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Establishing Reference Cardiorespiratory Fitness Parameters in Alzheimer's Disease

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ABSTRACT

Evidence is growing for aerobic exercise training as a viable means to attenuate cognitive losses associated with Alzheimer's disease. The mechanism of action for aerobic exercise's cognitive benefits is likely enhanced cardiorespiratory fitness and its response to incremental aerobic exercise have been incompletely evaluated in Alzheimer's disease. The aim of this analysis was to establish cardiorespiratory fitness reference values in older adults with mild to moderate Alzheimer's disease using a cardiopulmonary graded exercise testing. Ninety-seven community-dwelling older adults with mild to moderate Alzheimer's disease underwent a symptom limited cardiopulmonary graded exercise test on a cycle ergometer. Differences between sexes and between Alzheimer's disease participants with and without diagnosis of cardiovascular diseases were assessed by independent T-tests. Peak oxygen consumption was 10–20 % lower than those achieved by similar clinical populations on treadmill tests. As expected, males produced significantly higher peak oxygen consumption compared to females ($p = 0.02$). However, the presence of concurrent cardiovascular disease did not result in statistically significant lower peak oxygen consumption compared to those without cardiovascular disease. These data provide a frame of reference for metabolic, cardiovascular, and ventilatory function during cardiopulmonary graded exercise testing performed on cycle ergometer in older adults with mild to moderate Alzheimer's disease.

Introduction

Cardiorespiratory fitness (CRF) measured by peak oxygen uptake (VO_{2peak}) during cardiopulmonary exercise testing (CPET) has been shown to be the biggest predictor of future cardiovascular disease (CVD) and mortality [1]. The importance of CRF measurement is reflected by recommendations made in the last 5 years by the American Heart Association (AHA) that a national data bank be established for the establishment of CRF normative values [2]. Likewise, there is an increasing interest in exercise and fitness in Alzheimer's disease (AD) given the accumulating evidence supporting the potential therapeutic effects of aerobic exercise and fitness and the maintenance of cognitive health [3]. However, little data exist on the objective measurement of CRF in older adults with AD. Furthermore, the current understanding of CRF in persons with AD is limited to a few studies that have investigated VO_{2peak} obtained via CPET using treadmill protocols in patients with relatively mild AD only, with ranges of 19.4–21.6 ml/kg/min most commonly reported [4–8]. What partially makes the measurement of CRF using treadmill-based CPET challenging in individuals with AD is the increased prevalence of falls. In contrast, CPET using a cycle ergometer represents a safe and feasible mode for performing aerobic fitness testing in persons with AD.

Until recently, very few studies obtaining CRF parameters derived from cycle ergometry-based CPET have been published in older adults. Reported average VO_{2peak} values in healthy older adults in the seventh decade of life are 23.1 (sedentary men) and 21.2 ml/kg/min (sedentary women) on cycle ergometer tests [9]. Thus, available data on CRF and valid reference data in persons with

AD particularly for cycle ergometer-based CPET are needed. The aim of this study was to provide reference values for CRF from cycle ergometry-based CPET in persons with AD and compare the differences in CRF by sex and the presence of concurrent cardiovascular disease (CVD). It was hypothesized that: 1) VO_{2Peak} would be lower in our sample that completed CPET on cycle ergometer compared to historical averages that utilized treadmill-based CPET; 2) compared to women, men with mild to moderate AD would demonstrate significantly higher VO_{2Peak} and other CRF indicators; and 3) concurrent CVD would further reduce VO_{2Peak} and other indicators of CRF independent of sex.

Materials and Methods

Design

This study used a cross-section design to analyze baseline data from the FIT-AD Trial [10]. The FIT-AD trial is a randomized, controlled trial and is evaluating the effects of 6 months of aerobic exercise training on cognition and hippocampal volume in older adults with AD. This study complied with the current ethical regulations for research [11] and was approved by the university's Institutional Review Board (IRB). Both participants and caregivers gave written informed consent and assent respectively prior to any study proceedings.

