Peak oxygen uptake correlates with indices of sarcopenia, frailty, and cachexia in older Japanese outpatients

Masamitsu Sugie1,2,3*, Kazumasa Harada1,2, Tetsuya Takahashi1,3,4, Marina Nara1,3,5, Hajime Fujimoto2, Shunei Kyo6 & Hideki Ito7

1Department of Geriatric Health Promotion, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo, 173-0015, Japan; 2Department of Cardiology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 3Institute of Gerontology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 4Department of Rehabilitation, Juntendo University, Tokyo, Japan; 5Japanese Association for Healthy Life Expectancy, Tokyo, Japan; 6Department of Cardiac Surgery, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 7Department of Diabetes, Metabolism, and Endocrinology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan

Abstract

Background  Peak oxygen uptake (peak VO2) is known not only as an index of aerobic fitness but also one of an index of life expectancy. Frailty, sarcopenia, and cachexia are associated with a poor prognosis and high mortality. The purpose of this study was to determine the relationships of peak VO2 with the features of sarcopenia, frailty, and cachexia, to provide insight into which might mediate the poor prognosis.

Methods  The first group of participants was 175 community-dwelling older Japanese outpatients (58 men and 117 women; mean age 77.6 ± 6.4 years), in whom we assessed the features of sarcopenia, frailty, and cachexia, and measured peak VO2 during cardiopulmonary exercise. To confirm the relationships, we analysed another group of 162 participants (77.3 ± 5.5 years).

Results  There were significant correlations between peak VO2 and the features of sarcopenia, frailty, and cachexia, with the exception of high sensitivity C-reactive protein. Multiple linear regression analysis for the prediction of peak VO2 (mL/min) identified following formula: predicted peak VO2 = −11.6 × age (years) + 25.5 × haemoglobin concentration (g/dL) + 114.2 × skeletal muscle mass index (kg/m2) + 8.9 × hand grip strength (kg) + 226.4 × usual walking speed (m/s) − 65.8 × fatiguability (absence 0, presence 1) − 177.4 × chronic heart failure (absence 0, presence 1) + 437.1 (R2 = 0.627, P < 0.001). The validity of the formula was confirmed with another group (r = 0.78, P < 0.001).

Conclusions  This study has identified the features of sarcopenia, frailty, and cachexia that are related to peak VO2 in an older population.

Keywords  Frailty; Sarcopenia; Cachexia; Peak oxygen uptake; Life expectancy

Introduction

Peak oxygen uptake (peak VO2) is a function of oxygen delivery (cardiac output, haemoglobin, etc.) and oxygen utilization (muscle volume and function, etc.) and is influenced by ventilation, cardiac function, vascular function, and muscle function, in other words, respiration, circulation, and metabolism.1 It is known that the most reliable and powerful
prognostic index, not only for cardiac patients\textsuperscript{2,3} but also for the general population,\textsuperscript{4} is exercise tolerance (i.e. peak VO\textsubscript{2}).\textsuperscript{1}

Sarcopenia,\textsuperscript{5} frailty\textsuperscript{6} (including cognitive and psychological frailty\textsuperscript{7,8}), and cachexia\textsuperscript{9} have received significant attention in recent years. It is known that sarcopenia may develop prior to frailty (i.e. age-related sarcopenia\textsuperscript{10}) and represents one component of frailty.\textsuperscript{6,11} Furthermore, it has recently been shown that sarcopenia is strongly associated with cardiovascular mortality and all-cause mortality.\textsuperscript{12,13} Physical frailty is not only an indicator of pre disability but also a predictor of hospitalization, cardiovascular disease, and mortality.\textsuperscript{14} In addition, cognitive and psychological frailty\textsuperscript{7,8} are also associated with adverse health outcomes and death among physically frail people.\textsuperscript{15,16} Cachexia (including cardiac cachexia) has been shown to overlap with sarcopenia, and indeed, the patients may represent a subset of patients with sarcopenia (cachexia-related sarcopenia),\textsuperscript{10,17,18,19} which is associated with high mortality.\textsuperscript{20} Thus, all of these three states are associated with poor prognosis and/or mortality.

Although linear relationships have previously been demonstrated between peak VO\textsubscript{2} and sarcopenia, frailty, and cachexia,\textsuperscript{21} the relationships between peak VO\textsubscript{2} and the various features of sarcopenia, frailty, and cachexia remain to be established.

Clarification the relationships between peak VO\textsubscript{2} and the various features of sarcopenia, frailty, and cachexia might be useful to insight into why peak VO\textsubscript{2} are reliable and powerful prognostic index among not only for cardiac patients\textsuperscript{2,3} but also for the general population.\textsuperscript{4}

