Low skeletal muscle mass is associated with low aerobic capacity and increased mortality risk in patients with coronary heart disease – a CARE CR study

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Low skeletal muscle mass is associated with low aerobic capacity and increased mortality risk in patients with coronary heart disease – a CARE CR study

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Summary

Background In patients with chronic heart failure, there is a positive linear relationship between skeletal muscle mass (SMM) and peak oxygen consumption (VO2peak); an independent predictor of all-cause mortality. We investigated the association between SMM and VO2peak in patients with coronary heart disease (CHD) without a diagnosis of heart failure.

Methods Male patients with CHD underwent maximal cardiopulmonary exercise testing and dual X-ray absorptiometry assessment. VO2peak, the ventilatory anaerobic threshold and peak oxygen pulse were calculated. SMM was expressed as appendicular lean mass (lean mass in both arms and legs) and reported as skeletal muscle index (SMI; kg m⁻²), and as a proportion of total body mass (appendicular skeletal mass [ASM%]). Low SMM was defined as a SMI <7.26 kg m⁻², or ASM% <25.72%. Five-year all-cause mortality risk was calculated using the Calibre 5-year all-cause mortality risk score.

Results Sixty patients were assessed. Thirteen (21.7%) had low SMM. SMI and ASM% correlated positively with VO2peak (r = 0.431 and 0.473, respectively; P<0.001 for both). SMI and ASM% predicted 16.3% and 12.9% of the variance in VO2peak, respectively. SMI correlated most closely with peak oxygen pulse (r = 0.58; P<0.001). SMI predicted 40.3% of peak VO2/HR variance. ASM% was inversely associated with 5-year all-cause mortality risk (r = -0.365; P = 0.006).

Conclusion Skeletal muscle mass was positively correlated with VO2peak in patients with CHD. Peak oxygen pulse had the strongest association with SMM. Low ASM% was associated with a higher risk of all-cause mortality. The effects of exercise and nutritional strategies aimed at improving SMM and function in CHD patients should be investigated.

Introduction

Peak oxygen uptake (VO2peak), measured by a maximal cardiopulmonary exercise test (CPET) represents the upper limit of aerobic capacity. A low VO2peak is associated with the loss of independence in older individuals (Shephard, 2009) and increased all-cause and cardiovascular mortality in patients with coronary heart disease (CHD) (Keteyian et al., 2008). The physiological factors that limit VO2peak are summarized by the Fick equation (Bassett & Howley, 2000; Poole et al., 2012; Lundby et al., 2017):

\[
\text{VO2peak} = \text{cardiac output} \times (\text{a} - \text{vO2 diff})
\]

Where cardiac output is the product of heart rate (HR) and stroke volume (SV), and a-vO2 diff is the difference between arterial and venous O2 content, representing muscle O2 extraction. In healthy individuals, VO2peak is limited centrally; maximum cardiac output limits O2 delivery to the exercising muscle at the rate that it is required for aerobic resynthesis of ATP (Bassett & Howley, 2000; Lundby et al., 2017). However, in patients with chronic heart failure (CHF), a cascade of events alters peripheral muscle physiology. These include, reduced skeletal muscle oxidative enzyme activity, reduced mitochondrial density, decreased perfusion matching with oxidative muscle fibres (Poole et al., 2012) and decreased skeletal muscle mass (Cicoira et al., 2001). Consequently, the
peripheral muscle may become the primary limitation to $\dot{V}O_2_{peak}$ (Clark et al., 1996; Shelton et al., 2010; Poole et al., 2012). As CHF worsens, skeletal muscle mass (Collamati et al., 2016) and $\dot{V}O_2_{peak}$ decline (Piepoli et al., 2006; Fülster et al., 2013). However, this relationship has not yet been reported in patients with CHD. Around a quarter of patients with CHD have low muscle mass and function (sarcopenia) (Harada et al., 2016), compared with only 10% of adults older than 60 years (Shafiee et al., 2017). Patients with CHD are commonly physically inactive which, together with progression of the underlying CHD, may exacerbate loss of muscle mass. Patients with CHD who experience a marked loss of skeletal muscle mass may have a reduced $\dot{V}O_2_{peak}$ and consequently higher risk of early mortality. Identifying the relationship between skeletal muscle mass and $\dot{V}O_2_{peak}$ in patients with CHD may be important so that preventative exercise and nutritional interventions can be developed.

