Ventilatory efficiency is a stronger prognostic indicator than peak oxygen uptake or BMI in heart failure with reduced ejection fraction

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Disclosures

None.

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Chronic heart failure (HF) is a complex condition associated with poor prognosis.[1] In HF with reduced ejection fraction (HFrEF), $\dot{V}O_2$peak is a strong prognostic indicator for mortality, while at extremes of age, expressing $\dot{V}O_2$peak relative to age-predicted values is recommended.[2] However, it can be difficult to achieve a peak exercise test and in such cases the relationship between ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}CO_2$) may be able to guide prognosis. An elevated $\dot{V}_E/\dot{V}CO_2$ slope is associated with poor prognosis,[2] while the exact cut point might be modified by age.[3]

There is evidence in HF that having a high body mass index (BMI) may paradoxically confer 'protection' against mortality.[4,5] Studies examining these prognostic indicators in HF suggest that this "obesity paradox" may be evident in those with low cardiopulmonary fitness ($\dot{V}O_2$peak), but less apparent when fitness is preserved.[6-9] We hypothesised that, in patients with HFrEF, elevated $\dot{V}_E/\dot{V}CO_2$ slope would outperform $\dot{V}O_2$peak and BMI as a predictor of all-cause mortality, and that those with a low $\dot{V}_E/\dot{V}CO_2$ slope would have worse outcomes if they were also in the lower range for BMI.

A retrospective analysis was conducted on cardiopulmonary exercise testing (CPET) data from 312 HFrEF patients between 1997 and 2014. The study complied with the Declaration of Helsinki and was approved by Royal Perth Hospital Ethics Committee (REG 14-068). $\dot{V}O_2$peak was assessed using an incremental CPET performed on a treadmill. Regression line of $\dot{V}_E$ and $\dot{V}CO_2$ production was used to calculate $\dot{V}_E/\dot{V}CO_2$ slope. Patients were characterized as having "higher fitness" or "lower fitness" with cut points for $\dot{V}O_2$peak at $14 ml \cdot kg^{-1} \cdot min^{-1}$, for age-predicted $\dot{V}O_2$peak at 50% and for $\dot{V}_E/\dot{V}CO_2$ slope at 35. They were further characterised as having 'normal BMI' ($18.5\text{-}25.0 kg \cdot m^{-2}$) or 'high BMI' ($>25 kg \cdot m^{-2}$). This gave four classifications: ‘normal BMI and lower fitness (or slope)’, ‘high BMI and lower fitness’, ‘normal BMI and higher fitness’, or ‘high BMI and higher BMI’.

All-cause mortality was documented from hospital records and a mortality database to May 2016. Patients that received a cardiac transplant or ventricular assist device were censored. Baseline characteristics were calculated for the four fitness-overweight groups with one-way analysis and chi-square tests were conducted. Kaplan-Meier analysis was used to produce survival functions, which were compared between the groups using Log rank tests. Cox regression models were used for calculating hazard ratios (HR), using the fitness indicators as variables, expressed with 95% confidence intervals.

Clinical characteristics of groups based on $\dot{V}O_2$peak (ml·kg·min^{-1}) and BMI are reported in Table 1. All 3 fitness indicaters were independent predicters of mortality at 2 ($p<0.01$) and 5 years ($P<0.001$). Having higher or lower BMI was not an independent predictor of mortality. Cox regression showed having a high $\dot{V}_E/\dot{V}CO_2$ slope as the strongest predictor of mortality with HR of 6.83 (2.75-16.97) and 4.13 (2.34-7.25) for 2 and 5 years. Figure 1 shows survival for the different groups. Patients who had higher fitness based on $\dot{V}O_2$peak had better survival outcomes than their unfit counterparts, regardless of BMI. Whereas in the lower fitness group, those who had higher BMI had significantly higher survival those with normal BMI. When $\dot{V}_E/\dot{V}CO_2$ ($\geq$ or <35) was used, lower slope patients had better survival than their higher slope counterparts, regardless of their BMI. $\dot{V}_E/\dot{V}CO_2$ slope did not discriminate between the BMI categories in terms of survival.

Our findings confirm that fitness, and particularity ventilatory inefficiency (high $\dot{V}_E/\dot{V}CO_2$ slope), predicted mortality, whereas BMI did not. Those with elevated $\dot{V}_E/\dot{V}CO_2$ ($\geq$35) had lower survival, regardless of their BMI. These data confirm the prognostic significance of cardiopulmonary fitness and submaximal exercise derived ventilatory inefficiency.