Participants

The inclusion/exclusion criteria of the FIT-AD trial have previously been described in detail [10]. Briefly, older (> 65 years) English-speaking community-dwelling adults with diagnosed AD at a mild to moderate stage (defined as 0.5–2 on the Clinical Dementia Rating [CDR] scale and a score of 15–26 on the Mini-Mental State Examination [MMSE]) were enrolled in the study. Potential participants who had neurological/psychiatric disorders other than AD, chemical dependency, inability to cycle, or any contraindications to exercise per American College of Sports Medicine (ACSM) guidelines were excluded [12].

One hundred participants participated in baseline testing. Ninety-seven completed full CPET with gas exchange, three were excluded from analysis because of testing non-compliance (i. e., did not want to wear the mouthpiece needed for breath-by-breath CPET measurement). The average age of the study sample was 77.3 (6.7) with 57 % men (▶ **Table 1**). Thirty-two percent of the sample had a diagnosis of CVD in their medical history, including 37.5 % of men and 24.4 % of women. Of these, nine had coronary artery disease, 14 had an arrhythmia, 9 had carotid artery atherosclerotic disease resulting in stroke or transient ischemic attack, and 3 had a coagulopathy. In general, females were older and had higher BMI and MMSE scores compared to males, however these differences were not statistically significant.

Procedures

Pre-exercise instructions

Medical clearance from the primary care providers was obtained for the participants to take part in the CPET. Participants were instructed to refrain from performing strenuous exercise 24–48 h prior to the day of the CPET and to arrive in the post-absorptive state, with no smoking or caffeinated beverages permitted in the 3 h prior to the scheduled start of the CPET. Participants were advised to take all morning medications as directed by their primary care provider, with the exception of insulin.

Symptom-limited peak cycle-ergometer test

Participants began pedaling at a comfortable pedal frequency (40–60 rpm) at low resistance on a recumbent cycle ergometer (Precor 842i; Precor, Woodinville, WA, USA). The intensity of cycling was then increased every 3 min (one stage) by increasing the cycle resistance (and therefore watts [W]) to achieve an increase in energy expenditure of one metabolic equivalent (MET) (1 MET = 3.5 mL oxygen/kg body weight/minute: estimated resting oxygen consumption). MET calculations were based on metabolic calculations for the estimation of energy expenditure during leg cycling that are published by the ACSM [12]. Per the equation, MET calculations were individualized based on body mass and the distance per revolution of the flywheel of the Precor cycle ergometer [12]. This procedure was maintained until the participant was unable to maintain cycling rate or reached volitional fatigue (asked to stop) (VO_{2Peak}), met predefined stopping criteria indicative of a VO_2 max test, or had symptoms that indicated test termination as outlined by the ACSM. The predefined stopping criteria used for determining a max test included achieving at least 2 of the following: (a) heart rate in excess of 90 % of the age-predicted max heart rate (APMHR); (b) rating of perceived exertion (RPE - Borg RPE) of 17/20; (c) no increase in oxygen consumption with increasing exercise intensity; or (d) respiratory exchange ratio (RER) ≥ 1.10. Peak heart rate (HR_{peak}) was recorded as the highest heart rate recorded by electrogram during the test.

Outcome variables and assessment

Expired gases were measured continuously using breath-by-breath analysis averaged by 5–7 s by a respiratory mass spectrometer (MGA 1100, Beck's Physiological Systems, St. Louis, MO, USA). All measurements followed O_2 and CO_2 gas and airflow calibration using known precision calibration gases (MGC Diagnostics, St. Paul, MN, USA) and a 3L syringe (Hans Rudolph, Shawnee, KS, USA), respectively. The primary CRF outcome data assessed was $VO_{2peak.}$

▶ **Table 1** Demographic data.