We aimed to describe the association between skeletal muscle mass and $\dot{V}O_2_{peak}$ in male patients with CHD. We also assessed the relationship between skeletal muscle mass and other potentially important variables: peak oxygen pulse (peak $\dot{V}O_2$/HR) (Laukkanen et al., 2006), ventilatory anaerobic threshold (VAT) (Gitt et al., 2002), $\dot{V}E$/VCO₂ slope (Van de Veire et al., 2006), N-terminal pro B-type Natriuretic Peptide (NT-proBNP) (Omland et al., 2007) and CALIBER 5-year all-cause mortality risk (Rapsomaniki et al., 2014).

Methods

Study design

Data for this cross-sectional study included baseline measurements taken from male patients enrolled in the Cardiovascular and cardiorespiratory Adaptations to Routine Exercise-based Cardiac Rehabilitation (CARE CR) study (Nichols et al., 2018). Ethical approval was obtained from the Humber Bridge NHS Research Ethics Committee – Yorkshire and the Humber (13/YH/0278). Study procedures conform to the declaration of Helsinki 1964.

The study protocol for CARE CR has previously been reported (Nichols et al., 2018). Briefly, clinically stable male patients who had recently been discharged from hospital following an admission for stable angina, myocardial infarction (MI), coronary artery bypass graft (CABG) surgery or elective percutaneous coronary intervention (PCI) were recruited. Patients were asked to attend the research laboratory having not participated in strenuous exercise within the previous 24 h. Written informed consent was obtained prior to conducting any investigations.

Resting measurements

Resting HR and left arm brachial blood pressure were taken at the end of 15 min semi-supine rest using a 12-lead ECG (GE Healthcare, Buckinghamshire, UK) and an ECG-gated automated blood pressure cuff (Tango, SunTech Medical, Eynsham, UK). Stature (cm) was measured using a Leicester Height Measure (SECA, Birmingham, UK). Waist circumference measurements were taken 1 cm above the iliac crest, and hip measurements were taken from the widest aspect of the buttocks. Both measurements were recorded in cm, and the ratio of the two was calculated to determine waist-to-hip circumference ratio (ACSM 2017).

A 2D echocardiogram was used to determine left ventricular (LV) function. LV ejection fraction (LVEF) was calculated using Simpson’s method from measurements of end-diastolic and end-systolic volumes on apical four- chamber and two-chamber 2D views, following the guidelines of Lang and colleagues (Lang et al., 2015). LV systolic dysfunction was diagnosed if LVEF was ≤45%.

Body composition

Body composition was determined using dual X-ray absorptiometry [DEXA] (Lunar iDXA, 255 GE Healthcare). Total body mass (kg), lean body mass (kg) and total fat (%) were determined using the Lunar iDXA’s integrated software. BMI (kg m⁻²) was calculated using DEXA-derived total body mass. Appendicular lean mass (ALM; total lean mass in both arms and legs) was calculated (kg) and indexed to derive skeletal muscle index (SMI; measured in kg m⁻²). ALM was also reported as a percentage of total body mass (appendicular skeletal mass; ASM%). Low skeletal muscle mass was defined as an SMI of <7.26 kg m⁻² as recommended by international consensus guidelines (Cruz-Jentoft et al., 2010). A low ASM% was defined as <25-72% (Levine & Crimmins, 2012). This approach may be more appropriate for patients who are overweight/obese and have a higher absolute skeletal muscle mass, but low skeletal muscle mass relative to their total body mass.