High BMI has been reported to convey a survival advantage in those with established HF and lower fitness.[4,5,9] While we found this to be the case when fitness was stratisfied using $\dot{V}O_2$peak, it was less apparent when using ventilatory efficiency. Our results add to the growing evidence that suggest the obesity paradox is mostly due to confounding factors.[4,7,8]

The $\dot{V}_E/\dot{V}CO_2$ slope has demonstrated to confer predictive capacity which may exceed that associated with $\dot{V}O_2$peak.[2] our results indicate stronger predictive capacity for $\dot{V}_E/\dot{V}CO_2$ slope over $\dot{V}O_2$peak. These findings contribute to evidence that ventilatory inefficiency, derived from submaximal stages of a graded exercise test, are a valuable component of prognostic assessment for patients with HF.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest

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Table 1. Characteristics of individuals with heart failure (HF) at the time of testing stratified based on $\dot{V}O_2$peak (ml·kg·min^{-1}) and BMI.

	Normal BMI, higher fitness (n=67)	Normal BMI, lower fitness (n=30)	High BMI, higher fitness (n=146)	High BMI, lower fitness (n=69)	*P* < 0.05* *P* < 0.01**
Male, n (%)	50 (68)	19 (63)	129 (89)	58(84)	NF vs HF*;NL vs HF*; NL vs HL*
Age, *yrs (SD)*	47 (15)	56 (15)	56 (10)	51(13)	NS
BMI, *kg·m^{-2} (SD)*	22.4 (1.7)	22.0 (1.6)	30.3 (3.6)	29.6 (3.3)	NF vs HF**; HL vs NL**
$\dot{V}O_2$peak , *ml·kg^{-1}·min^{-1} (SD)*	21.1 (5.9)	11.1 (2.0)	20.4 (5.1)	11.3 (2.0)	NF vs NL**; HF vs HU**
$\dot{V}O_2$peak *% age-pred. (SD)*	60 (15.0)	37 (8.2)	60 (12.9)	36 (6.8)	NF vs NL**HF vs HL**
$\dot{V}E/\dot{V}CO_2$ slope	34.4 (7.9)	48.9 (14.2)	30.9 (5.8)	39.9 (9.11)	NF vs NL**; HF vs HL**
Peak HR bpm (SD)	132 (36)	108 (26)	138 (33)	106 (33)	NF vs NL**; HF vs HL**
Peak SBP mmHg (SD)	121 (32)	111 (14)	142 (20)	114 (26)	NF vs NL**; HF vs HL**
Peak RER (SD)	1.11(0.07)	1.12 (0.07)	1.12 (0.07)	1.11(0.09)	NS
LVEF % (*SD)*	27 (12)	27 (16)	25 (10)	29 (12)	NS

NYHA class, *(SD)*	2.7 (0.84)	3.2 (0.58)	2.5 (0.84)	3.1 (0.79)	NL vs NF*; HL vs HF**; NF vs HF*; NL vs HF*;
Ischaemic aetiology, %	25	28	30	54	HL vs HF; NF, NL**
Hx hypertension, *%*	10	17	19	46	HL vs HF, NF, NL**; HF vs NF*; HL vs NL*
Hx type 2 diabetes, *%*	3	14	16	33	HL vs HF, NF, NL**
Hx hypercholesterolemia, %	9	7	17	30	HL vs HF, NF, NL**

NF, normal BMI, higher fitness; NL, normal BMI lower fitness; HF, high BMI, higher fitness; HL, high BMI, lower Fitness; SD, standard deviation; NS, not significant; BMI, body mass index; $\dot{V}O_2$peak, peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$ slope, ratio ventilation:carbon dioxide output; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure, RER, respiratory exchange ratio; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Hx, history

Figure 1. (A) The effect of fitness, expressed as $\dot{V}O_2peak \geq$ or $<$ 14 ml·kg^{-1}·min^{-1} in patients who had high or low BMI, on mortality over 5 years. Higher fitness groups had lower mortality vs lower fitness groups, regardless of BMI, at both 2 and 5 years follow-up ($P<0.01$). The lower fitness group with high BMI had lower mortality at 2 (0=0.008) and 5 years (P=0.037) than the lower fitness with low BMI group.

(B) The effect fitness, expressed as $\dot{V}O2peak \geq$ or $<$ 50% age-predicted in patients who had high or low BMI, on mortality over 5 years. Higher fitness groups had lower mortality than lower fitness groups, regardless of BMI at 2 and 5 years ($P<0.01$). The lower fitness group with high BMI had lower mortality at 2 (0=0.008) but not 5 years (P=0.177) than the lower fitness with low BMI group.

