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

Alessandro Mezzani, MD, FESC; Andrea Giordano, PhD; Klara Komici, MD; Ugo Corrà, MD

Background—It is not known whether determinants of ventilation (VE)/volume of exhaled carbon dioxide (VCO₂) slope during incremental exercise may differ at different stages of reduced ejection fraction chronic heart failure natural history.

Methods and Results—VE/VCO₂ slope was fitted up to lowest VE/VCO₂ ratio, that is, a proxy of the VE/perfusion ratio devoid of nonmetabolic stimuli to ventilatory drive. VE/VCO₂ 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/VCO₂ slopes in 2 different tertiles were selected. Determinants of VE/VCO₂ slope changes across tertile pairs 1 versus 2, 2 versus 3, and 1 versus 3 were assessed by exploring changes in VE and VCO₂ at lowest VE/VCO₂ and those in VE/work rate (W) and VCO₂/W slope. Resting and peak cardiac output (CO) were calculated as VO₂/determined arteriovenous O₂ difference and the CO/W slope analyzed. Notwithstanding a progressively lower W with increasing tertile, VE at lowest VE/VCO₂ and VE/W slope were significantly higher in tertiles 2 and 3 versus tertile 1. Conversely, VCO₂ at lowest VE/VCO₂ and CO/W slope significantly decreased across tertiles, whereas VCO₂/W slope did not. Difference (Δ) in VE/W slope between tertiles accounted for 71% of ΔVE/VCO₂ slope variance, with ΔVCO₂/W slope explaining an additional 26% (model r²=0.99; r²=0.97; P<0.0001). Similar results were obtained substituting ΔVCO₂/W slope with ΔCO/W slope.

Conclusions—Ventilatory overactivation is the predominant cause of VE/VCO₂ 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 (VCO₂) 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/VCO₂ slope increase observed with increasing severity of CHF.¹⁻⁷ However, which of the 2 is the main cause of increased VE/VCO₂ slope in CHF has not been established as yet. In this regard, a crucial methodological issue is that all available studies dealing with VE/VCO₂ slope determinants have had a cross-sectional design, ruling out the possibility of exploiting the informative content of VE and VCO₂ 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/VCO₂ slope or ratio equals 863/pCO₂×(1−Vd/Vt), where pCO₂ is the arterial CO₂ partial pressure and Vd/Vt is the physiological dead space/tidal volume ratio.⁸ Accordingly, an increase of VE/VCO₂ 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/VCO₂ slope modifications over time, VE should be matched as closely as possible to metabolic CO₂ production in the absence of nonmetabolic stimuli (ie, anxiety and/or lactic-acid–generated H⁺) to ventilatory drive possibly reducing pCO₂. In fact, in this physiological context, (1) no acute hyperventilation occurs and stability of body CO₂ stores is expected, (2) changes in VCO₂ are more closely linked to those in cardiac output by Fick’s principle, and (3) the lowest VE/VCO₂ ratio represents

From the Exercise Pathophysiology Laboratory, Cardiac Rehabilitation Division (A.M., K.K., U.C.) and Bioengineering Service (A.G.), Istituti Clinici Scientifici Maugeri SB–Scientific Institute of Veruno IRCCS, Veruno (NO), Italy.

Correspondence to: Alessandro Mezzani, MD, FESC, Exercise Pathophysiology Laboratory, Cardiac Rehabilitation Division, Istituti Clinici Scientifici Maugeri SB–Scientific Institute of Veruno IRCCS, Via per Revislate, 13, 28010 Veruno (NO), Italy. E-mail: alessandro.mezzani@icsmaugeri.it
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the point in time when VE is best matched to perfusion relative to $V_{\text{CO}_2}$ and can be used as a proxy of the VE/perfusion ratio.\textsuperscript{9–12}

The aim of this study was to evaluate the relative contribution of VE and $V_{\text{CO}_2}$ to changes in VE/$V_{\text{CO}_2}$ slope over time in individual CHF patients. VE and $V_{\text{CO}_2}$ were evaluated as: (1) absolute values at lowest VE/$V_{\text{CO}_2}$; (2) change in VE and $V_{\text{CO}_2}$ 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 $V_{\text{O}_2}$/estimated arteriovenous $O_2$ difference, were also evaluated to enable more-reliable inferences about the relationship between VE/$V_{\text{CO}_2}$ slope and hemodynamics changes. All parameters were compared between different VE/$V_{\text{CO}_2}$ 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 $\geq$3 months at the time of CPET; (2) echocardiographic left ventricular ejection fraction $\leq$40%; (3) CPET stopped for fatigue and/or dyspnea with peak respiratory exchange ratio of $\geq$1.05; and (4) availability of at least 2 tests in the same patient over the evaluated time period. Accordingly, 1662 tests (carried out in 464 patients) were eligible for the study and divided into 3 groups based on tertiles of VE/$V_{\text{CO}_2}$ slope, namely, $<$27.5 (tertile 1), $\geq$27.5 to $<$32.0 (tertile 2), and $\geq$32.0 (tertile 3).