Therefore, we first aimed to investigate the relationship between peak VO\textsubscript{2} and the features of sarcopenia, frailty, and cachexia in a group of older community-dwelling Japanese participants, and second, to validate these relationships using a second group of participants. In addition, because there have been only one study of peak VO\textsubscript{2} in community-dwelling older Japanese adults,\textsuperscript{1} we also aimed to determine the relationship between peak VO\textsubscript{2} and age in these groups. In this study, we used the features of sarcopenia, frailty, and cachexia identified by the Asian Working Group for Sarcopenia criteria,\textsuperscript{22} the Japanese version of the Cardiovascular Health Study,\textsuperscript{23} and ‘Cachexia: A new definition’.\textsuperscript{9} were: age < 65 years, impaired vision, impaired hearing, musculoskeletal impairment that might interfere with the ability to perform the symptom-limited exercise test, and any clinically unstable condition. Potential participants who habitually performed exercise training were also excluded from the study. Habitual exercise training was defined as the performance of a repetitive activity more than three times a week, for the purpose of improving and/or maintaining physical performance, and included aerobic training (walking or swimming), resistance training, or a combination of these methods (cycling). The participants’ clinical characteristics are summarized in Tables 1 and 2. We have previously reported the clinical characteristics of this group of participants after they had been allocated to five groups: robust, pre-frail, sarcopenic, frail and cachexic.\textsuperscript{21} Participants were classified into robust, pre-frail, frail, sarcopenia, or cachexia groups using the following method. First, we counted the number of participants with sarcopenia. After excluding those with cachexia, we counted the number of participants with frailty. Next, after excluding those with cachexia and frailty, we counted the number of participants with sarcopenia, according to the report ‘From sarcopenia to frailty’ by Fried et al.\textsuperscript{6} and Morley et al.\textsuperscript{6,11} After excluding participants with cachexia, frailty, and sarcopenia, we counted the number of participants who were pre-frail. Finally, after excluding those with cachexia, frailty, sarcopenia, and pre-frailty, the remaining participants were considered robust.\textsuperscript{21}

Of the 175 community dwelling older adults, 17\% (n = 30) were robust, 40\% (n = 70) were pre-frail, 12\% (n = 21) were sarcopenia, 25\% (n = 44) had frail, and 6\% (n = 10) had cachexia.\textsuperscript{21} The number of participants with overlapping states based on the original definitions as follows: of 10 participants in the cachexia group, two were also classified as sarcopenia and pre-frail, one as frail, and seven as sarcopenia and frail. Of the 44 participants in the frail group, 32 were also classified as frail and 12 as sarcopenia. All 21 participants in the sarcopenia group were classified with overlapping pre-frailty. Of all participants (n = 175), the prevalence rates of overlapping states were 17\% (n = 30) for robust, 53\% (n = 93) for pre-frailty, 24\% (n = 42) for sarcopenia, 30\% (n = 52) for frailty, and 6\% (n = 10) for cachexia.\textsuperscript{21}

To confirm the validity of the peak VO\textsubscript{2} prediction formula obtained, the same tests were conducted in another group of participants (32 men and 130 women; mean age 77.3 ± 5.5 years (range 65–96 years)), who were consecutively recruited using the same inclusion and exclusion criteria.

**Methods**

**Participants**

The participants were 175 older community-dwelling adults (58 men and 117 women) who lived in the Tokyo metropolitan area. The mean age of the participants was 77.6 years (range 65–97 years). None of the participants were hospitalized at the time of the study, but all of them were receiving outpatient treatment at our hospital. The exclusion criteria were:

**Laboratory assays**

All the participants had fasting blood samples drawn from a large antecubital vein to determine haemoglobin concentration (Hb), red cell distribution width (RDW), serum albumin, and high-sensitivity C-reactive protein concentration. Hb
Table 1  Characteristics of the participants

| Characteristic                          | All (175) | Male (58) | Female (117) |
|-----------------------------------------|-----------|-----------|--------------|
| Age (years)                             | 77.6 ± 6.4 (65.0–97.0) | 78.3 ± 7.2 (65.0–97.0) | 77.2 ± 6.0 (65.0–93.0) |
| Height (cm)                             | 153.9 ± 8.3 (133.0–179.0) | 162.3 ± 7.3 (142.0–179.0) | 149.8 ± 6.1 (133.0–162.0) |
| Body weight (kg)                        | 54.2 ± 10.0 (32.6–79.3) | 60.7 ± 9.9 (40.8–79.3) | 51.0 ± 8.4 (32.6–78.5) |
| Body mass index (kg/m²)                 | 22.8 ± 3.5 (14.8–34.0) | 23.0 ± 3.2 (15.9–29.4) | 22.7 ± 3.7 (14.8–34.0) |
| Haemoglobin (g/dL)                      | 12.8 ± 1.4 (7.0–17.0) | 13.2 ± 1.4 (10.0–15.0) | 12.7 ± 1.4 (7.0–17.0) |
| Red cell distribution width (%)         | 13.7 ± 1.2 (12.0–22.9) | 14.0 ± 1.3 (12.3–18.9) | 13.6 ± 1.18 (12.0–22.9) |
| Serum albumin (g/dL)                    | 4.0 ± 0.4 (2.9–7.3) | 3.9 ± 0.6 (2.9–7.3) | 4.0 ± 0.3 (3.0–4.6) |
| High-sensitivity C-reactive protein (mg/dL) | 0.1 ± 0.2 (0.0–1.4) | 0.2 ± 0.3 (0.0–1.4) | 0.1 ± 0.1 (0.0–0.8) |
| Skeletal muscle mass index (kg/m²)      | 6.2 ± 0.9 (4.4–8.4) | 6.7 ± 1.0 (4.5–8.4) | 5.9 ± 0.7 (4.4–8.1) |
| Total body fat mass index (kg/m²)       | 7.3 ± 2.7 (2.5–16.0) | 6.2 ± 2.2 (2.5–12.4) | 7.9 ± 2.7 (3.0–16.0) |
| Hand grip strength (kg)                 | 20.0 ± 6.6 (6.0–37.0) | 25.7 ± 6.8 (12.0–37.0) | 17.3 ± 4.3 (6.0–27.0) |
| Usual walking speed (m/s)               | 0.9 ± 0.2 (0.2–1.5) | 0.9 ± 0.3 (0.2–1.4) | 1.0 ± 0.2 (0.4–1.5) |
| MoCA-J score                            | 23.5 ± 4.0 (10.0–30.0) | 22.9 ± 3.8 (10.0–29.0) | 23.8 ± 4.1 (10.0–30.0) |
| GDS-15 score                            | 3.7 ± 3.2 (0.0–15.0) | 4.5 ± 3.6 (0.0–15.0) | 3.3 ± 2.9 (0.0–12.0) |
| Peak VO₂ (ml/min)                       | 895.3 ± 290.7 (261.0–1698.0) | 992.0 ± 306.5 (261.0–1698.0) | 847.8 ± 271.5 (329.0–1613.0) |
| Peak VO₂/Watt (ml/min/kg)               | 16.4 ± 4.4 (6.2–28.5) | 16.3 ± 4.4 (6.2–25.2) | 16.5 ± 4.5 (7.2–28.5) |
| Peak heart rate (bpm)                   | 122.8 ± 22.3 (72.0–182.0) | 120.5 ± 23.8 (73.0–180.0) | 123.9 ± 21.6 (72.0–182.0) |
| Peak VO₂/heart rate (ml/beat)           | 7.3 ± 2.2 (3.0–15.0) | 8.3 ± 2.6 (4.0–15.0) | 6.8 ± 1.7 (3.0–11.0) |
| Peak watts                              | 68.4 ± 25.5 (6.0–124.0) | 75.3 ± 24.9 (19.0–124.0) | 65.0 ± 25.1 (6.0–118.0) |
| Peak metabolic equivalent               | 4.7 ± 1.3 (1.8–8.3) | 4.7 ± 1.3 (1.8–7.2) | 4.7 ± 1.3 (2.1–8.3) |
| ΔVO₂/ΔLOAD (mL/W)                       | 8.6 ± 2.5 (0.7–14.7) | 9.5 ± 2.1 (3.5–14.7) | 8.2 ± 2.6 (0.7–14.5) |
| VE/VCO₂ slope                           | 34.1 ± 9.6 (13.0–74.0) | 35.5 ± 10.6 (13.0–74.0) | 33.5 ± 9.1 (20.0–66.0) |

