

# Gender and age normalization and ventilation efficiency during exercise in heart failure with reduced ejection fraction

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## Abstract

**Aims** Ventilation vs. carbon dioxide production ( $VE/VCO_2$ ) is among the strongest cardiopulmonary exercise testing prognostic parameters in heart failure (HF). It is usually reported as an absolute value. The current definition of normal  $VE/VCO_2$  slope values is inadequate, since it was built from small groups of subjects with a particularly limited number of women and elderly. We aimed to define  $VE/VCO_2$  slope prediction formulas in a sizable population and to test whether the prognostic power of  $VE/VCO_2$  slope in HF was different if expressed as a percentage of the predicted value or as an absolute value.

**Methods and results** We calculated the linear regressions between age and  $VE/VCO_2$  slope in 1136 healthy subjects (68% male, age  $44.9 \pm 14.5$ , range 13–83 years). We then applied age-adjusted and sex-adjusted formulas to predict  $VE/VCO_2$  slope to HF patients included in the metabolic exercise test data combined with cardiac and kidney indexes score database, which counts 6112 patients (82% male, age  $61.4 \pm 12.8$ , left ventricular ejection fraction  $33.2 \pm 10.5\%$ , peak $VO_2$   $14.8 \pm 4.9$ , mL/min/kg,  $VE/VCO_2$  slope  $32.7 \pm 7.7$ ) from 24 HF centres. Finally, we evaluated whether the use of absolute values vs. percentages of predicted  $VE/VCO_2$  affected HF prognosis prediction (composite of cardiovascular mortality + urgent transplant or left ventricular assist device). We did so in the entire cardiac and kidney indexes score population and separately in HF patients with severe (peak $VO_2 < 14$  mL/min/kg,  $n = 2919$ , 61.1 events/1000 pts/year) or moderate (peak $VO_2 \geq 14$  mL/min/kg,  $n = 3183$ , 19.9

events/1000 pts/year) HF. In the healthy population, we obtained the following equations: female,  $VE/VCO_2 = 0.052 \times \text{Age} + 23.808$  ( $r = 0.192$ ); male,  $VE/VCO_2 = 0.095 \times \text{Age} + 20.227$  ( $r = 0.371$ ) ( $P = 0.007$ ). We applied these formulas to calculate the percentages of predicted  $VE/VCO_2$  values. The 2-year survival prognostic power of  $VE/VCO_2$  slope was strong, and it was similar if expressed as absolute value or as a percentage of predicted value (AUCs 0.686 and 0.690, respectively). In contrast, in severe HF patients, AUCs significantly differed between absolute values (0.637) and percentages of predicted values (0.650,  $P = 0.0026$ ). Moreover,  $VE/VCO_2$  slope expressed as a percentage of predicted value allowed to reclassify 6.6% of peak  $VO_2 < 14$  mL/min/kg patients (net reclassification improvement = 0.066,  $P = 0.0015$ ).

**Conclusions** The percentage of predicted  $VE/VCO_2$  slope value strengthens the prognostic power of  $VE/VCO_2$  in severe HF patients, and it should be preferred over the absolute value for HF prognostication. Furthermore, the widespread use of  $VE/VCO_2$  slope expressed as percentage of predicted value can improve our ability to identify HF patients at high risk, which is a goal of utmost clinical relevance.

**Keywords** Cardiopulmonary exercise test; Prognosis; Ventilation efficiency; Heart failure

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## Introduction

In spite of new treatments and updated clinical management, heart failure (HF) is still characterized by high rates of mortality and morbidity.<sup>1</sup> Therefore, refining prognostic stratification in HF is of utmost importance to guide patients' clinical management strategy.

Cardiopulmonary exercise testing (CPET) is a strongly established tool to assess functional status and prognosis in HF, so that its use is recommended to identify patients at high risk and those eligible for heart transplant.<sup>2–5</sup> Among the bulk of variables provided by CPET, the most useful parameters widely recognized to assess prognosis are oxygen consumption at peak exercise (peak  $VO_2$ ) and ventilatory efficiency assessed through the measurement of the slope of the relationship between minute ventilation and carbon dioxide production ( $VE/VCO_2$ ).<sup>6,7</sup> Peak  $VO_2$ , proposed since 1985,<sup>8</sup> has long been considered the gold standard for assessing HF severity and prognosis through CPET; however, an important prognostic role has been more recently reported also for  $VE/VCO_2$ .<sup>6,9</sup> Indeed,  $VE/VCO_2$  slope has been proven strongly associated with pulmonary and cardiac function and with pulmonary haemodynamics and prognosis.<sup>9–11</sup>