Maximal cardiopulmonary exercise test

The cardiopulmonary exercise testing adhered to established guidelines and recommendations (American Thoracic Society/American College of Chest Physicians 2003; Balady et al., 2010; Nichols et al., 2015; Taylor et al., 2015) and was performed using the modified Bruce treadmill protocol (Bruce et al., 1973) (GE Healthcare). A 12-lead ECG was monitored continuously throughout the test. An ECG-gated automated BP measurement was recorded at the start of the test and at the second minute of each test stage until the end of the test. Rating of perceived exertion (RPE) scores (6-20) was recorded at peak exercise (Borg, 1982). Breath-by-breath metabolic gas exchange data were collected using an Oxycron Pro metabolic cart (Jaeger, Hoenchburg, Germany). $\dot{V}O_2_{peak}$ was defined as the mean $\dot{V}O_2$ (ml) over the last 30 s of the test. $\dot{V}O_2_{peak}$ was also adjusted for body mass (ml kg⁻¹ min⁻¹). The VAT was analysed by two independent investigators using the V-slope method (Beaver et al., 1986) with data averaged over the middle five of seven consecutive breaths. The VAT was reported
in ml, and standardized to patient body mass (ml kg\(^{-1}\) min\(^{-1}\)). \(\dot{V}O_2/HR\) (ml per beat) and \(VE/ VCO_2\) slope were calculated as previously described (Nichols et al., 2015, 2018).

### Pulse wave velocity

Pulse wave velocity (PWV) between the brachium and ankle was measured (Vascular Explorer, Enverdis GmbH, Düsseldorf, Germany) after 15 min of semi-supine rest (torso elevated 45\(^\circ\)) in a quiet temperature controlled room (21\(^\circ\)C). A blood pressure cuff was placed proximally to the left cubital fossa (brachial artery) and another placed proximally to the medial malleolus. Photoplethysmographic sensors were placed on the patients left index finger and left hallux. Oscillations in the pulse waves alter the volume of the blood pressure cuff and are converted to a PWV. A shorter PWV (ms) indicates more severe arterial stiffness and/or worse peripheral vascular health. The reproducibility of PWV measurement at a single time point has been shown to be good (intraclass correlation 0.72–0.86) (Sutton-Tyrrell et al., 2001).

### Blood samples

Resting venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA), potassium oxalate and serum separating tubes (SST). EDTA and potassium oxalate tubes were spun in a refrigerated (4\(^\circ\)C) centrifuge at 3000 revolutions per min, for 15 min immediately after the blood draw. Samples collected in SST tubes were allowed to clot for 30 min prior to being centrifuged under the same conditions. Haematocrit and haemoglobin concentrations, neutrophil and lymphocyte count, and NT-proBNP were analysed using a registered National Health Service (NHS) pathology laboratory (Castle Hill Hospital, Hull). All samples not analysed on the day of collection were stored in a –80\(^\circ\)C freezer. The ABX Pentra 400 biochemistry auto analyser (Horiba, Montpellier, France) was used to analyse serum plasma glucose, and high sensitivity C-reactive protein (hs-CRP) in duplicate. Calibration and quality controls were conducted in accordance with manufacturer’s guidelines.

### Prognosis – Calibre 5-year all-cause mortality risk

Five-year risk of all-cause mortality was calculated for each patient using the comprehensive online (https://www.calibernetwork.org/model) Calibre 5-year risk score (Rapsomaniki et al., 2014). The Calibre risk score has been developed in a population of 100 000 patients with CHD. The model has good calibration and discrimination in internal and external validation (C-Index 0.811) for all-cause mortality. Importantly, the model does not include any fitness measurements in its calculation. Five-year risk of all-cause mortality was reported as a percentage. The variables included in the Calibre score are shown in Table 1.

### Statistical analysis

Statistical analysis was performed using SPSS version 22 (IBM, New York, NY, USA). The distribution of the data were assessed visually and using the Shapiro–Wilk test. Categorical data are reported as percentages. Continuous normally distributed variables are displayed as mean with 95% confidence intervals (95% CI) or standard deviation (±) where specified. Non-normally distributed data are displayed as median (range). Pearson’s (normally distributed), Spearman’s correlations (non-normally distributed) and age-adjusted partial correlations were used to assess the relationship between indices of skeletal muscle mass and variables of interest. An r value of <0.25, 0.26–0.50, 0.51–0.75, and, >0.75 were considered weak, moderate, fair and strong associations, respectively (Berg & Latic, 2008). Scatter plots of partial correlations were constructed using the residuals of the independent skeletal muscle indices and dependent variables. Where a variable was significantly associated with SMI or ASM\(^\%\), receiver operating characteristic (ROC) curves were used to investigate the sensitivity and specificity of predicting low skeletal muscle mass. Patients with a low skeletal muscle mass (SMI <7.26 Kg m\(^{-2}\) or ASM\(^\%\) <25-72%) were treated as the dichotomous ‘state-variable’ for the ROC curve. Statistical significance was set at \(P = 0.05\).

