficiency becomes evident. These findings are consistent with ventilatory overactivation as the mechanistic cause of increased VE/VCO_2 slope at initial stages of the disease, with hemodynamic impairment as an additional determinant in more-advanced CHF patients. Knowledge of such a hierarchical course of ventilatory inefficiency pathophysiology may lead clinicians to a better assessment of clinical conditions and a more-mindful choice of therapeutic options in the CHF population.

Author Contributions

Mezzani conceived and planned the study. Mezzani and Giordano analyzed the data. Mezzani and Komici wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings and reporting of the work.

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Disclosures

None.

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Different Determinants of Ventilatory Inefficiency at Different Stages of Reduced Ejection Fraction Chronic Heart Failure Natural History

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