Peak  $VO_2$  data are reported either as absolute values or as percentages of a normal predicted value. The latter is nowadays preferred in the general HF population for HF prognosis,<sup>10,12</sup> although heart transplant guidelines use an absolute/kg peak  $VO_2$  value as a cut-off.<sup>5</sup> Several studies have been performed to build peak  $VO_2$  predicted values.<sup>12–14</sup> At present, the most frequently applied peak  $VO_2$  prediction formulas are those by Hansen *et al.*<sup>14</sup> and Jones *et al.*<sup>15</sup> In contrast, data are less defined with respect to  $VE/VCO_2$ . A cut-off value of 34 was proposed a few years ago, and it is still currently used to discriminate patients at high risk of mortality.<sup>6,16,17</sup> However, the use of a unique, non-gender-specific, absolute value might nowadays not be applicable to all age

groups of patients. Only a few studies, with a limited number of subjects, have been conducted to better define  $VE/VCO_2$  slope characteristics across the normal population.<sup>18–21</sup> Those studies reported higher values in females than in males and a positive correlation between  $VE/VCO_2$  slope and age, but an accepted formula for a  $VE/VCO_2$  slope predicted value is still lacking.

Accordingly, aims of the present study were to define normal values of  $VE/VCO_2$  slope in a large population of healthy subjects and to test whether the prognostic role of  $VE/VCO_2$  slope in the HF population would be different if expressed as percentage of predicted value, as calculated by these equations, or as absolute value.

## Methods

### Population

In the first part of the project, we assessed CPET data obtained in nine of our laboratories over the last 20 years (1998–2018). The population was represented by 1136 healthy subjects of either gender, aged between 13 and 83 years. All available maximal tests in healthy subjects were included.

We calculated the linear regression between age and  $VE/VCO_2$  relationship slope, in the entire population, and separately for males and females.

In the second part of the study, the equations derived from the healthy population were applied to the metabolix exercise combined with cardiac and kidney indexes (MECKI) score HF population, which includes 6112 HF patients enrolled between 1993 and 2015 and followed in 23 Italian HF centres.<sup>22</sup> The MECKI score registry inclusion/exclusion criteria and patient follow-up methodology have been

reported elsewhere in detail.<sup>10</sup> In brief, inclusion criteria of MECKI score patients were previous or present HF symptoms and former documentation of left ventricular ejection fraction (LVEF) <40%, unchanged HF medications for at least 3 months, ability to perform a CPET, and no major treatment or intervention scheduled. Exclusion criteria were history of pulmonary embolism, moderate-to-severe aortic or mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina, and significant ECG alterations, or presence of any clinical comorbidity interfering with exercise performance. Patient follow-up was performed according to each centre's protocol.

We calculated the percentage of the predicted value of VE/VCO<sub>2</sub> slope in the 6112 HF patients, using, as referral, the equations found in the healthy population for males and females. The prognostic significance of VE/VCO<sub>2</sub> slope expressed as absolute value was then compared with the percentage of predicted value. Following the MECKI score criteria,<sup>10</sup> prognosis was assessed as the composite of cardiovascular mortality + urgent transplant or left ventricular assist device implant.

The present research protocol complies with the Declaration of Helsinki, and it was approved by the Ethical Committee of Centro Cardiologico Monzino, IRCCS (CCM-127).

### Cardiopulmonary exercise test

All healthy subjects performed a progressive incremental ramp protocol using an electronically braked cycle ergometer. In the MECKI score registry, CPET was performed and reported according to standard criteria.<sup>23</sup> Specifically, the majority of HF patients (94%,  $n = 5768$ ) performed CPET using a ramp protocol on an electronically braked cycle ergometer, while the remaining (6%,  $n = 344$ ) performed CPET on a treadmill with a modified Bruce protocol. Both in HF patients and in healthy subjects, the cycle ergometer CPET protocol was set to reach peak exercise in ~10 min, but tests were stopped as subjects reported maximal effort.<sup>24</sup> Peak VO<sub>2</sub> was calculated as the 20 s average of the highest recorded VO<sub>2</sub>, while VE/VCO<sub>2</sub> slope was calculated as the slope of the linear relationship between VE and VCO<sub>2</sub> from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Peak VO<sub>2</sub> predicted value percentage was calculated according to Hansen et al.<sup>14</sup> Peak exercise respiratory exchange ratio was measured as VCO<sub>2</sub>/VO<sub>2</sub>.

## Results

The population of the present study was made up of 1136 healthy subjects (773 male, 68%) and 6112 patients with HF (5001 male, 82%). Characteristics of the healthy subjects and results of CPETs are reported in *Table 1*. No differences

were found in terms of age between genders; VO<sub>2</sub> was significantly higher in males ( $P < 0.001$  for absolute values), and VE/VCO<sub>2</sub> slope was higher in females ( $P < 0.001$ ).