Up to six dependent variables with the strongest, significant age-adjusted partial correlations were selected for inclusion within separate stepwise multivariate regression models. The main outcome variables selected were \(\dot{V}O_2/HR\), VAT, peak \(\dot{V}O_2/HR\), CPET duration, Calibre 5-year all-cause mortality risk and NT-proBNP.

### Results

Sixty male patients (aged, 62.1 ± 10.0 years; BMI, 28.8 ± 3.7 kg m\(^{-2}\)) were recruited. Patient characteristics, comorbidities and medications are reported in Tables 2, 3 and 4, respectively. Fifteen patients (25.0%) had sustained a ST-elevation MI, 19 (31.7%) a non-ST-elevation MI, 16 (26.7%) underwent elective PCI, 6 (10.0%) CABG and 4 (6.7%) had exertional angina. Comorbidities are shown in Table 3. Median time from cardiac event to baseline assessment was 54 days (range 22–220 days). Mean resting HR was 82 bpm ± 14 bpm. Mean resting systolic and diastolic blood pressure was 127 ± 17 mmHg and 58 ± 9 mmHg, respectively. Four patients (6-6%) had a LVEF <45%, ten (16-7%) had an NT-proBNP >400 pg l\(^{-1}\) and one (1-7%) had an NT-proBNP >2000 pg l\(^{-1}\). The proportion of patients with low skeletal muscle mass was 16-7% by SMI and 11-7% by ASM\(^\%\). However, only four patients had both a low SMI and ASM\(^\%\), meaning that 13 (21-7%) had a low SMI or ASM\(^\%\).

Correlations between ALM, SMI, ASM\(^\%\) and dependent variables of interest are presented in Table 5. The associations between ALM, SMI and \(\dot{V}O_2/HR\) (ml) were \(r = 0.566\) (\(P<0.001\)) and \(r = 0.473\) (\(P<0.001\), respectively. The
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<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>Continuous variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Age</td>
</tr>
<tr>
<td>Belongs to most deprived quintile</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>CAD diagnosis and severity</td>
<td>HDL</td>
</tr>
<tr>
<td>Interventions (last 6 months)</td>
<td>Heart rate</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Hypertension/BP lowering medication</td>
<td>White cell count</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Heart failure</td>
<td>GLP-1 (pg l⁻¹)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>Calibe 5-year risk (%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>NT-proBNP (pg l⁻¹)</td>
</tr>
<tr>
<td>Stroke</td>
<td>hs-CRP (mg l⁻¹)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>Glucose (mmol l⁻¹)</td>
</tr>
<tr>
<td>COPD</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Cancer</td>
<td>Diastolic BP</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>

BMI, body mass index; ALM, appendicular lean mass; SMI, skeletal muscle index; ASM%, appendicular skeletal mass; VO₂peak, peak oxygen uptake; VAT, ventilatory anaerobic threshold; VO₂/HR, oxygen pulse; HR, heart rate; bpm, beats per minute; VE/VO₂ slope, ventilatory efficiency with respect to carbon dioxide elimination; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; hs, high sensitivity.

Association between ASM% and VO₂peak (ml kg⁻¹ min⁻¹) was r = 0.420 (P = 0.001). The strongest associations between indices of skeletal muscle mass and secondary outcome measures were observed between; ALM and peak VO₂/HR (r = 0.633; P<0.001); SMI VO₂/HR (r = 0.575; P<0.001) and ASM% and VO₂peak [ml kg⁻¹ min⁻¹] (r = 0.431; P<0.001). CPET variables that were significantly associated with ALM, SMI and ASM% are shown in Fig. 1. ASM% was the only method of characterizing skeletal muscle mass resulting in a significant association with PWV, NT-proBNP and Calibre 5-year all-cause mortality risk.