Variable	Value
Male	56 (57.4)
Age (yrs)	77.3 (6.7)
Height (cm)	164.8 (9.7)
Weight (kg)	75.8 (16.2)
BMI	28.7 (5.2)
MMSE	21.5 (3.4)
CVD	31 (32.0)
B-blocker	10 (10.3)
Ach-I	60 (61.9)

Continuous variables expressed as means (SD); categorical variables as number (%). BMI, body mass index; MMSE, Mini-Mental State Examination; CVD, cardiovascular disease; Ach-I, acetylcholinesterase inhibitor.

Additional CRF indicators measured and assessed at peak exercise included: volume of carbon dioxide produced (VCO_{2peak}), minute ventilation (V_{Epeak}), $RER_{peak,}$ breathing frequency (BF_{peak}), tidal volume (TV_{peak}), O_2 pulse (O_2 $pulse_{peak}$), ventilatory equivalents for oxygen ($EqVO_2$) and carbon dioxide ($EqVCO_2$), and VO_2/work rate ratio. VO_{2peak} and VCO_{2peak} were defined as the median oxygen consumption and carbon dioxide production during the last 30 s before cessation of exercise. V_{Epeak}, RER_{peak}, and BF_{peak} were also determined from the median expired gases during the last 30 s of exercise. BF_{peak} and V_{Epeak} were used to calculate TV_{peak}. O_2 $pulse_{peak}$ was calculated by dividing VO_{2Peak} (ml/min) by HR_{peak}, and expressed as ml/beat. Peak ventilatory efficiency was calculated as EqVO2 (V_{Epeak}/ VO_{2peak}) and $EqVCO_2$ (V_{Epeak}/ VCO_{2peak}). The VO_2/work rate relationship was determined by dividing VO_{2Peak} (ml/min) with peak W output on the cycle ergometer and expressed as ml/min/W.

Statistical analysis

Descriptive statistics were performed first for each variable, using means and standard deviations (SD) for continuous variables and frequency for categorical variables. Variables were tested for normality using the Shapiro-Wilk test, and variables that did not follow a normal distribution, including VO_{2peak}, VCO_{2peak}, V_{Epeak}, RER_{peak}, BF_{peak}, TV_{peak}, and watts, were log-transformed. When running the independent samples t-tests with variables on the logarithmic scale, there were no differences compared to running the independent samples t-tests without log transformation. Hence, non-transformed data were analyzed using independent sample t-tests to assess the difference between sex and between participants with and without a diagnosis of CVD. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS 22 (IBM Corp., Armonk, NY, USA).

Results

The average VO_{2peak} achieved in this sample of individuals with mild to moderate AD was 1253 ml/min (16.9 ml/kg/min). When stratified by sex, VO_{2peak} was 1402 ml/min (17.8 ml/kg/min) for men and 1060 ml/min (15.8 ml/kg/min) for women, respectively ($p = 0.02$) (▶ **Table 2**). Men with AD had significantly higher VO_{2peak} (12.1 %) ($p = 0.02$), V_{Epeak} (26.6 %) ($p < 0.01$), TV_{peak} (37.5 %) ($p < 0.01$), and O_2 $pulse_{peak}$ (33.0 %) ($p < 0.01$) but significantly lower BF_{peak}

▶ **Table 2** Cardiopulmonary exercise testing reference values in persons with mild to moderate Alzheimer's disease with and without cardiovascular disease.