Skeletal muscle mass index, total body fat mass index, and body mass index

Table 2  Characteristics of the diseases and symptoms of the participants

| Characteristic                          | All (n = 175) (%) | Male (n = 58) (%) | Female (n = 117) (%) |
|-----------------------------------------|-------------------|-------------------|----------------------|
| Hypertension                            | 99 (56.6)         | 30 (51.5)         | 69 (59.1)            |
| Diabetes mellitus                       | 35 (20.0)         | 10 (16.6)         | 25 (21.7)            |
| Dyslipidaemia                           | 59 (33.7)         | 13 (21.8)         | 46 (39.6)            |
| Atrial fibrillation                     | 16 (9.1)          | 8 (13.8)          | 8 (6.8)              |
| Coronary artery disease                 | 37 (21.1)         | 14 (23.9)         | 23 (19.8)            |
| Post-cardiac operation                  | 12 (6.9)          | 3 (5.5)           | 9 (7.5)              |
| Osteoporosis                            | 7 (4.0)           | 0 (0.0)           | 7 (6.0)              |
| Lumbar canal stenosis                   | 12 (6.9)          | 3 (5.9)           | 9 (7.3)              |
| Knee osteoarthritis                     | 15 (8.6)          | 2 (3.2)           | 13 (11.2)            |
| Dementia                                | 5 (2.9)           | 1 (1.4)           | 4 (3.6)              |
| Chronic heart failure                   | 17 (9.7)          | 11 (19.5)         | 6 (5.1)              |
| Ejection fraction ≤40%                   | 8 (4.6)           | 6 (10.3)          | 2 (1.7)              |
| 40–49%                                  | 3 (1.7)           | 3 (5.2)           | 0 (0.0)              |
| ≥50%                                    | 6 (3.4)           | 2 (3.4)           | 4 (3.4)              |
| Cerebral infarction                     | 16 (9.1)          | 6 (11.0)          | 10 (8.2)             |
| Chronic obstructive pulmonary disease   | 4 (2.3)           | 3 (5.5)           | 1 (0.7)              |
| Chronic kidney disease                  | 6 (3.4)           | 4 (6.5)           | 2 (1.9)              |
| Cancer                                  | 15 (8.6)          | 8 (12.9)          | 8 (6.4)              |
| Fatigability                            | 51 (29.1)         | 21 (35.5)         | 30 (26.0)            |
| Low physical activity of daily life     | 53 (30.3)         | 18 (30.5)         | 35 (30.2)            |
| Anorexia                                | 43 (24.6)         | 13 (23.1)         | 30 (25.3)            |

and RDW were analysed using a Sysmex XE-5000 automated haematology system (Sysmex Corporation, Hyogo, Japan), serum albumin was analysed using the bromocresol purple assay (Shino-Test Corporation, Tokyo, Japan) and high-sensitivity C-reactive protein concentration was analysed using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken Corporation, Tokyo, Japan). Skeletal muscle mass index, total body fat mass index, and body mass index

Appendicular skeletal muscle mass was measured using total body dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, Tokyo, Japan). The sum of the muscle mass of the four limbs was considered to be the appendicular skeletal
muscle mass, and the skeletal muscle mass index (SMI) was calculated as the appendicular skeletal muscle mass, divided by height in metres, squared (kg/m²). Total body fat mass index was calculated as total body fat mass, divided by height in metres, squared (kg/m²). Body mass index (BMI) was calculated as body mass, divided by height in metres, squared (kg/m²).