**ROC curve analysis**

Receiver operating characteristic curve analysis was conducted on variables that were significantly associated with measurements of SMI or ASM%. The area under the curve (AUC) for each prognostic variable is shown in Table 6. For SMI, peak VO₂/HR had the greatest predictive capacity (AUC = 0.767; P = 0.008). Values >13.3 ml per beat was predictive of a low SMI. When patients with a low SMI or ASM% were combined, peak VO₂/HR AUC was 0.764 (P = 0.004). A peak VO₂/HR <14.3 ml per beat was most predictive of patients with a low SMI or ASM%. Patients with a NT-proBNP >112·5 pg l⁻¹, a Calibre risk score >3.0% or a modified Bruce treadmill duration <17 min 43 s were also more likely to have a low ASM%.
Table 5  Correlation and partial correlations between appendicular lean mass, skeletal muscle index, appendicular skeletal mass and dependent variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Appendicular lean mass</th>
<th>Skeletal muscle index</th>
<th>Appendicular skeletal mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson's corr. (r) P-value</td>
<td>Partial corr. (r) P-value</td>
<td>Pearson's corr. (r) P-value</td>
</tr>
<tr>
<td>V̂O₂\text{peak} (ml)</td>
<td>0.666 0.001*</td>
<td>0.566 &lt;0.001*</td>
<td>0.577 &lt;0.001*</td>
</tr>
<tr>
<td>V̂O₂\text{peak} (ml kg(^{-1}) min(^{-1}))</td>
<td>0.189 0.148</td>
<td>-0.007 0.962</td>
<td>0.196 0.134</td>
</tr>
<tr>
<td>VAT (ml)</td>
<td>0.502 0.001*</td>
<td>0.360 0.006*</td>
<td>0.496 &lt;0.001*</td>
</tr>
<tr>
<td>VAT (ml kg(^{-1}) min(^{-1}))</td>
<td>0.053 0.686</td>
<td>-0.092 0.502</td>
<td>0.127 0.333</td>
</tr>
<tr>
<td>Peak V̂O₂/HR (ml per beat)</td>
<td>0.711 0.001*</td>
<td>0.633 &lt;0.001*</td>
<td>0.643 &lt;0.001*</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>0.165 0.208</td>
<td>-0.042 0.751</td>
<td>0.110 0.402</td>
</tr>
<tr>
<td>V̂E/V̂CO₂ slope</td>
<td>-0.272 -0.036*</td>
<td>0.078 0.566</td>
<td>-0.270 0.037*</td>
</tr>
<tr>
<td>CPET duration (s)</td>
<td>0.182 0.165</td>
<td>0.014 0.920</td>
<td>0.206 0.114</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.153 0.244</td>
<td>0.077 0.574</td>
<td>0.137 0.297</td>
</tr>
<tr>
<td>Calibre 5-year risk (%)</td>
<td>-0.426 -0.001*</td>
<td>-0.230 0.870</td>
<td>-0.372 0.003*</td>
</tr>
<tr>
<td>NT-proBNP (pg l(^{-1}))</td>
<td>0.295 0.025*</td>
<td>0.155 0.254</td>
<td>-0.253 0.056</td>
</tr>
<tr>
<td>hs-CRP(mg l(^{-1}))</td>
<td>-0.092 0.486</td>
<td>-0.101 0.458</td>
<td>0.000 0.999</td>
</tr>
<tr>
<td>Glucose (mmol l(^{-1}))</td>
<td>0.036 0.789</td>
<td>-0.051 0.708</td>
<td>0.135 0.314</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>0.149 0.254</td>
<td>0.153 0.261</td>
<td>0.151 0.249</td>
</tr>
</tbody>
</table>

corr., correlation; V̂O₂\text{peak}, peak oxygen uptake; VAT, ventilatory anaerobic threshold; V̂O₂/HR, oxygen pulse; HR, heart rate; bpm, beats per minute; V̂E/V̂CO₂ slope, ventilatory efficiency with respect to carbon dioxide elimination; CPET, cardiopulmonary exercise test; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; hs, high sensitivity.

*Significant.

*Spearman correlation.
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was the only significant predictor of peak VO₂peak, these variables explained 58% of variance for VO₂peak and the VAT (ml). For VO₂peak, 52-5% of variance was explained by SMI and age, with SMI accounting for 16-3%. For VAT, 35-8% of variance was explained by SMI and age. About 12-1% of variance was explained by VAT alone. Interestingly, only SMI was an independent predictor for peak VO₂/HR. 40-3% of variance was accounted for by VO₂/HR.