HF patients' characteristics are reported in *Table 2* for the entire population and for either gender separately. Treatment included ACE inhibitors in 75% of cases, angiotensin receptor blockers in 19%, beta-blockers in 87%, diuretics in 80%, and mineralcorticoid receptor antagonists in 52%.<sup>2</sup>

In healthy individuals, a significant correlation between VE/VCO<sub>2</sub> slope and age was found both in males and in females ( $P < 0.001$ ). Linear regression between the VE/VCO<sub>2</sub> slope of healthy subjects and their age is shown in *Figure 1* for the total population (upper panel), in males (middle panel), and in females (lower panel). Specifically, the following regression equations were calculated: entire population predicted VE/VCO<sub>2</sub> =  $0.080 \times \text{Age} + 21.413$  ( $r = 0.303$ ), female gender predicted VE/VCO<sub>2</sub> =  $0.052 \times \text{Age} + 23.808$  ( $r = 0.192$ ), and male gender predicted VE/VCO<sub>2</sub> =  $0.095 \times \text{Age} + 20.227$  ( $r = 0.371$ ). The male and female VE/VCO<sub>2</sub> slope predictions resulted significantly different ( $P = 0.007$ ).

The two gender-specific equations were used to calculate the percentage of predicted values of VE/VCO<sub>2</sub> in the HF population. Average VE/VCO<sub>2</sub> slope and percentage of predicted VE/VCO<sub>2</sub> values are reported in *Table 2* for the entire population and for both genders.

HF patients were evaluated considering the entire HF population ( $n = 6112$ ) or grouping patients according to HF severity based on peak VO<sub>2</sub>, using the cut-off value of 14 mL/min/kg. *Table 3* shows the differences between these groups.

In *Table 4*, we report the AUCs at 2 years of follow-up for VE/VCO<sub>2</sub> slope and percentage of predicted value in the total population, dividing the population according to HF severity. AUCs were significantly different in HF patients with peak VO<sub>2</sub> < 14 mL/min/kg. *Figure 2* shows the ROC in patients with peak VO<sub>2</sub> < 14 mL/min/kg in the left panel and with peak VO<sub>2</sub> ≥ 14 mL/min/kg in the right panel ( $P = 0.0026$ ).

VE/VCO<sub>2</sub> expressed as percentage of predicted value allowed reclassifying 6.6% of patients (net reclassification improvement = 0.066,  $P = 0.0015$ ).

## Discussion

In the present study, we built VE/VCO<sub>2</sub> slope prediction equations based on a large population of normal subjects, and we applied these formulas to the MECKI score database. VE/VCO<sub>2</sub> reported as a percentage of predicted value confirmed to be a strong prognostic predictor in HF patients, but with a power similar to that observed using absolute VE/VCO<sub>2</sub> values. However, in patients with severe HF, defined as those with low peak VO<sub>2</sub>, data reported as percentages of predicted value have a stronger prognostic capacity.

**Table 1** Characteristics of the healthy subjects

	Total population (1136)	Male (773)	Female (363)	P
Age (years)	44.9 ± 14.5	45.2 ± 14.6	44.4 ± 14.3	ns
Weight (kg)	72.5 ± 13.8	78.2 ± 11.6	60.3 ± 9.6	<0.001
Height (cm)	172.6 ± 10.3	176.4 ± 9.4	164.5 ± 6.9	<0.001
Peak VO <sub>2</sub> (mL/min)	2287 ± 799	2636 ± 709	1550 ± 355	<0.001
Peak VO <sub>2</sub> (mL/min/kg)	31.7 ± 9.8	34.2 ± 10.0	26.2 ± 6.5	<0.001
Peak VO <sub>2</sub> (% of predicted)	94.4 ± 22.2	84.2 ± 24.1	92.6 ± 18.5	0.035
VE/VCO <sub>2</sub> slope	25.0 ± 3.8	24.5 ± 3.7	26.1 ± 3.9	<0.001
Workload (watt)	175 ± 74	203 ± 70	115 ± 36	<0.001
Peak RER	1.3 ± 0.1	1.3 ± 0.1	1.1 ± 0.1	ns
Peak VE (L/min)	74.9 ± 25.5	84.2 ± 24.1	55.3 ± 15.1	<0.001
Peak HR (bpm)	157 ± 22	158 ± 22	156 ± 21	ns

Peak VO<sub>2</sub>, oxygen uptake at peak exercise; VE/VCO<sub>2</sub> slope, ventilatory efficiency by means of CO<sub>2</sub> production/ventilation relationship; RER, respiratory exchange ratio; VE, ventilation; HR, heart rate.