	Women			Men		
	All	**With CVD**	**No CVD**	**All**	**With CVD**	**No CVD**
Subjects	41	10	31	56	21	35
Age	77.3 (6.2)	77.5 (6.8)	77.3 (6.1)	77.2 (7.0)	77.6 (6.1)	77.4 (7.6)
MMSE	21.9 (3.5)	22.0 (3.5)	21.9 (3.3)	21.3 (3.4)	21.0 (2.7)	21.5 (3.6)
BMI	28.9 (5.2)	30.0 (3.0)	28.8 (5.6)	28.5 (5.2)	29.7 (5.1)	27.5 (5.2)
Test Duration (min)	8.2 (3.0)	7.3 (2.3)	8.6 (3.2)	11.6 (3.3) * *	10.4 (3.6)	12.1 (2.8)
Watts	93.4 (29.7)	87.7 (34.5)	95.4 (28.2)	122.1 (37.1) * *	115.8 (35.4)	123.3 (38.9)
HR_{peak} (bpm)	121.8 (14.3)	124.0 (10.5)	121.1 (15.5)	116.0 (19.0)	111.1 (17.4)	117.5 (19.4)
%$APMHR_{Peak}$	86.3 (10.8)	87.7 (10.0)	86.6 (11.0)	79.2 (16.7) * *	75.7 (21.2)	80.6 (13.4)
RPE_{peak}	15.6 (1.7)	16.0 (1.6)	15.6 (2.0)	15.5 (2.3)	14.9 (2.2)	15.8 (2.3)
$METS_{peak}$	6.1 (1.4)	5.4 (0.6)	6.2 (1.4)	6.8 (1.4) * *	6.4 (1.2)	6.9 (1.5)
$V_{E\ peak}$ (L/min)	40.1 (7.1)	40.5 (5.3)	39.8 (7.8)	52.4 (13.8) * *	50.6 (13.3)	52.7 (14.1)
RR_{peak} (breaths/min)	32.3 (7.4)	32.8 (8.5)	32.0 (7.3)	28.3 (4.8) * *	28.1 (5.0)	28.5 (4.9)
$V_{T\ peak}$ (V_E/RR)	1.3 (0.3)	1.3 (0.2)	1.3 (0.3)	1.9 (0.4) * *	1.8 (0.4)	1.9 (0.4)
$VO_{2\ Peak}$ (L/min)	1.05 (0.20)	1.07 (0.19)	1.06 (0.24)	1.40 (0.35) * *	1.36 (0.33)	1.40 (0.36)
$VO_{2\ Peak}$ (ml/kg/min)	15.8 (3.7)	14.6 (3.2)	16.1 (3.9)	17.8 (4.6) * *	16.8 (3.7)	18.3 (5.0)
$VCO_{2\ Peak}$ (L/min)	1.12 (0.22)	1.07 (0.22)	1.14 (0.23)	1.56 (0.50) * *	1.50 (0.46)	1.56 (0.51)
$VCO_{2\ Peak}$ (ml/kg/min)	16.8 (4.5)	14.7 (2.8)	17.2 (4.6)	19.9 (6.4) * *	18.6 (5.7)	20.4 (6.7)
RER_{Peak}	1.08 (0.10)	1.06 (0.06)	1.07 (0.09)	1.11 (0.11)	1.10 (0.10)	1.10 (0.11)
$EqVO_{2\ Peak}$	38.6 (7.0)	39.6 (8.2)	37.8 (4.2)	38.1 (5.9)	37.4 (5.4)	38.4 (6.4)
$EqVCO_{2\ Peak}$	36.2 (5.7)	39.0 (8.1)	35.3 (4.7)	34.8 (5.2)	34.4 (4.2)	35.4 (5.8)
O_2Pulse_{Peak} (ml/beat)	8.6 (1.6)	8.7 (2.3)	8.6 (1.4)	12.0 (3.3) * *	11.6 (4.1)	12.3 (2.7)
VO_2/ Work $Rate_{Peak}$ (ml/min/W)	11.8 (3.3)	12.4 (2.8)	11.6 (3.5)	11.9 (2.1)	12.2 (2.5)	11.8 (1.8)

Values are expressed as means (SD). * Significantly different from individuals (within the same sex with CVD) ($P = 0.05$). * * Significantly different from women ($P = 0.05$). MMSE, Mini-Mental State Examination; BMI, body mass index; HR, heart rate; APMHR, age-predicted max heart rate; RPE, rating of perceived exertion; METS, metabolic equivalent of task; V_E, minute ventilation; RR, respiratory rate; V_T, tidal volume; VO_2, volume of oxygen consumed; VCO_2, volume of carbon dioxide produced; RER, respiratory exchange ratio; $EqVO_2$, ventilatory equivalents oxygen; $EqVCO_2$, ventilatory equivalents carbon dioxide; O_2 Pulse, oxygen pulse.