**Physical performance evaluation**

To determine their usual walking speed (u-WS; m/s), we asked participants to walk along a straight 11-m walkway on a flat floor, once, at their usual speed. Walking speed was measured over a 5 m distance between markers placed 3 and 8 m from the start of the walkway. Two trials were conducted per person, with the shorter time being used in the analyses.

Hand grip strength (HGS) is a valid indicator of overall muscle strength, and it is a particularly useful indicator of upper-extremity strength. HGS was assessed twice for each hand, alternately, using a Smedley-type JAMAR hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). The highest value obtained was used in the analyses.

All the physical performance parameters were assessed for each participant by trained research assistants.

**Assessment of weight loss, exhaustion, physical activity, and anorexia**

According to the Japanese version of the Cardiovascular Health Study,23 weight loss was assessed by a response of ‘yes’ to the question, ‘Have you lost 2 kg or more in the past six months?’23 and exhaustion was considered to be present if the participant responded with ‘yes’ to the following questions: ‘In the last two weeks, have you felt tired for no reason?’

We evaluated the role of physical activity by asking the following questions about time spent engaged in sports and exercise: (i) ‘Do you engage in moderate levels of physical exercise or sports aimed at health?’ and (ii) ‘Do you engage in low levels of physical exercise aimed at health?’ Participants who answered ‘no’ to both of these questions were classified as low activity.23

Anorexia was defined to be present if the participant responded with ‘very poor’ and ‘poor’ to following questions: ‘My appetite is’ a. very poor, b. poor, c. average, d. good, and e. very good.24

**Assessment of cognitive function and depression**

The Montreal Cognitive Assessment (MoCA) is a screening tool that has been validated in many different countries, including Japan (MoCA-J).25 It is normally used in the clinical setting for the detection of mild cognitive impairment or early dementia in older adults. The range of scores obtained is 0–30, with higher scores indicating better cognitive performance. The MoCA-J was selected as the main cognitive test, because of its greater sensitivity for the detection of mild cognitive impairment in community-dwelling people than the Mini-Mental State Examination.25

Depression status was assessed using the Geriatric Depression Scale-15 (GDS-15),26 which is a commonly used instrument for depression screening in the general geriatric population. The GDS-15 is a questionnaire that does not focus on somatic symptoms or contain any questions about suicide. All 15 items are scored as either 0 or 1, and the total score ranges from 0 to 15. Scores from 5 to 9 indicate a minor depressive disorder and scores ≥ 10 indicate a major depressive disorder.

Trained research assistants assessed each participant’s cognitive function and depression status.

**Echocardiography**

All the participants underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer (Vivid E9®, GE Healthcare, Tokyo, Japan). Measurements for the left ventricle were obtained from the parasternal long-axis and apical four-chamber views, in accordance with standard criteria. Left ventricular ejection fraction (EF) was automatically calculated using the modified Simpson rule in the apical two-chamber and four-chamber views. We categorized the results into reduced EF (<40%), mid-range EF (40–49%), and preserved EF (≥50%), according to the 2016 guidelines of the European Society of Cardiology for the diagnosis and treatment of acute and chronic heart failure.27

**Cardiopulmonary exercise test**

All participants underwent a symptom-limited bicycle ergometer cardiopulmonary exercise test (CPET) using an upright, electromagnetically braked cycle ergometer (Aerobike Strength Ergo-8; Mitsubishi Electric Corporation, Tokyo, Japan), a metabolic analyser (Aero Monitor AE-310S; Minato Medical Science Company Limited, Osaka, Japan), and electrocardiography (ML-9000 stress test system; Fukuda Denshi Company Limited, Tokyo, Japan). The exercise test began with a 3 min rest on the ergometer, which was followed by a 4 min warm-up at 0 watt (W) at 60 rpm. The load was then increased incrementally by 15 W/min. All the CPET parameters were measured from the beginning of the initial rest period on the cycle ergometer until the end of the exercise session.
The CPET was terminated on the participant’s request, if abnormal physiologic responses occurred, or if the participant was unable to continue to perform the exercise correctly. The VO₂ obtained was smoothed using an eight-breath moving average. Peak VO₂ was defined as the highest VO₂ value obtained during the last minute of the CPET. When the respiratory exchange ratio (carbon dioxide uptake/oxygen uptake (VCO₂/VO₂)) was <1.0 at peak exercise, the test was considered inadequate, because of poor effort, and the peak exercise data were not used in the analyses. In the present study, we used peak VO₂ (mL/min), rather than peak VO₂/body mass (mL/min/kg), because we wished to determine the relationship between peak VO₂ and sarcopenia, frailty, and cachexia-related factors, which include BMI and SMI.

Statistical analyses

A required sample size of 160 participants was calculated to provide 80% power, using α = 0.05, β = 0.20, 21 predictors, anticipated effect size = 0.15, and G*Power sample size software, Version 3.1.9.2 (Heinrich Heine Universität, Düsseldorf, Germany).

Pearson’s correlation analysis was performed to determine the relationship between peak VO₂ and biochemical parameters or physiologic assessments, and Spearman’s correlation analysis was performed to determine the relationship between peak VO₂ and MoCA-J score or GDS-15 score. Multiple linear regression analysis were used to predict peak VO₂ and were adjusted for age, sex, Hb, SMI, total body fat mass index, HGS, u-WS, MoCA-J score, and GDS-15 score, but not with high-sensitivity C-reactive protein (Table 3 and Supporting Information, Data S1).