Subsequently, a further selection was made looking for availability of test pairs in different VE/$V_{\text{CO}_2}$ 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/$V_{\text{CO}_2}$ 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 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.

Daily $\beta$-blocker carvedilol-equivalent dose was calculated for patients on bisoprolol and nebivolol as dose $\times$5 and as dose/4 for those on metoprolol.\textsuperscript{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.

**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; $V_{\text{CO}_2}$, volume of exhaled carbon dioxide; VE, ventilation.
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, VCO₂, and VO₂ 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 VO₂ was recorded as the mean of values observed during the last 30 seconds of the exercise phase and the first ventilatory threshold (1stVT) estimated by the V-slope and/or respiratory equivalents methods.11,12

Predicted VO₂max and VE/VCO₂ slope values were determined according to formulae outlined by Wasserman et al12 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 VO₂ and estimated arteriovenous O₂ difference values as CO (L/min) = VO₂ (mL/min)/arteriovenous O₂ difference (mL/L).14,15

Resting and peak arterial O₂ content (CaO₂) were calculated as CaO₂ (mL/dL)=Hb (g/dL)×1.34 (mL O₂/g Hb)×SaO₂, where Hb is hemoglobin concentration, 1.34 is hemoglobin O₂ binding capacity, and SaO₂ is arterial hemoglobin O₂ saturation. Because of exercise-induced hemoconcentration, a value of Hb increased by 5% with respect to baseline was used to calculate peak CaO₂12,15 and, based on data from previous work15–17 and our laboratory, resting and peak SaO₂ were assumed to be equal to 0.97. According to available data, the resting and peak O₂ 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 O₂ difference, as follows:

Resting arterio — venous O₂ difference

= (Hb × 1.34 × 0.97) - [(Hb × 1.34 × 0.97) × 0.6]

Peak arterio — venous O₂ difference

= (Hb × 1.34 × 0.97) - [(Hb × 1.34 × 0.97) × 0.2]

Table 1 shows the variability of peak CO estimate when using the above-mentioned method, according to different peak O₂ extraction and peak SaO₂ combinations in a hypothetical patient with peak VO₂ of 1000 mL/min and peak hemoglobin of 14.0 g/dL. For the peak O₂ extraction value used in the present study (ie, 80%), a ±0.01 change in peak SaO₂ would result in a ±1% change in peak CO. Conversely, for the peak SaO₂ value used in the present study (ie, 0.97), a ±5% change in peak O₂ extraction would result in a ±6% change in peak CO.

Descriptors of Ventilatory and Hemodynamic Efficiency

Lowest VE/VCO₂ and VE/VCO₂ slope

For VE/VCO₂ 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 pCO₂10–12 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/VCO₂ or respiratory compensation point,11,12 is overcome before exercise end, making VE/VCO₂ increase more steeply because of the stimulus to ventilatory drive induced by lactic-acid–derived H⁺ ions, or (2) lowest VE/VCO₂ coincides with exercise phase end and no breakpoint of the VE versus VCO₂ relationship is detected, thus excluding acute hyperventilation during exercise. Lowest VE/VCO₂ was visually identified by 2 experienced operators (A.M. and K.K.), who examined the VE/VCO₂ versus time relationship plotted in 10-second–averaged values after deleting errant breath-by-breath data lying >4 SD away from

Table 1. Peak Cardiac Output Estimate Changes According to Different Peak O₂ Extraction and Peak Arterial Hemoglobin O₂ Saturation Estimate Combinations

<table>
<thead>
<tr>
<th>Peak SaO₂ estimate</th>
<th>70%</th>
<th>75%</th>
<th>80%</th>
<th>85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95</td>
<td>8.02</td>
<td>7.48</td>
<td>7.01</td>
<td>6.60</td>
</tr>
<tr>
<td>0.96</td>
<td>7.93</td>
<td>7.41</td>
<td>6.94</td>
<td>6.53</td>
</tr>
<tr>
<td>0.97</td>
<td>7.85</td>
<td>7.33</td>
<td>6.87</td>
<td>6.46</td>
</tr>
<tr>
<td>0.98</td>
<td>7.78</td>
<td>7.26</td>
<td>6.80</td>
<td>6.40</td>
</tr>
<tr>
<td>0.99</td>
<td>7.69</td>
<td>7.18</td>
<td>6.73</td>
<td>6.34</td>
</tr>
<tr>
<td>1.00</td>
<td>7.61</td>
<td>7.11</td>
<td>6.66</td>
<td>6.27</td>
</tr>
</tbody>
</table>