(–13.2 %) ($p < 0.01$) compared to women. Both men and women with CVD had reduced VO_{2peak} compared to their counterparts without CVD diagnosis; however, these differences were not significant.

Ninety-four (97 %) of participants achieved a $RER_{Peak} \geq 1.0$. Forty-five (46 %, 26 men and 19 women) of the participants met criteria for VO_{2max} test (▶ **Table 3**). Additionally, 82 % of the total sample met at least one criteria used to determine if VO_2 max was obtained. Specifically, 38 % achieved $RER_{Peak} \geq 1.1$ and 34 % reached an $HR_{Peak} \geq 90$ % APMHR (or 37 % of persons not taking beta blockers), whereas 25 % had evidence of O_2 plateau, and 41 % reported an $RPE_{peak} \geq 17$.

Discussion

To our knowledge, this is the first study that has fully investigated and reported parameters of CRF in older adults with mild to moderate AD completing a peak cycle ergometer CPET. Comparisons among other studies investigating VO_{2peak} in older adults with AD are challenging because 1) previous studies that have implemented CPET have utilized treadmills [4–6, 13, 14], and 2) data have not been presented as sex differences. In persons with AD with an MMSE range of 23.1–28.8, CPET performed on treadmills yielded VO_{2peak} values ranging from 19.4–21.6 ml/kg/min [4, 5, 14]. However, two studies yielded substantially higher VO_{2peak} levels of 33.7 and 34.7 ml/kg/min [6, 13]. It should be pointed out that the indicators used in the determination of maximal tests in this sample are similar to those previously reported including RER_{Peak} (1.07–1.1) [6, 13], but are lower pertaining to HR_{Peak} (128–141bpm) [5, 6] and RPE_{Peak} [4–6]. In healthy, middle-aged adults, CPET performed on a cycle ergometer generates VO_{2peak} that is typically 10–20 % lower than when performed on the treadmill [15]. Therefore, when a 10–20 % increase in VO_{2peak} is applied to our data set, men would expect to have a corresponding VO_{2peak} of 19.6–21.4 ml/kg/min, whereas in women VO_{2peak} values would increase to 17.3–19.0 ml/kg/min. Such extrapolations align with VO_{2peak} values gathered from older adults with AD who completed treadmill-based CPET [4, 5, 14]. However, historical VO_{2peak} averages in cognitively healthy septuagenarians completing peak cycle ergometer CPET were 23.1 and 21.2 ml/kg/min in males and females, respectively [16]. In comparison to these age-matched, otherwise healthy, historical averages, our sample had a 26 and 29 % lower VO_{2peak} for males and females respectively. Interestingly, both men and women with CVD had reduced VO_{2peak} compared to their counterparts without CVD diagnosis; however, these differences were not significant.

▶ **Table 3** Cardiopulmonary exercise testing reference values in persons with mild to moderate Alzheimer's disease who reached criteria for VO_2 max.