Table 4 shows the results of the multiple linear regression analyses. These showed that age (B = −11.6, P < 0.001), Hb (B = 25.5, P = 0.021), SMI (B = 114.2, P < 0.001), HGS (B = 8.9, P = 0.008), u-WS (B = 226.4, P = 0.003), fatigability (B = −65.8, P = 0.044), and CHF (B = −177.4, P = 0.002) were independently related to peak VO₂ (mL/min) (R² = 0.627), after adjustment for potentially confounders.

We used the outputs of the multiple linear regression analyses to create a formula for the prediction of peak VO₂ (mL/min). This was predicted peak VO₂ (mL/min) = −11.6 × age (years) + 25.5 × Hb (g/dL) + 114.2 × SMI (kg/m²) + 8.9 × HGS (kg) + 226.4 × u-WS (m/s) − 65.8 × fatigability (absence 0, presence 1) − 177.4 × CHF (absence 0, presence 1) + 437.1. We then tested the validity of the formula using the second group of participants and found a significant correlation (r = 0.78, P < 0.001) between the peak VO₂ (mL/min), measured using CPET, and the peak VO₂ (mL/min) predicted using the formula (Figure 1).

In the combined group of 337 older people, there was a significant relationship (r = −0.46, P < 0.001) between age and peak VO₂ (Figure 2).

Table 3  Correlation coefficients for the relationships between peak VO₂ and sarcopenia, frailty, and cachexia-related factors

| Characteristic                      | All (n = 175) |
|------------------------------------|--------------|
|                                     | r            | P              |
| Age (years)                        | −0.470       | <0.001         |
| Body mass index (kg/m²)            | 0.379        | <0.001         |
| Haemoglobin (g/dL)                 | 0.450        | <0.001         |
| Red cell distribution width (%)    | −0.205       | 0.004          |
| Serum albumin (g/dL)               | 0.212        | 0.005          |
| High-sensitivity C-reactive protein (mg/dL) | −0.091  | 0.297          |
| Skeletal muscle mass index (kg/m²) | 0.488        | <0.001         |
| Total body fat mass index (kg/m²)  | 0.408        | <0.001         |
| Hand grip strength (kg)            | 0.566        | <0.001         |
| Usual walking speed (m/s)          | 0.449        | <0.001         |
| MoCA-J score                       | 0.285        | <0.001         |
| GDS-15 score                       | −0.194       | 0.007          |

GDS-15: Geriatric depression scale -15; MoCA-J, Japanese version of the Montreal Cognitive Assessment; VO₂: oxygen uptake.

Results

The clinical characteristics of the participants are summarized in Tables 1 and 2. The correlations between peak VO₂ and biochemical, physiologic, physical, cognitive, and psychologic parameters are shown in Table 3. There were significant correlations between peak VO₂ and age, BMI, Hb, RDW, serum albumin, SMI, total body fat mass index, HGS, u-WS, MoCA-J score, and GDS-15 score, but not with high-sensitivity C-reactive protein (Table 3 and Supporting Information, Data S1).

Table 4 shows the results of the multiple linear regression analyses. These showed that age (B = −11.6, P < 0.001), Hb (B = 25.5, P = 0.021), SMI (B = 114.2, P < 0.001), HGS (B = 8.9, P = 0.008), u-WS (B = 226.4, P = 0.003), fatigability (B = −65.8, P = 0.044), and CHF (B = −177.4, P = 0.002) were independently related to peak VO₂ (mL/min) (R² = 0.627), after adjustment for potentially confounders.

We used the outputs of the multiple linear regression analyses to create a formula for the prediction of peak VO₂ (mL/min). This was predicted peak VO₂ (mL/min) = −11.6 × age (years) + 25.5 × Hb (g/dL) + 114.2 × SMI (kg/m²) + 8.9 × HGS (kg) + 226.4 × u-WS (m/s) − 65.8 × fatigability (absence 0, presence 1) − 177.4 × CHF (absence 0, presence 1) + 437.1. We then tested the validity of the formula using the second group of participants and found a significant correlation (r = 0.78, P < 0.001) between the peak VO₂ (mL/min), measured using CPET, and the peak VO₂ (mL/min) predicted using the formula (Figure 1).

In the combined group of 337 older people, there was a significant relationship (r = −0.46, P < 0.001) between age and peak VO₂ (Figure 2).

Table 3  Correlation coefficients for the relationships between peak VO₂ and sarcopenia, frailty, and cachexia-related factors

| Characteristic                      | All (n = 175) |
|------------------------------------|--------------|
|                                     | r            | P              |
| Age (years)                        | −0.470       | <0.001         |
| Body mass index (kg/m²)            | 0.379        | <0.001         |
| Haemoglobin (g/dL)                 | 0.450        | <0.001         |
| Red cell distribution width (%)    | −0.205       | 0.004          |
| Serum albumin (g/dL)               | 0.212        | 0.005          |
| High-sensitivity C-reactive protein (mg/dL) | −0.091  | 0.297          |
| Skeletal muscle mass index (kg/m²) | 0.488        | <0.001         |
| Total body fat mass index (kg/m²)  | 0.408        | <0.001         |
| Hand grip strength (kg)            | 0.566        | <0.001         |
| Usual walking speed (m/s)          | 0.449        | <0.001         |
| MoCA-J score                       | 0.285        | <0.001         |
| GDS-15 score                       | −0.194       | 0.007          |

GDS-15: Geriatric depression scale -15; MoCA-J, Japanese version of the Montreal Cognitive Assessment; VO₂: oxygen uptake.
Discussion

Our study used data from consecutively recruited, older outpatients attending a geriatric clinic who lived in the Tokyo metropolitan area. The first aim of this study was to determine the relationships between peak VO2 and multiple features of sarcopenia, frailty, and cachexia. Although sarcopenia, frailty, and cachexia may be prevented and/or reversed by exercise training, previous studies have used mortality as an outcome. However, peak VO2, a bi-directionally changeable index, might be one of the useful outcomes. Therefore, clarification of the relationships between peak VO2 and the features of sarcopenia, frailty, and cachexia might provide important insights into which factors are closely related to poor prognosis and which factors are important to reverse these syndromes by intervention.