Similar to SMI, ASM% and age (both P<0.001) were independent predictors of VO₂peak and VAT. For VO₂peak, 52.5% of variance was explained by SMI and age, with SMI accounting for 16.3%. For VAT, 35.8% of variance was explained by SMI and age. About 12.1% of variance was explained by VAT alone. Interestingly, only SMI was an independent predictor for peak VO₂/HR. 40.3% of variance was accounted for by VO₂/HR.

Table 6 Area under the curve for variables associated low skeletal muscle mass (95% confidence intervals).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area under the curve</th>
<th>P-value</th>
<th>Area under the curve</th>
<th>P-value</th>
<th>Area under the curve</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMI</td>
<td></td>
<td></td>
<td>ASM%</td>
<td></td>
<td>SMI &amp; ASM%</td>
<td></td>
</tr>
<tr>
<td>VO₂peak (ml)</td>
<td>0.649 (0.478–0.820)</td>
<td>0.139</td>
<td>–</td>
<td>–</td>
<td>0.675 (0.527–0.823)</td>
<td>0.055</td>
</tr>
<tr>
<td>VO₂peak (ml kg⁻¹ min⁻¹)</td>
<td>–</td>
<td>–</td>
<td>0.726 (0.510–0.943)</td>
<td>0.053</td>
<td>0.615 (0.430–0.810)</td>
<td>0.206</td>
</tr>
<tr>
<td>Peak VO₂/HR (ml per beat)</td>
<td>0.767 (0.613–0.921)</td>
<td>0.008*</td>
<td>–</td>
<td>–</td>
<td>0.764 (0.632–0.895)</td>
<td>0.004*</td>
</tr>
<tr>
<td>VAT (ml)</td>
<td>0.594 (0.399–0.789)</td>
<td>0.351</td>
<td>–</td>
<td>–</td>
<td>0.620 (0.455–0.786)</td>
<td>0.187</td>
</tr>
<tr>
<td>VAT (ml kg⁻¹ min⁻¹)</td>
<td>–</td>
<td>–</td>
<td>0.679 (0.454–0.904)</td>
<td>0.126</td>
<td>0.561 (0.368–0.755)</td>
<td>0.501</td>
</tr>
<tr>
<td>CPET duration (s)</td>
<td>–</td>
<td>–</td>
<td>0.744 (0.510–0.943)</td>
<td>0.037*</td>
<td>0.648 (0.466–0.830)</td>
<td>0.104</td>
</tr>
<tr>
<td>Calibre 5-year risk (%)</td>
<td>–</td>
<td>–</td>
<td>0.805 (0.600–1.00)</td>
<td>0.009*</td>
<td>0.383 (0.191–0.574)</td>
<td>0.202</td>
</tr>
<tr>
<td>NT-proBNP (pg l⁻¹)</td>
<td>–</td>
<td>–</td>
<td>0.759 (0.511–1.00)</td>
<td>0.027*</td>
<td>0.623 (0.420–0.825)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

SMI, skeletal muscle index; ASM%, appendicular skeletal mass; VO₂peak, peak oxygen uptake; VO₂/HR, oxygen pulse; VAT, ventilatory anaerobic threshold; CPET, cardiopulmonary exercise test; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*Significant.

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mass (ml kg⁻¹ min⁻¹). 38.8% of VO₂peak (ml kg⁻¹ min⁻¹) and 17.8% of VAT (ml kg⁻¹ min⁻¹) variance was accounted for by ASM% and age. ASM% alone accounted for 12.9% of VO₂peak variance, compared to 6.3% for VAT. Age and ASM% were also independent predictors of NT-proBNP (P<0.001) with age accounting for 20.5% of NT-proBNP variance and ASM% accounting for 7.2% (combined model; 27.2%). ASM% accounted for 9.4% of total Calibre 5-year all-cause mortality risk score variance (P<0.001).