The table reports peak cardiac output estimates using Fick’s principle according to different peak O₂ extraction and peak arterial hemoglobin O₂ saturation combinations. For descriptive purposes, peak cardiac output (L/min) is calculated using a peak VO₂ value of 1000 mL/min and a peak hemoglobin value of 14.0 g/dL. The gray cell corresponds to the peak O₂ extraction and peak hemoglobin O₂ saturation estimate combination used in the present study. See text for further details. Peak SaO₂ = peak arterial hemoglobin oxygen saturation.
the local mean. Lowest VE/VCO₂ 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/VCO₂ slope fitting window was delimited excluding resting data and, when present, data following the lowest VE/VCO₂.

**VE/work rate, VCO₂/work rate, and CO/work rate slopes**

The VE/work rate and VCO₂/work rate slopes (VE/W slope and VCO₂/W slope, respectively) were calculated as the difference in VE and VCO₂ from 1 minute after the work rate started to increase to the point of lowest VE/VCO₂, divided by work rate at lowest VE/VCO₂. 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 VCO₂. Of note, even in the absence of acute hyperventilation, VE/W slope and VCO₂/W slope steepness does increase above 1stVT because of the “excess VCO₂” generated by anaerobic metabolism activation and lactic acid buffering. Accordingly, VE/W slope and VCO₂/W slope were also calculated using 1stVT as the upper limit of the fitting window (1stVT VE/W slope and 1stVT VCO₂/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, VCO₂/W slope, time elapsed between CPETs, and carvedilol-equivalent β-blocker dose to that in VE/VCO₂ slope when moving from a lower to a higher tertile. Level of statistical significance was set at a 2-tailed P value of ≤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/VCO₂ 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 VO₂ values significantly and progressively decreased across tertiles, whereas peak heart rate (HR) and peak O₂ 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/VCO₂ 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/VCO₂ slope was inversely correlated with peak VO₂ (r=0.50; P<0.0001). A progressive and significant increase of lowest VE/VCO₂ with increasing tertile paralleled that of VE/VCO₂ slope. In the whole study population, lowest VE/VCO₂ was reached at 71±13%, 67±14% and 72±14% of peak work rate, peak VE, and peak VCO₂, respectively. The number of patients reaching lowest VE/VCO₂ 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 VCO₂ at lowest VE/VCO₂ in the 1 versus 2, 2 versus 3, and 1 versus 3 groups are shown in Figure 2. VE at lowest VE/VCO₂ 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
Ventilatory Inefficiency Causes in Heart Failure  Mezzani et al

Table 2. Demographic and Clinical-Instrumental Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Tertile 1 (&lt;27.5)</th>
<th>Tertile 2 (≥27.5 to &lt;32.0)</th>
<th>Tertile 3 (≥32.0)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>294</td>
<td>99</td>
<td>103</td>
<td>92</td>
<td>...</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>284 (97)</td>
<td>95 (96)</td>
<td>99 (96)</td>
<td>90 (98)</td>
<td>0.71</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>55±10</td>
<td>58±10*</td>
<td>61±10*</td>
<td>0.0011</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.28±4.56</td>
<td>26.37±4.87</td>
<td>26.08±4.24</td>
<td>26.41±4.60</td>
<td>0.85</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>13.5±1.4</td>
<td>13.9±1.3</td>
<td>13.4±1.4*</td>
<td>13.2±1.5*</td>
<td>0.0068</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.1±0.6</td>
<td>1.9±0.6</td>
<td>2.1±0.6*</td>
<td>2.3±0.6†</td>
<td>0.0002</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±7</td>
<td>26±8</td>
<td>26±7</td>
<td>24±7</td>
<td>0.11</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>89±16</td>
<td>91±17</td>
<td>89±17</td>
<td>86±14</td>
<td>0.34</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>85±18</td>
<td>88±18</td>
<td>84±18</td>
<td>82±16</td>
<td>0.15</td>
</tr>
<tr>
<td>β-blocker type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>46 (16)</td>
<td>12 (12)</td>
<td>17 (16)</td>
<td>17 (18)</td>
<td>0.54</td>
</tr>
<tr>
<td>CAR</td>
<td>158 (54)</td>
<td>54 (55)</td>
<td>56 (55)</td>
<td>48 (52)</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>No β-b</td>
<td>9 (3)</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Carvedilol-equivalent β-blocker dose, mg/day</td>
<td>19.5±13.5</td>
<td>20.6±13.4</td>
<td>19.6±13.3</td>
<td>18.4±13.7</td>
<td>0.62</td>
</tr>
<tr>
<td>ACE-I, n (%)</td>
<td>272 (92)</td>
<td>94 (94)</td>
<td>103 (100)</td>
<td>82 (89)</td>
<td>0.31</td>
</tr>
<tr>
<td>Loop diuretic, n (%)</td>
<td>269 (91)</td>
<td>88 (89)</td>
<td>96 (93)</td>
<td>85 (92)</td>
<td>0.52</td>
</tr>
<tr>
<td>Loop diuretic dose, mg/day</td>
<td>81.1±83.9</td>
<td>62.7±45.6</td>
<td>71.5±82.1</td>
<td>110.9±106.5†</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