**Table 2** Characteristics of the heart failure patients

	Total population (6112)	Male (5001)	Female (1111)	P
Age (years)	61.4 ± 12.8	61.3 ± 12.6	61.7 ± 13.5	ns
Height (cm)	169.8 ± 8.3	171.8 ± 7.2	161.1 ± 7.2	<0.001
Weight (kg)	77.4 ± 14.7	79.7 ± 13.9	67.1 ± 13.5	<0.001
NYHA I <i>n</i> (%)	919 (15%)	805 (16%)	114 (10%)	<0.001
NYHA II <i>n</i> (%)	3455 (57%)	2792 (56%)	664 (60%)	
NYHA III <i>n</i> (%)	1660 (27%)	1337 (23%)	322 (29%)	
NYHA IV <i>n</i> (%)	75 (1%)	65 (1%)	10 (1%)	
Peak VO <sub>2</sub> (mL/min)	1148 ± 433	1209 ± 435	874 ± 287	<0.001
Peak VO <sub>2</sub> (mL/min/kg)	14.8 ± 4.9	15.2 ± 4.9	13.2 ± 4.2	<0.001
Peak VO <sub>2</sub> (% of predicted)	56.0 ± 17.4	54.5 ± 16.9	62.8 ± 18.2	<0.001
VE/VCO <sub>2</sub> slope	32.8 ± 7.7	32.7 ± 7.7	33.2 ± 7.8	0.039
VE/VCO <sub>2</sub> slope (% pred)	124.0 ± 30.7	121.7 ± 30.6	124.5 ± 30.6	0.007
Workload (watt)	83 ± 34	87 ± 35	63 ± 24	<0.001
Peak RER	1.11 ± 0.12	1.12 ± 0.12	1.10 ± 0.13	<0.001
Peak VE (L/min)	46.3 ± 14.7	48.5 ± 14.5	36.3 ± 11.3	<0.001
Peak HR (bpm)	119 ± 25	120 ± 25	121 ± 26	0.04
Periodic breathing <i>n</i> (%)	1028 (17%)	883 (18%)	145 (13%)	<0.001
LVEF (%)	33.2 ± 10.5	32.4 ± 10.1	36.7 ± 11.6	<0.001
Haemoglobin (g/dL)	13.5 ± 1.6	13.6 ± 1.6	12.7 ± 1.3	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	71.4 ± 23.9	72.3 ± 23.9	67.4 ± 23.6	<0.001
HR rest (bpm)	71 ± 12	71 ± 13	72 ± 12	0.008
BNP (ng/mL) <sup>a</sup>	235 [91–631]	261 [100–703]	157 [78–409]	<0.001
Idiopathic aetiology <i>n</i> (%)	2399 (39%)	1889 (38%)	510 (46%)	<0.001
Ischaemic aetiology <i>n</i> (%)	2794 (46%)	2518 (50%)	276 (25%)	
Valvular aetiology <i>n</i> (%)	272 (4%)	177 (4%)	95 (9%)	
ICD <i>n</i> (%)	1905 (3%)	1660 (33%)	245 (22%)	<0.001
CRT <i>n</i> (%)	748 (12%)	629 (13%)	119 (11%)	0.041
Mortality rate (events/1000 pts/year)	39.2	41.9	26.9	0.06

NYHA, New York Heart Association class; peak VO<sub>2</sub>, oxygen uptake at peak exercise; VE/VCO<sub>2</sub> slope, ventilatory efficiency by means of CO<sub>2</sub> production/ventilation relationship; RER, respiratory exchange ratio; VE, ventilation; HR, heart rate; eGFR, glomerular filtration rate estimated by modification of diet in renal disease formula; BNP, brain natriuretic peptide; ICD, implantable cardiac defibrillator; CRT, cardio resynchronization therapy.