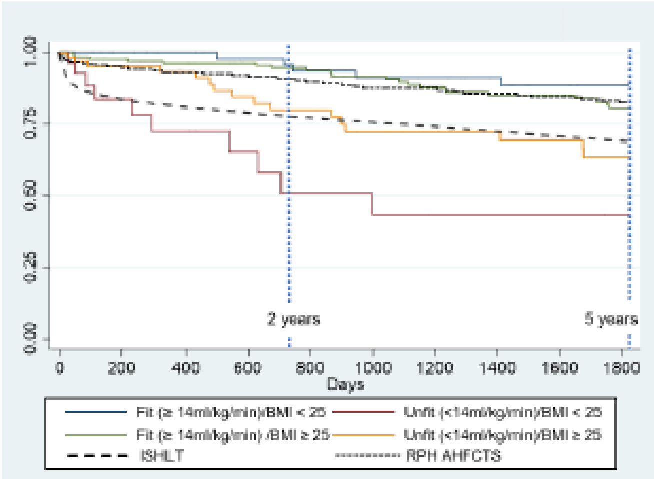
(C) The effect of ventilatory efficiency, expressed relative to $\dot{V}_E/\dot{V}CO_2 \geq$ or $<$ 35, in patients who had high or low BMI on all events over 5 years. Low slope subjects had lower mortality than a high slope subjects, regardless of whether they had normal BMI ($P<0.001$) or high BMI ($P<0.05$), over both 2 and 5 years.

ISHLT and RPH AHFCTS post-transplant survival statistics are superimposed.[10]

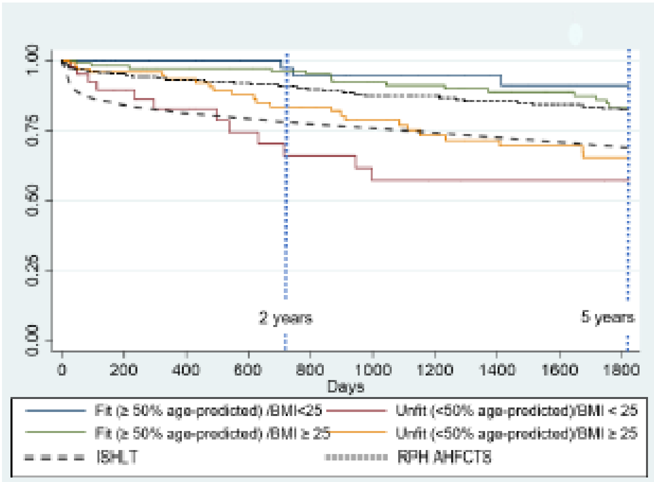
BMI, Body mass index; ISHLT, International Society for Heart & Lung Transplantation; RPH AHFCTS, Royal Perth Hospital Advanced Heart Failure and Cardiac Transplant Service; $\dot{V}E/\dot{V}C$ O2 slope, ratio ventilation:carbon dioxide output.

Figure 1

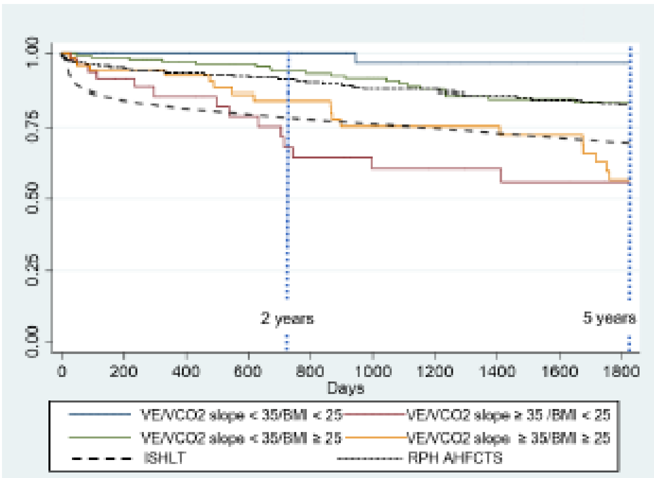
A.


1.00
0.75
0.50
0.25
0.00
2 years
5 years
0 200 400 600 800 1000 1200 1400 1600 1800
Days
Fit (≥ 14ml/kg/min)/BMI < 25
Unfit (<14ml/kg/min)/BMI < 25
Fit (≥ 14ml/kg/min) /BMI ≥ 25
Unfit (<14ml/kg/min)/BMI ≥ 25
ISHLT
RPH AHFCTS

B.


1.00
0.75
0.50
0.25
0.00
2 years
5 years
0 200 400 600 800 1000 1200 1400 1600 1800
Days
Fit (≥ 50% age-predicted) /BMI<25
Unfit (<50% age-predicted)/BMI < 25
Fit (≥ 50% age-predicted) /BMI ≥ 25
Unfit (<50% age-predicted)/BMI ≥ 25
ISHLT
RPH AHFCTS

C.


1.00
0.75
0.50
0.25
0.00
2 years
5 years
0 200 400 600 800 1000 1200 1400 1600 1800
Days
VE/VCO2 slope < 35/BMI < 25
VE/VCO2 slope ≥ 35 /BMI < 25
VE/VCO2 slope < 35/BMI ≥ 25
VE/VCO2 slope ≥ 35/BMI ≥ 25
ISHLT
RPH AHFCTS