We have shown that peak VO2 is independently associated with age, Hb, physical function (SMI, HGS, & u-WS), fatiguability, and CHF (Table 4). Although relationships between peak VO2 and indexes such as age, anaemia, SMI, HGS, u-WS, fatiguability, and CHF have previously been reported, no previous studies have investigated the relationship between peak VO2 and this cluster of sarcopenia, frailty, and cachexia-related factors.

Peak VO2 is a function of oxygen delivery (cardiac output, haemoglobin, etc.) and oxygen utilization (muscle volume and function, etc.) and is influenced by ventilation, cardiac function, vascular function, and muscle function, in other words, respiration, circulation, and metabolism. Although there have been many studies showing that peak VO2 decreases with age, and the relationship between peak VO2 and age has been reported in healthy Japanese individuals aged 20–78 years, there have been no studies of the relationship between peak VO2 and age in community-dwelling Japanese adults of ≥65 years. In the present study, we have shown a significant relationship between peak VO2 and age in 337 adults aged 65–97 years (Figure 2), although this was not strong \( r = 0.46 \). This is likely to be because the decline in peak VO2 is determined not only by age but also by changes in body composition and power.

We have previously reported associations between peak VO2 and SMI, and peak VO2 and HGS, which we suggested might be underpinned by the degradation of sarcomeric proteins in both skeletal muscle and cardiomyocytes via the

---

Table 4 Multiple linear regression analysis for the prediction of peak VO2

| Characteristic                  | \( B \) | \( \beta \) | \( P \) value | LCI     | UCI     |
|--------------------------------|---------|------------|--------------|---------|---------|
| Age (years)                    | 437.1   | 2.699      | 0.192        | −222.705| 1096.905|
| Haemoglobin (g/dL)             | 25.466  | 0.138      | <0.001       | −16.97  | 46.988  |
| Skeletal muscle mass index (kg/m^2) | 114.17  | 0.392      | <0.001       | 76.428  | 151.912 |
| Hand grip strength (kg)        | 8.882   | 0.225      | 0.008        | 2.406   | 15.359  |
| Usual walking speed (m/s)      | 226.4   | 0.210      | 0.003        | 77.558  | 375.241 |
| Fatiguability                  | −65.772 | −0.116     | 0.044        | −128.684| −1.861  |
| Chronic heart failure          | −177.414| −0.187     | 0.002        | −288.349| −66.478 |
| \( R^2 \)                      | 0.627   |            |              |         |         |

Adjusted for sex, total body fat mass index, MoCA-J score, GDS-15 score, anorexia, low physical activity in daily life, hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation, chronic heart failure, chronic kidney disease, cancer, and red cell distribution.

GDS-15, Geriatric Depression Scale-15; MoCA-J, Japanese version of the Montreal Cognitive Assessment.

---

Figure 1 Scatter plot showing the relationship between the measured peak VO2 and the predicted peak VO2, \( n = 162 \) participants; linear correlation with \( r = 0.78 \). VO2, oxygen uptake.

Figure 2 Scatter diagram showing the relationship between the measured peak VO2 and age, \( n = 336 \) participants; linear correlation with \( r = −0.46 \). VO2, oxygen uptake.
VO2 is an important prognosis indicator, not only in heart failureserved left ventricular EF.42 Finally, De Becker ure with low left ventricular EF, but also in cases with pre-death in the general population,48 the present
ubiquitin
Peak VO2 with indices of sarcopenia, frailty, and cachexia 147

Although there were significant relationships between peak VO2 and MoCA-J and GDS-15 scores (Table 3), no independent relationships were identified in multiple regression analysis (Table 4). Previously, it was reported that higher VO2 max is associated with better global cognitive function43,44 and low VO2 max is associated with more severe depressive symptoms.45 However, no relationship was previously identified between fatiguability and cognitive function and depression in frail older individuals.46 It is more intuitive that fatiguability (a symptom of physical frailty) is likely to be more closely associated with peak VO2, a physical index of exercise tolerance, than cognitive function and depression (cognitive and psychological frailty), because fatiguability is a physical symptom that develops because of loss of muscle protein, muscle weakness, cytokine abnormalities, and lower protein synthesis.41

Additionally, although RDW, which has been widely studied by heart failure researchers, is known not only as a marker of exercise intolerance (i.e. peak VO2) in patients with CHF47 but also as a strong and independent risk factor for death in the general population,48 the present findings show that RDW is not an independent marker of peak VO2 in community-dwelling older people.

The results of the present study can be summarized using the following formula for the prediction of peak VO2, which was derived from the multiple linear regression analyses: peak VO2 = −11.6 × age (years) + 25.5 × Hb (g/dl) + 114.2 × SMI (kg/m²) + 8.9 × HGS (kg) + 226.4 × u-WS (m/s) − 65.8 × fatigability (absence 0, presence 1) − 177.4 × CHF (absence 0, presence 1) + 437.1, and has an R² of 0.627. To confirm the validity of this formula, we studied another group of 162 consecutively-recruited participants and found a significant correlation between their peak VO2 (mL/min), measured using CPET, and their predicted peak VO2 (mL/min) (r = 0.78, P < 0.001).