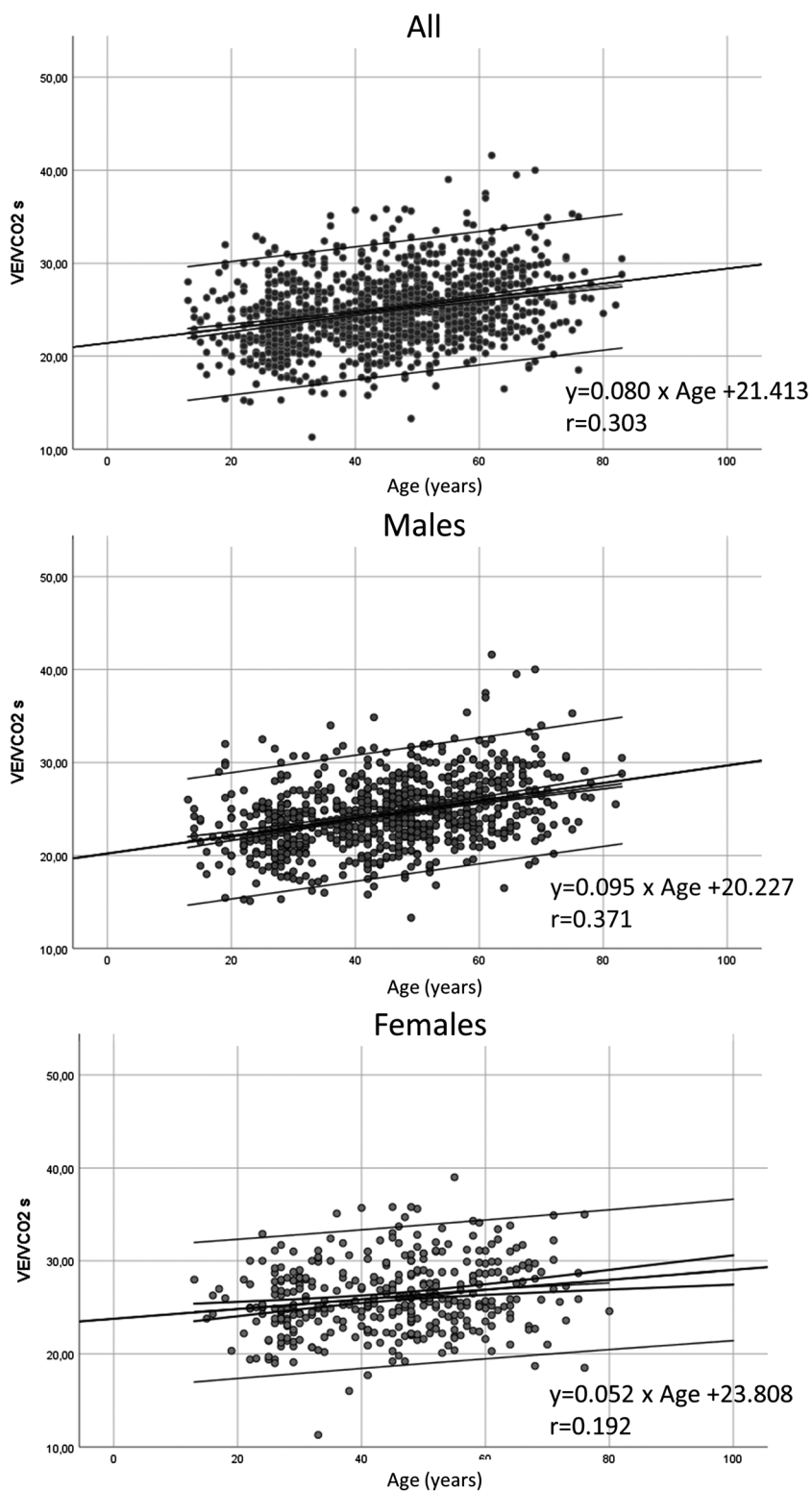
<sup>a</sup>BNP value was available in 2774 cases.

The formula we derived for VE/VCO<sub>2</sub> prediction is similar to those previously reported, but it was built on a much larger number of healthy individuals of both genders (Table 5). We preferred to put together our own standards for a few reasons: (i) to utilize the same laboratories used for HF patients' evaluation; (ii) to base our prediction on a much larger population comprehensive of both genders with subjects of all ages; (iii) to include data of several laboratories with a prolonged recruitment time; (iv) to be sure that subjects with any symptoms, known disease, or taking

any treatment were excluded; (v) finally, but most importantly, to exclude highly trained subjects and athletes, so that the population analysed presumably has the same living habits as tested patients. Accordingly, peak VO<sub>2</sub> observed in the present healthy population was 93 and 84% of the predicted value in females and males, respectively, as calculated on a US-based population.<sup>14</sup>

It should be acknowledged that healthy individuals were only tested on a cycle ergometer, so that it is unknown whether subjects tested with treadmill show a different

**Figure 1** Linear regression between VE/VCO<sub>2</sub> and age in the total population and according to gender. Equations describing the linear regression between VE/VCO<sub>2</sub> and age in all healthy subjects (upper panel), in males (middle panel) and in females (lower panel) are reported.