Discussion

To our knowledge, this is the first study to investigate the relationship between skeletal muscle mass and VO₂peak in patients with CHD. We identified that a lower skeletal muscle mass was associated with a lower VO₂peak, an observation previously reported in patients with CHF (Cicoira et al., 2001). We also investigated the relationship between other important prognostic indicators, including peak VO₂/HR. Our data suggest that skeletal muscle mass may be more closely associated with peak VO₂/HR, rather than VO₂peak. Similar to previously reported data in patients with CHD (Harada et al., 2016), we found that more than one-fifth of patients had a low skeletal muscle mass; a higher proportion than reported among adults over the age of 60 years (10%) (Shafiee et al., 2017). A lower skeletal muscle mass was associated with a higher 5-year all-cause mortality risk.

Peak oxygen uptake

Sarcopenia and/or a low muscle mass are associated with increased mortality risk (Cawthon et al., 2007) and difficulties performing daily activities (Janssen, 2006). A low VO₂peak is also associated with a higher mortality risk (Keteyian et al., 2008) and difficulties performing daily activities (Shephard, 2009). Consistent with data reported on patients with CHF (r = 0.46 to r = 0.70) (Cicoira et al., 2001; Piepoli et al., 2006), we found that ALM was positively associated with VO₂peak (r = 0.566). Although dependent on the methods used to scale VO₂peak, this relationship was maintained when ALM was standardized to stature (SMI; r = 0.473) and body mass (ASM%; r = 431). However, whilst ALM (43.4%), SMI (16.3%) and ASM% (12.9%) were independent predictors of VO₂peak, we were unable to replicate the same predictive strength (54-65%) reported by Cicoira et al. in non-cachexic patients with CHF. This may be because patients with CHF can have severe skeletal muscle abnormalities (Clark et al., 1996; Vescovo et al., 1996; Piepoli et al., 2010; Poole et al., 2012) that limit exercise tolerance as a consequence of the disease (Shelton et al., 2010). Given that CHD represents an earlier stage of cardiovascular dysfunction than CHF, skeletal muscle abnormalities may occur at an earlier stage of cardiovascular dysfunction. Skeletal muscle mass may therefore play a greater role in limiting VO₂peak among patients with CHF, compared with patients who have CHD. Our observation may suggest that adverse changes in skeletal muscle mass and quality associated with cardiovascular dysfunction exist on a continuum. If this were true, early optimization strategies that target peripheral muscle in addition to cardiac function may be important for disease prevention.

Peak VO₂/HR was most closely associated with indices of skeletal muscle mass. ALM and SMI separately accounted for 49.8% and 40.3% of the variance in peak VO₂/HR, respectively. These indices of skeletal muscle mass not only had a stronger association with peak VO₂/HR (r = 0.575 to r = 0.633) compared to VO₂peak (r = 0.566), but also had the largest AUC (0.767; 95% CI 0.613–0.921; P = 0.008). Unlike VO₂peak, peak VO₂/HR had good sensitivity and specificity for detecting patients with a low SMI. A threshold of 13-3 ml per beat was identified as the point below which, patients were more likely to have a low SMI (7.26 kg m⁻²). Simple rearrangement of the Fick equation means that peak VO₂/HR becomes independent of HR; a factor that we (r = −0.042, −0.073, 0.026; P<0.05 for all) and others (Horwich et al., 2009; Piepoli et al., 2017) have found to be unrelated to skeletal muscle. Instead, reported peak VO₂/HR characterizes SV and a-VO₂ difference (peripheral O₂ extraction) which may explain why it appears to be more closely related to skeletal muscle mass than VO₂peak, in patients with CHD. However, whilst skeletal muscle mass has previously been identified as an independent predictor of peak VO₂/HR (74%) in hypertensive men and women (Lim et al., 2005), the association between peak indices of skeletal muscle mass and peak VO₂/HR in our study was smaller [40-3–49.8%] (Lim et al., 2005). Nonetheless, this is an interesting finding and should be further explored in a larger cohort.