	Women		Men	
	Yes	**No**	**Yes**	**No**
Subjects	19	22	26	30
Age	77.3 (7.1)	77.4 (5.4)	75.5 (7.3)	78.8 (6.6)
MMSE	22.8 (3.3)	20.9 (3.5)	21.1 (3.8)	21.5 (3.1)
BMI	29.3 (5.7)	28.5 (5.1)	28.5 (5.2)	28.5 (5.4)
Test Duration (min)	8.6 (2.6)	8.9 (3.9)	13.3 (3.2)	11.5 (2.8)
Watts	92.4 (32.3)	94.3 (28.0)	129.9 (34.5)	115.2 (39.6)
HR_{peak} (bpm)	130.3 (10.7) *	114.6 (13.1)	127.5 (17.4) *	106.2 (14.4)
$\%APMHR_{Peak}$	0.93 (.09) *	0.80 (0.1)	0.87 (.13) *	0.75 (0.10)
RPE_{peak}	16.8 (1.2) *	14.6 (1.9)	16.2 (1.9) *	14.9 (2.4)
$METS_{peak}$	5.9 (1.6)	6.2 (1.2)	7.2 (1.4) *	6.4 (1.3)
$V_{E\ peak}$ (L/min)	41.7 (7.3)	38.7 (7.0)	59.2 (13.7) *	46.3 (11.1)
RR_{peak} (breaths/min)	33.0 (8.4)	31.7 (6.6)	29.7 (4.4)	26.9 (4.8)
$V_{T\ peak}$ (V_E/RR)	1.3 (.3)	1.2 (.2)	2.0 (.5) *	1.7 (.4)
$VO_{2\ Peak}$ (L/min)	1.05 (.21)	1.06 (.19)	1.48 (.38)	1.31 (.31)
$VO_{2\ Peak}$ (ml/kg/min)	16.0 (4.2)	15.6 (3.3)	19.5 (5.1) *	16.3 (3.4)
$VCO_{2\ Peak}$ (L/min)	1.18 (.26)	1.07 (.18)	1.74 (.60)	1.41 (.36)
$VCO_{2\ Peak}$ (ml/kg/min)	17.8 (4.7)	16.0 (4.2)	22.9 (7.0) *	17.3 (4.6)
RER_{Peak}	1.11 (.09)	1.05 (.11)	1.17 (.11) *	1.05 (.08)
$EqVO_{2\ Peak}$	40.1 (7.7)	37.3 (6.2)	40.7 (6.2) *	35.8 (4.7)
$EqVCO_{2\ Peak}$	36.2 (7.1)	36.2 (4.2)	35.1 (6.1)	34.5 (4.4)
O_2Pulse_{Peak} (ml/beat)	7.9 (1.6) *	9.2 (1.4)	12.0 (2.8)	12.5 (3.0)
VO_2/ Work $Rate_{Peak}$ (ml/min/W)	11.9 (3.3)	11.7 (3.4)	11.9 (1.8)	11.9 (2.4)

Values are expressed as means (SD). * Significantly different from individuals (within the same sex with CVD) ($P = 0.05$). MMSE, Mini-Mental State Examination; BMI, body mass index; HR, heart rate; APMHR, age-predicted max heart rate; RPE, rating of perceived exertion; METS, metabolic equivalent of task; V_E, minute ventilation; RR, respiratory rate; V_T, tidal volume; VO_2, volume of oxygen consumed; VCO_2, volume of carbon dioxide produced; RER, respiratory exchange ratio; $EqVO_2$, ventilatory equivalents oxygen; $EqVCO_2$, ventilatory equivalents carbon dioxide; O_2 Pulse, oxygen pulse.

The pathophysiology of AD is incompletely understood, however growing evidence suggests a multifactorial pathology of AD and that cardio- and cerebrovascular dysfunction coexists in most older adults with AD [17]. This heart-brain pathology hypothesizes that because the brain is limited by intracellular energy substrates to sustain neuronal metabolism and critically depends on the cardiovascular system's ability to deliver oxygen and glucose, age-related impairment of cardiovascular function may impair cerebral blood flow regulation and disrupt neuronal homeostasis [18]. Likewise, VO_{2peak} is limited by physiological deficiencies within the lung-heart-arterial-muscle axis, but in its simplest model, it is the product of cardiac output and arteriovenous oxygen difference [19]. Therefore, it is plausible that deficiencies in cardiac output, arterial delivery of oxygen, or its utilization would create a micro-environment primed for AD pathology (i. e. the cardiorespiratory fitness hypothesis [20]). Indeed, research findings in older persons without dementia have shown that cerebrovascular conductance is enhanced in those with higher VO_{2peak}, suggesting that the cardiovascular benefits that have been reported previously in the systemic circulation are also conferred to the brain [21]. Furthermore, researchers have established the independent prediction of both mean arterial pressure and cerebrovascular conductance by VO_2 peak [21]. Furthermore, researchers have established the independent prediction of both mean arterial pressure and cerebrovascular conductance by VO_2 peak [21], suggesting that CRF may have some protective effects on the vasculature.