**Table 3** Characteristics of patients according to heart failure severity

	VO <sub>2</sub> ≥ 14 mL/min/kg (n = 3183)	VO <sub>2</sub> < 14 mL/min/kg (n = 2919)	P
Age (years)	58.0 ± 12.8	65.1 ± 11.6	<0.001
Gender (male)	2768 (89%)	2233 (76%)	<0.001
Height (cm)	170.8 ± 8.1	168.7 ± 8.4	<0.001
Weight (kg)	77.5 ± 13.9	77.3 ± 15.5	ns
NYHA I n (%)	748 (23%)	171 (5%)	<0.001
NYHA II n (%)	1908 (60%)	1544 (53%)	
NYHA III n (%)	506 (16%)	1147 (39%)	
NYHA IV n (%)	18 (1%)	57 (2%)	
Peak VO <sub>2</sub> (mL/min)	1422 ± 391	851 ± 234	<0.001
Peak VO <sub>2</sub> (mL/min/kg)	18.4 ± 4.0	11.0 ± 2.0	<0.001
Peak VO <sub>2</sub> (% of predicted)	66.0 ± 15.0	45.1 ± 12.7	<0.001
VE/VCO <sub>2</sub> slope	29.9 ± 5.6	35.9 ± 8.5	<0.001
VE/VCO <sub>2</sub> slope (% of predicted)	114.7 ± 23.6	134.1 ± 34.1	<0.001
Workload (watt)	60.9 ± 25.1	40.7 ± 18.4	<0.001
Peak RER	1.12 ± 0.11	1.10 ± 0.13	<0.001
Peak VE (L/min)	53.1 ± 14.4	38.8 ± 11.2	<0.001
Peak HR (bpm)	127 ± 23	111 ± 24	<0.001
Periodic breathing n (%)	365 (%)	660 (23%)	<0.001
LVEF (%)	34.4 ± 10.2	31.9 ± 10.7	<0.001
Haemoglobin (g/dL)	13.8 ± 1.5	13.1 ± 1.6	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	77.4 ± 22.5	65.2 ± 23.8	<0.001
HR rest (bpm)	70 ± 12	71 ± 13	<0.001
BNP (ng/mL)	160 [73–462]	340 [122–801]	<0.001
Idiopathic aetiology n (%)	1417 (46%)	977 (34%)	<0.001
Ischaemic aetiology n (%)	1319 (41%)	1471 (50%)	
Valvular aetiology n (%)	110 (3.5%)	162 (6%)	
ICD n (%)	877 (28%)	1026 (35%)	<0.001
CRT n (%)	303 (10%)	442 (15%)	<0.001
Mortality rate (events/1000 pts/year)	19.9	61.1	<0.001

LVEF, left ventricular ejection fraction; Peak VO<sub>2</sub>, oxygen uptake at peak exercise; VE/VCO<sub>2</sub> slope, ventilatory efficiency by means of CO<sub>2</sub> production/ventilation relationship; GFR, glomerular filtration rate estimated by modification of diet in renal disease formula; BNP, brain natriuretic peptide, NYHA, New York Heart Association class; ICD, implantable cardiac defibrillator; CRT, cardio resynchronization therapy.

**Table 4** AUC at 2 years of follow-up for VE/VCO<sub>2</sub> slope and percentage of predicted value in the total population and according to heart failure severity

	VE/VCO <sub>2</sub> slope	VE/VCO <sub>2</sub> slope percentage of predicted value	P
Entire population	0.686	0.690	ns
Peak VO <sub>2</sub> < 14 mL/min/kg	0.637	0.650	0.0026
Peak VO <sub>2</sub> ≥ 14 mL/min/kg	0.658	0.655	ns

Peak VO<sub>2</sub>, oxygen uptake at peak exercise; VE/VCO<sub>2</sub> slope, ventilatory efficiency by means of CO<sub>2</sub> production/ventilation relationship.