In general, peak VO2 is calculated using the Fick principle:
Peak VO2 = Stroke Volume × Heart rate × arterial–venous oxygen difference (AVO2diff).38 It is known that the most reliable and powerful prognostic index, not only for cardiac patients2,3 but also for the general population,4 is exercise tolerance (i.e. peak VO2).1

Indeed, it was known that ‘Each 1-MET (i.e. VO2 of approximately 3.5 ml per kilogram of body weight per minute) increase in exercise capacity conferred a 12 percent improvement in survival among men’44 and ‘The Framingham Risk Score-adjusted mortality risk decreased by 17% for every 1-MET increase, among women’.49

However, it is remain unknown why peak VO2 are reliable and powerful prognostic index in general population. The present findings, from another point of view of Fick principle, suggest mechanisms for how sarcopenia, age-related sarcopenia,10 and cachexia-related sarcopenia10,17–19 related with peak VO2 among community-dwelling older general population.

Thus, clarified the relationships between peak VO2 and the various features of sarcopenia, frailty, and cachexia in this study, might be useful to insight into why peak VO2 are reliable and powerful prognostic index among general population.

Although we have previously demonstrated relationships of sarcopenia, frailty, and cachexia with age, BMI, and peak VO2,21 the evaluation of peakVO2 in older adults is sometimes challenging; therefore, this reliable and novelty formula for the prediction of peak VO2, with non-invasive and not under stress, may be useful clinically.

There were several limitations to this study. Firstly, the study was confined to Japanese adults in one geographical location. Further multicentre studies should investigate whether the formula for the prediction of peak VO2 is suitable for use with other Japanese populations and other ethnicities. Secondly, the participants were recruited in a clinic caring for patients with chronic diseases; therefore, the results may not be applicable to high active elderly peoples such as senior long distance runners and athletes. Thirdly, we did not measure interleukin-6, which is an important mediator of cachexia.9 Fourthly, the sample size was small to investigate after divided into both of sex. It needs to investigate sex specificity with larger sample. Further research is needed to improve the accuracy of the generated formula and to determine whether SMI, measured using bio-impedance, is a useful inclusion. Additionally, activity is considered to be an important factor that affects VO2, but in this study, the relationship with VO2 was not clarified because the activity was investigated by questionnaire. Further research is needed to clarify the relationship between VO2 and activity using with activity metre. In the future, the relationship between the changes in peak VO2 and the changes in the features of sarcopenia, frailty, and cachexia should be studied longitudinally, to provide further insight into the features that would be most effective to target therapeutically to improve life expectancy.

DOI: 10.1002/rco2.45

147
In conclusion, the present study has shown that peak VO\(_2\) is associated with features of sarcopenia, frailty, and cachexia (age, Hb, SMI, HGS, u-RS, the symptom of fatigability, and CHF) in community-dwelling older adults.

Acknowledgements

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle.\(^{30}\) We thank Andrea Baird, MD, Bonnie Lynch, PhD, and Mark Cleasby, PhD, from Edanz Group (www.edanzediting.com/ac) for editing drafts of this manuscript.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Scatter plot showing the relationship between the measured peak VO\(_2\) and skeletal muscle mass index (\(r = 0.488\)), hemoglobin (\(r = 0.450\)), hand grip strength (\(r = 0.566\)) and usual walking speed (\(r = 0.449\)) in Table 3. \(n = 175\) participants; VO\(_2\), Oxygen uptake.

Conflict of interest

All authors have no conflicts of interest involving this work.

References

1. Itoh H, Ajsaka R, Koike A, Makita S, Omiya K, Kato Y, et al. Heart rate and blood pressure response to ramp exercise and exercise capacity in relation to age, gender, and mode of exercise in a healthy population. J Cardiol 2013;61:71–78.
2. Kubozono T, Itoh H, Oikawa K, Tajima A, Maeda T, Aizawa T, et al. Peak VO(2) is more potent than B-type natriuretic peptide as a prognostic parameter in cardiac patients. Circ J: official j Jap Circ Soc 2008;72:575–581.
3. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–786.
4. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
5. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–423.
6. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottlieben J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56: M146–M156.
7. Malmsdrom TK, Morley JE. The frail brain. J Am Med Dir Assoc 2013;14:453–455.
8. Panza F, Solfrizzi V, Frisardi V, Maggi S, Sancarlo D, Adante F, et al. Different models of frailty in predementia and dementia syndromes. J Nutr Health Aging 2011;15:711–719.
9. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr(Edinburgh, Scot- land) 2008;27:793–799.
10. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. Clin Nutr(Edinburgh, Scotland) 2010;29:154–159.
11. Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. J Cachexia Sarcopenia Muscle 2014;5:5–8.
12. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenia obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc 2014;62:253–260.
13. Bahat G, Ilhan B. Sarcopenia and the cardiometabolic syndrome: a narrative review. Europ Ger Med 2016;7:220–223.
14. Verma G, O’Laughlin JP, Bunker L, Peterson S, Frishman WH. Trial of time: review of frailty and cardiovascular disease. Cardiol Rev 2017;25:236–240.
15. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc 2017;18:252–258.
16. Lohman MC, Mezuk B, Dumenci L. Depression and frailty: concurrent risks for adverse health outcomes. Aging Ment Health 2017;21:399–408.
17. Rolland Y, Abellan van Kan G, Gillette-Guyonnet S, Vellas B. Cachexia versus sarcopenia. Curr Opin Clin Nutr Metab Care 2011;14:15–21.
18. Evans WI. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr 2010;91:1123–1127.

19. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr (Edinburgh, Scotland) 2007;26:389–399.