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.

Discussion

The results of the present study provide new insights into CHF exercise pathophysiology. Our major finding is that changes in VE/VCO₂ 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/VCO₂ 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/
severely increased VE/VCO₂ 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/VCO₂ slope in the more-advanced CHF stages.

Studies investigating the pathophysiological basis for an increased VE/VCO₂ slope in CHF have reported conflicting results. Enhanced ventilatory reflex sensitivity because of autonomic imbalance, early exercise-induced metabolic acidosis, lowered chemoceptive pCO₂ set point, and restrictive respiratory pattern with increased respiratory rate 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/VCO₂ slope.5–7 However, it is not clear whether relative hyperventilation or VE/perfusion mismatch plays the major role in increasing VE/VCO₂ 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/VCO₂ slope in CHF, no stratification of data by increasing VE/VCO₂ slope values has ever been carried out. This is the first protocol to systematically evaluate dynamic changes in VE and VCO₂ as related to those in VE/VCO₂ slope over the natural course of CHF, thus enabling modifications in VE/VCO₂ 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/VCO₂ 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/VCO₂ 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 1st VT VE/W slope with increasing tertile in 1 versus 2, 2 versus 3, and 1 versus 3 (Figure 3 and Table 3); and (3) the strong direct relationship linking ΔVE/VCO₂ slope and ΔVE/W slope (Figure 4), with the latter accounting for around three quarters of ΔVE/VCO₂ slope variance. Notably, an increased VE/W slope was evident...
since the very beginning of exercise in all VE/VCO\textsubscript{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\textsubscript{2} set point. Even if no data have yet been reported about autonomic overactivation in CHF stratified by different VE/VCO\textsubscript{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\textsubscript{2} slope and peak VO\textsubscript{2}.\textsuperscript{3,22,23} In addition, a derangement in cardiopulmonary reflex control occurs early in the course of CHF.\textsuperscript{24,25} In this regard, Ponikowski et al have described an increased VE/VCO\textsubscript{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.\textsuperscript{26} These data are consistent with the slightly increased ventilatory drive we documented in patients with a slight increase of VE/VCO\textsubscript{2} slope in the presence of an unchanged CO/W slope.

On the other hand, VCO\textsubscript{2} at lowest VE/VCO\textsubscript{2} progressively and significantly decreased with increasing VE/VCO\textsubscript{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\textsubscript{2}/W slope among tertiles, making VCO\textsubscript{2} at lowest VE/VCO\textsubscript{2} diminish, on

**Table 4.** Comparisons of Ventilatory and Hemodynamic Efficiency Descriptors Between Different VE/VCO\textsubscript{2} Slope Tertile Pairs