**Table 5** Regressions proposed to calculate predicted VE/VCO<sub>2</sub> slope

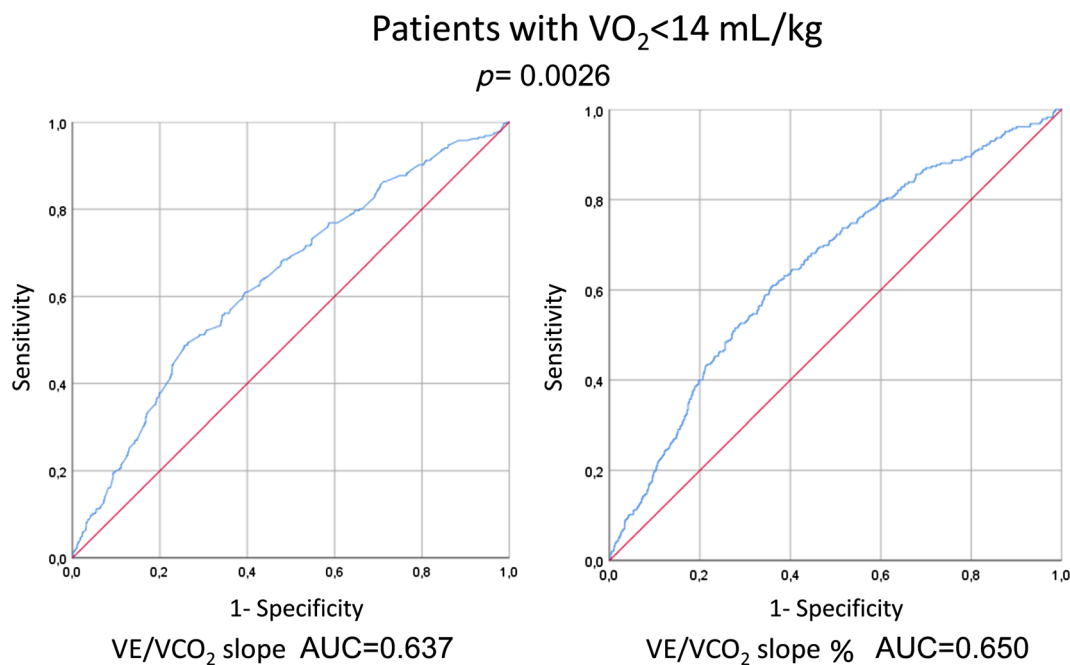
Paper	N (male/female)	Male	Female	Age	Ergometer
Salvioni 2019	1136 (773/363)	Y = 0.095*age + 20.2	Y = 0.052*age + 23.8	13–83	Cycle ergometer
SHIP (Koch 2009)	534 (253/281)	Y = (-1.5*age + 0.5*age <sup>2</sup> + 2.5sex-0.5*age*sex) + 22 <sup>a</sup>		25–80	Cycle ergometer
Kleber 2000	101 (45/56)	Y = 0.13*age + 19.9	Y = 0.12*age + 24.4	16–75	Treadmill
Neder 2001	120 (60/60)	Y = 0.12*age + 21	Y = 0.08*age + 25.2	20–80	Cycle ergometer
Poulin 1994	224 (128/96)	Y = 0.29*age + 7.69	Y = 0.20*age + 10.08	55–86	Treadmill
Sun 2002	474 (310/164)	Y = (0.082*age – 0.0723*height) + 34.38		37–74	Cycle ergometer/treadmill

<sup>a</sup>Age was graded in five classes (25–35, 35–44, 45–54, 55–64, and ≥64 years) and coded for the calculation.

VE/VCO<sub>2</sub> relationship. However, two of the previous prediction formulas were based only on subjects exercising on a treadmill.<sup>21,25</sup> The values obtained for a 50-year-old subject

with our equations are in between those reported by these two studies. Moreover, both in healthy individuals and in MECKI score patients, we used a ramp exercise protocol

**Figure 2** Receiver operating curves in patients with severe heart failure at a 2-year follow-up. The area under the curve (AUC) of VE/VCO<sub>2</sub> in patients with peak VO<sub>2</sub> < 14 mL/min/kg was significantly different if expressed as absolute value or as percentage of the predicted value ( $P = 0.0026$ ).



aimed at achieving peak exercise in about 10 min, a detail not clear in all previous studies in normal subjects. As regards HF patients, it is of note that MECKI score patients included a minority of cases who performed a CPET on a treadmill (6%). However, results were very similar with and without those cases, so that we decided to report results regardless of the ergometer used.

We applied our VE/VCO<sub>2</sub> prediction equation to HF patients enrolled in the MECKI score database. The MECKI score database is an established multicentre Italian registry, first published in 2013, that comprehends HF patients who underwent maximal CPET.<sup>10</sup> So far, 6112 patients have been enrolled, with a median follow-up of 3.67 years (1341 days, interquartile range 630–2353 days). The MECKI score registry was undertaken to assess the risk of cardiovascular mortality, urgent heart transplant, and left ventricular assist device in HF patients able to perform a CPET. The MECKI score database is constantly updated, and 24 HF units have contributed to the database by sharing their results so far.<sup>22</sup>

The prognostic power of the VE/VCO<sub>2</sub> slope we observed confirms the strong prognostic capability of this measurement, similar to that previously reported in several studies.<sup>9,16,17</sup> Except for the report by Kleber et al.,<sup>21</sup> previous studies and guidelines used the absolute value of VE/VCO<sub>2</sub> slope, and specifically, the value of 34 was suggested. However, it is well known that the slope of the VE/VCO<sub>2</sub> relationship in normal subjects is gender specific and increases with age. Interestingly, Sinagra et al.,<sup>26</sup> in a population of young patients with cardiomyopathy (age 50 ± 11 years), reported a