20. Kalantar-Zadeh K, Rhee C, Sim JI, Stenvinkel P, Anker SD, Kovesdy CP. Why cachexia kills: examining the causality of poor outcomes in wasting conditions. J Cachexia Sarcopenia Muscle 2013;4:89–94.

21. Sugie M, Harada K, Takahashi T, Nara M, Koyama T, Fujimoto H, et al. Muscle wasting diseases has two distinct trajectories on the 3-dimensional age-BMI-peak VO2 scatterplot. Journal of Cachexia. Sarcop Mus Clin Rep 2018;3:e00069.

22. Chen LK, Lee WJ, Peng LN, Liu JK, Arai H, Akishita M. Recent advances in Sarcopenia. Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2016;17:767.e1–767.e7.

23. Makizako H, Shimada H, Doi T, Tsutsumimoto K, Suzuki T. Impact of physical frailty on disability in community-dwelling older adults: a prospective cohort study. BMJ Open 2015;5:e008462, https://doi.org/10.1136/bmjopen-2015-008462.

24. Wilson MM, Thomas DR, Rubenstein LZ, Chibnall JT, Anderson S, Bae A, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. Am J Clin Nutr 2005;82:1074–1081.

25. Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, et al. Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal Cognitive Assessment. Geriatr Gerontol Int 2010;10:225–232.

26. Bae JN, Cho MJ. Development of the Korean version of the Geriatric Depression Scale and its short form among elderly psychiatric patients. J Psychosom Res 2004;57:297–305.

27. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.

28. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873–934.

29. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging Clin Exp Res 2017;29:35–42.

30. Sugie M, Harada K, Takahashi T, Nara M, Kim H, Koyama T, et al. Effectiveness of exercise-training on frailty and the specificity of exercise effectiveness on frailty-related indices among community-dwelling robust, pre-frailty and frailty older peoples. J Gerontol Geriatr Res 2018;7:491.

31. Binder EF, Schechtman KB, Ehsani AA, Steger-May K, Brown M, Sinacore DR, et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. J Am Geriatr Soc 2002;50:1921–1928.

32. Wilms B, Schmid SM, Luley K, Wissemann J, Lehnert H. Prevention and treatment of cachexia: exercise and nutritional therapy. Internist 2016;57:971–977.

33. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing 2018;47:193–200.

34. Liu P, Hao Q, Hai S, Wang H, Cao L, Dong B. Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: a systematic review and meta-analysis. Maturitas 2017;103:16–22.

35. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. J Cachexia Sarcopenia Muscle 2016;7:507–509.

36. Pollock ML, Mengelkoch LJ, Graves JE, Lowenthal DT, Limacher MC, Foster C, et al. Twenty-year follow-up of aerobic power and body composition of older track athletes. J Appl Physiol (1985) 1997;82:1508–1516.

37. Otto JM, O’Doherty AE, Hennis PJ, Cooper JA, Grocott MP, Snowdon C, et al. Association between preoperative haemoglobin concentration and cardiopulmonary exercise variables: a multicentre study. Perioper med (London, England) 2013;2:18; https://doi.org/10.1186/2047-0525-2-18.

38. Sugie M, Harada K, Takahashi T, Nara M, Ishikawa J, Koyama T, et al. Relationship between skeletal muscle mass and cardiac function during exercise in community-dwelling older adults. ESC Heart Failure 2017;4:409–416.

39. Sugie M, Harada K, Takahashi T, Nara M, Ishikawa J, Tanaka J, et al. Relationship between hand grip strength and peak VO2 in community-dwelling elderly outpatients. J Sarcopenia, Sarcop Mus Clin Rep 2018;3: https://doi.org/10.17987/jscm-cvnj31i.4.8.

40. Coen PM, Jubrias SA, Distefano G, Amati F, Mackey DC, Glynn NW, et al. Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. J Gerontol A Biol Sci Med Sci 2018;68:447–455.

41. De Becker P, Roeykens J, Reynolds M, McGregor N, De Meirleir K. Exercise capacity in chronic fatigue syndrome. Arch Intern Med 2000;160:3270–3277.

42. Malhotra R, Bakken K, D’Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart failure 2016;4:607–616.

43. Feundenberg P, Petrovic K, Sen A, Toghofer AM, Fixa A, Hofer E, et al. Fitness and cognition in the elderly: the Austrian Stroke Prevention Study. Neurology 2016;86:418–424.

44. Sugie M, Harada K, Takahashi T, Nara M, Kawai H, Fujiwara Y, et al. Peak exercise stroke volume effects on cognitive impairment in community-dwelling people with preserved ejection fraction. ESC Heart Fail 2018;5:876–883.

45. Tolmunen T, Laukkanen JA, Hintikka J, Kurl S, Viinamaki H, Salonen R, et al. Low maximal oxygen uptake is associated with elevated depressive symptoms in middle-aged men. Eur J Epidemiol 2006;21:701–706.

46. Panagiotakish SH, Simos P, Zaganas I, Basta M, Persynska GS, Fountoulakis N, et al. Self-reported fatigue as a risk index for dementia diagnosis. Europ Ger Med 2018;9:211–217.

47. Van Craenenbroeck EM, Pelle AJ, Beckers PJ, Possemiers NM, Ramakers C, Vrints CJ, et al. Red cell distribution width as a marker of impaired exercise tolerance in patients with chronic heart failure. Eur J Heart Fail 2012;14:54–60.

48. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86–105.

49. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554–1559.

50. von Haehling S, Morley JE, Coats AJ, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2017. J Cachexia Sarcopenia Muscle 2017;8:1081–1083.