<table>
<thead>
<tr>
<th>Tertile 1 (&lt;27.5)</th>
<th>Tertile 2 (27.5 to &lt;32.0)</th>
<th>Tertile 3 (≥32.0)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/W slope, mL/min per watt</td>
<td>1 vs 2 266.49</td>
<td>321.50</td>
<td>...</td>
</tr>
<tr>
<td>2 vs 3 ...</td>
<td>316.45</td>
<td>374.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 vs 3 270.54</td>
<td>...</td>
<td>400.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1\textsuperscript{st} VT VE/W slope, mL/min per watt</td>
<td>1 vs 2 227.74</td>
<td>286.94</td>
<td>...</td>
</tr>
<tr>
<td>2 vs 3 ...</td>
<td>294.70</td>
<td>323.95</td>
<td>0.07</td>
</tr>
<tr>
<td>1 vs 3 267.67</td>
<td>...</td>
<td>348.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VCO\textsubscript{2}/W slope, mL/min per watt</td>
<td>1 vs 2 10.8±1.7</td>
<td>10.8±1.6</td>
<td>...</td>
</tr>
<tr>
<td>2 vs 3 ...</td>
<td>10.6±1.5</td>
<td>10.3±1.5</td>
<td>0.20</td>
</tr>
<tr>
<td>1 vs 3 11.0±1.9</td>
<td>...</td>
<td>10.8±1.6</td>
<td>0.62</td>
</tr>
<tr>
<td>1\textsuperscript{st} VT VCO\textsubscript{2}/W slope, mL/min per watt</td>
<td>1 vs 2 9.3±2.3</td>
<td>9.8±2.4</td>
<td>...</td>
</tr>
<tr>
<td>2 vs 3 ...</td>
<td>9.7±1.9</td>
<td>9.0±2.9</td>
<td>0.16</td>
</tr>
<tr>
<td>1 vs 3 10.6±2.0</td>
<td>...</td>
<td>9.2±1.9</td>
<td>0.006</td>
</tr>
<tr>
<td>CO/W slope, mL/min per watt</td>
<td>1 vs 2 49±16</td>
<td>50±14</td>
<td>...</td>
</tr>
<tr>
<td>2 vs 3 ...</td>
<td>50±14</td>
<td>44±15</td>
<td>0.058</td>
</tr>
<tr>
<td>1 vs 3 56±11</td>
<td>...</td>
<td>45±14</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

1\textsuperscript{st} VT 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\textsubscript{2}, volume of exhaled carbon dioxide; VE, ventilation.
average, as expected according to corresponding work rate reduction. This may lead to hypothesize an invariant hemodynamic picture across different tertiles. A similar \( \text{VCO}_2/\text{W} \) 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 \( \text{VCO}_2 \)” which could somewhat distort the relationship between \( \text{VCO}_2/\text{W} \) slope and hemodynamic on-response. In any case, in the 2 versus 3 and 1 versus 3

**Figure 3.** Ventilation, \( \text{VCO}_2 \), 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 \((1^{\text{st}}\text{VT})\), lowest \( \text{VE}/\text{VCO}_2 \), and peak exercise, respectively. Data are expressed as mean±SD. The \( \text{VE}/\text{W} \) slope and \( 1^{\text{st}}\text{VT} \) \( \text{VE}/\text{W} \) slope (A) progressively increase across \( \text{VE}/\text{VCO}_2 \) tertiles, whereas the \( \text{VCO}_2/\text{W} \) slope does not (B). On the contrary, both \( 1^{\text{st}}\text{VT} \) \( \text{VCO}_2/\text{W} \) slope (B) and cardiac output/\( \text{W} \) 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 \( \text{VE}/\text{VCO}_2 \) slope. \( \text{CO} \) indicates cardiac output; \( \text{VCO}_2 \), volume of exhaled carbon dioxide; \( \text{VE} \), ventilation. \(* P<0.05 \) versus tertiles 2 and 3 for both \( \text{VE}/\text{W} \) and \( 1^{\text{st}}\text{VT} \) \( \text{VE}/\text{W} \) slopes; \( \dagger P<0.05 \) versus tertile 3 for both \( \text{VE}/\text{W} \) and \( 1^{\text{st}}\text{VT} \) \( \text{VE}/\text{W} \) slopes; \( \ddagger P<0.05 \) versus tertile 1 and 2 for \( 1^{\text{st}}\text{VT} \) \( \text{VCO}_2/\text{W} \) slope (B) and \( \text{CO}/\text{W} \) slope (C).

**Figure 4.** \( \Delta \text{VE}/\text{VCO}_2 \) slope as a function of \( \Delta \text{VE}/\text{W} \) slope, \( \Delta \text{VCO}_2/\text{W} \) slope, and \( \Delta \text{CO}/\text{W} \) slope in the study population. \( \Delta \text{VE}/\text{VCO}_2 \) slope is directly related to \( \Delta \text{VE}/\text{W} \) slope (A) and inversely to \( \Delta \text{CO}/\text{W} \) slope (C). Conversely, no correlation at all is detected between \( \Delta \text{VE}/\text{VCO}_2 \) slope and \( \Delta \text{VCO}_2/\text{W} \) slope (B). \( \text{CO} \) indicates cardiac output; \( \text{VCO}_2 \), volume of exhaled carbon dioxide; \( \text{VE} \), ventilation; \( \text{W} \), work rate.
groups, $^{13}$VCO$_2$/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$^{16,27}$ 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$^{12}$ 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.$^9,30$ 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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