VE/VCO<sub>2</sub> prognostic cut-off value of 29, lower than the generally used 34, but understandable considering the young age and the prevalent male gender. Similarly, Magrì et al. reported a VE/VCO<sub>2</sub> prognostic cut-off value of 31 for patients with hypertrophic cardiomyopathy.<sup>27</sup> Recently, age-dependent VE/VCO<sub>2</sub> slope prognostic cut-off values for HF patients have been suggested, with a different value for preserved and reduced LVEF HF patients.<sup>28</sup> It is of note that VE/VCO<sub>2</sub> slope is included in a few scores as a continuum, avoiding any cut-off value.<sup>10,29</sup> To group patients for HF severity, we used a peak VO<sub>2</sub> cut-off value of 14 mL/min/kg. The choice of this value is totally arbitrary and based on historical reasons,<sup>30</sup> and an absolute peak VO<sub>2</sub> value (12/14 mL/min/kg) is still used by HF transplant guidelines.<sup>2</sup> Notably, the group identified by peak VO<sub>2</sub> < 14 mL/min/kg showed several parameters suggestive of a more severe HF, such as LVEF, haemoglobin, kidney function, and Brain Natriuretic Peptide (Table 3). Finally, and by chance, the cut-off value of 14 mL/min/kg allowed to identify two groups of almost equal size.

In HF patients with moderate HF, as evaluated by peak VO<sub>2</sub> ≥ 14 mL/min/kg, the prognostic power of VE/VCO<sub>2</sub> reported as an absolute value or as a percentage of predicted value are basically the same. This may be due to the overall low event rate in patients with moderate HF and by the low number of females. Indeed, in females, peak VO<sub>2</sub> as an absolute value is generally low, but prognosis is better.<sup>31–33</sup> Different considerations must be made for patients with peak VO<sub>2</sub> < 14 mL/min/kg. In this population, characterized by more events, a higher number of females, and an older age, the use of VE/VCO<sub>2</sub> slope

as a percentage of predicted value significantly increased its prognostic power, and it allowed correctly reclassifying 6.6% of cases. Notably, patients with severe HF are those who need a more precise prognosis. Accordingly, we strongly suggest that VE/VCO<sub>2</sub> slope is reported as a percentage of predicted value at least in this category of HF patients.

The present study has some important limitations that need to be acknowledged. First, patients were in stable clinical condition and therapeutic regimen since at least 3 months so that patients with recent clinical instabilization were not analysed. Second, patients with preserved LVEF were not evaluated<sup>34–36</sup>; consequently, our results cannot be extrapolated to these patient populations. Third, variables used for risk calculation were collected at enrolment, giving a static picture of the patients without accounting for possible changes in clinical status and management with potential prognostic impact, such as device implantation and changes in HF medications. Fourth, the lack of treadmill as an ergometer in the healthy subjects, as well as the small number of HF patients tested with a treadmill, limits the applicability of our formula to treadmill cases. Fifth, we built the VE/VCO<sub>2</sub> prediction equation from—and applied it to—subjects who underwent an exercise protocol characterized by a progressively increasing workload aimed at achieving peak exercise in ~10 min. Consequently, the application of these prediction equations to different protocols or to exercise tests of different durations may be erroneous, although it has been shown that VE/VCO<sub>2</sub> slope in a ramp protocol is independent of exercise tolerance.<sup>24</sup> Finally, the population of HF subjects comes from a single country (Italy), and racial variables are not taken into account. Therefore, the results obtained in this population could not be extrapolated to a population of different ethnicity.

In conclusion, we propose a new prediction equation for VE/VCO<sub>2</sub> slope, based on a large population of healthy subjects of both genders. We also showed that VE/VCO<sub>2</sub> slope percentage of predicted value strengthens the prognostic power of VE/VCO<sub>2</sub> slope in HF patients with severe exercise performance impairment. Accordingly, percentage of predicted VE/VCO<sub>2</sub> slope value should be preferred to its absolute value for HF prognosis prediction in patients with history of low LVEF.

## Statistical analysis

Quantitative variables were reported as mean ± SD or median and interquartile range as appropriate. Categorical variables were reported as frequency and percentage. Linear regression analysis was performed to assess the best fitting linear relationship between VE/VCO<sub>2</sub> slope and age. Differences between male and female regression equations were analysed by a linear model including the interaction factor by age

and gender. The equations found, calculated separately in males and females, were then used for the prediction of normal values (VE/VCO<sub>2</sub> slope percentage) in the HF population. Receiver operating characteristic (ROC) curves were calculated, and the area under the ROC curve (AUC) with 95% CI was used to compare the prognostic power of VE/VCO<sub>2</sub> slope and of VE/VCO<sub>2</sub> slope percentage at 2 years. Net reclassification improvement was employed to assess the potential of VE/VCO<sub>2</sub> percentage to improve risk prediction in comparison to VE/VCO<sub>2</sub> as absolute value. All statistics were performed with SPSS for windows (IBM SPSS Statistics 25).

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## Conflict of interest

None declared.

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