The weaker relationship between indices of skeletal muscle mass and peak VO₂/HR observed in our study may indicate that patients with CHD have a different physiological response to maximal exercise, compared to patients with hypertension. Under normal circumstances, VO₂/HR rises progressively throughout an incremental exercise test until it reaches a plateau associated with normal physiological limitation to exercise (Whipp et al., 1996). However, in patients with CHD, VO₂/HR may prematurely decrease during incremental exercise due to ischaemia-induced myocardial wall-motion abnormalities which cause a reduction in SV (Belardinelli et al., 2003). This is thought to occur prior to ST-segment changes detected using electrocardiogram, or symptoms of angina (Nesto & Kowalchuk, 1987). If myocardial blood flow is not restored through surgical or medical intervention, VO₂/HR would be lower than expected at peak exercise and may attenuate the association between VO₂/HR, a-VO₂ difference and skeletal muscle mass. Alternatively, a low peak VO₂/HR may indicate greater cardiac dysfunction and consequently, more severe skeletal muscle abnormalities. However, whilst we cannot confirm either of these scenarios, peak VO₂/HR was a better predictor of SMI than any other measured variable, including VO₂peak, the gold-standard measurement of aerobic exercise capacity. Formal screening for sarcopenia in patients
who are incidentally found to have a low peak VO₂/HR may be beneficial.

**Prognostically important associations with skeletal muscle mass**

Although SMI was associated with peak VO₂/HR, ASM% was not. However, ASM% was inversely associated with prognostically important variables including; VO₂peak, PWV, 5-year all-cause mortality risk, a higher NT-proBNP and, body fat percentage even when controlling for age. Although not specifically investigated by our study, the faster PWV speeds observed among patients with a lower SMI indicates more severe arterial stiffness and greater abnormalities in peripheral cardiovascular health, something reported among patients with CHF (Poole et al., 2012). Furthermore, the higher NT-proBNP values reported among patients with a lower ASM% suggests more advanced CHD, or the early development of CHF which may exacerbate the loss of skeletal muscle mass (Collamati et al., 2016). The association between higher body fat percentage and relative lower skeletal muscle mass may also indicate the onset of sarcopenic obesity, fat infiltration of skeletal muscle and therefore reduced muscle quality (Narici & Maffulli, 2010).

**Strengths and weaknesses**

This is the first study to use gold-standard measurement techniques (DXA and CPET) to investigate the relationship between low skeletal muscle mass and reduced aerobic exercise capacity in CHD patients. In addition, this study included a representative cohort of male patients with CHD and the statistical methods employed controlled for several variables that are commonly associated with reduced skeletal muscle mass and aerobic exercise capacity. However, this study has limitations; first, we did not assess muscle function, which meant that we could not report the prevalence of sarcopenia in our cohort. Second, our findings in our male only cohort may not be relevant to females with CHD. In addition, the sample size used in this population was relatively small. Finally, whilst the associations identified in our cross-sectional cohort study are interesting, a prospective long-term follow-up study is required. This would help to determine whether progression of CHD confers with reduced skeletal muscle mass and whether this relates to prognostically important variables and/or the development of CHF.

**Conclusion**

We found a high incidence of low skeletal muscle mass in our cohort of patients with CHD. When standardized to body mass (ASM%), low skeletal muscle mass conferred a higher predicted risk of all-cause mortality. Low skeletal muscle mass was associated with a low VO₂peak in patients with CHD; however, the relationship was complex and dependent on the method used to scale skeletal muscle mass and VO₂peak. Interestingly, our data show that there was a stronger association between SMI and peak VO₂/HR. The relationship between low skeletal muscle mass, prognostic indices and aerobic fitness suggests that adverse changes in skeletal muscle mass may be initiated before the diagnosis or development of CHF. These findings may highlight a need for preventative exercise and nutritional strategies to improve skeletal muscle mass and quality in patients with CHD.

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**Conflict of interest**

SN received salary match-funding from City Health Care Partnership CIC (Hull, UK) during the data collection period of this study. The authors declare no other conflict of interest.

**Author contributions**

SN contributed to project conception and design, acquisition, analysis and interpretation of data, drafted and critically revised the manuscript. AFO’D contributed to analysis and interpretation of data, and drafted and critically revised the manuscript. CT contributed to the acquisition of data and critically revised the manuscript. ALC contributed to project design and critically revised the manuscript. SC and LI contributed to project conception and design, analysis and interpretation of data, drafted and critically revised the manuscript. All authors have given their final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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We confirm that this manuscript is not under review with any other Journal. This manuscript has not previously been submitted or reviewed by another Journal. Findings reported in this manuscript have not been presented at any conference.
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