Although there are genetic contributors to VO_{2peak}[22], physical activity levels also play an important role in the attenuation of the typical decline of VO_{2peak} seen with aging. Indeed, there is strong epidemiological evidence suggesting a linkage of higher midlife physical activity levels and reduced AD risk later in life. Likewise, it is well documented that older adults with AD are less physically active relative to age- and sex-matched, cognitively healthy older adults [23, 24]. Hence, it is likely that reduced CRF parameters in older adults with AD are at least partially attributable to reduced habitual physical activity. In addition, AD pathology in the brain decreases prefrontal lobe function, which leads to executive dysfunction, reduced motivation, and disorganization [25]. These changes further reduce the participation in physical activity and exercise. Last, reduced physical activity and impaired cognition form a vicious cycle that exacerbates physical inactivity and cognitive decline, causing continuing deterioration in CRF.

Another important finding in the study was that there were expected, statistically significant sex differences among peak CRF variables measured during CPET in older adults with mild to moderate AD. Our findings further show that there is a sex difference in VO_{2peak}, which is consistent with the literature, as women typically have a 20–25 % lower VO_{2peak} compared to men [26]. Despite overall reductions in VO_{2peak} seen in older adults with AD, it is evident that men with AD still possess the capacity to generate higher VO_{2peak} than women with AD. This relationship is similar to what is seen in healthy adults across the lifespan [22], even after values are adjusted to body size. Our findings also suggest that older men with mild to moderate AD may still have larger stroke volumes as indicated by the significantly higher ($p < 0.01$) O_2 $pulse_{peak}$ (12.0 ml/beat vs. 8.6 ml/beat). However, it should be noted that O_2 $pulse_{peak}$ in both males and females was still lower than what has been classically reported in cognitively healthy, older adults in their seventh decade of life who have completed symptom-limited, peak cycle ergometry CPET [16]. Specifically, our finding of a reduced O_2 $pulse_{peak}$ may provide initial evidence of a reduced stroke volume in older adults with mild to moderate AD, independent of concurrent cardiovascular disease status, and may provide insight to mechanisms contributing to the lower VO_{2peak} seen in this population.

In line with previous literature, our study shows that there are also sex differences in pulmonary function at peak exercise. Men had both significantly higher $V_{E\,Peak}$ (52.4 vs. 40.1 L/min) and TV_{Peak} (1.9 vs. 1.3) ($p < .01$), but lower BF_{Peak} ($p < 0.01$) compared to women with mild to moderate AD. Although limited in comparisons, the $V_{E\,Peak}$ reported in our sample is substantially lower than reference values obtained in both cognitively healthy males and females (ages 70–79) completing peak cycle ergometer CPET (81.0 and 49.9 L/min, respectively) [16]. Blunted respiratory response to CPET has been documented previously in persons with AD [4]. however, the mechanisms have only recently began to be explored in animal models [27].

Interestingly, there were no significant differences among indicators of CRF in persons with CVD compared to those without CVD. Although men and women without CVD did demonstrate greater VO_{2peak} compared to counterparts with CVD, these differences did not reach significance ($p = 0.25$ and $p = 0.27$, respectively). This finding contrasts that of large studies where men and women without CVD had significantly higher indicators of CRF (including VO_{2peak}) compared to non-CVD counterparts [28]. The lack of statistical significance shown in this study may be the result of a small sample size or may be due to systemic changes in AD [25], which like CVD, can negatively influence the physiological function of the lung-heart-arterial-muscle axis.

Collectively, and of clinical importance, the lower VO_{2peak} values seen in persons with mild to moderate AD result in a lessened "physiologic reserve," or the physiologic capacity to increase VO_2 during activities. It is possible that reduced CRF values seen in our cohort at peak exercise could be related in part to the lower work effort. However, many of the CRF parameters at peak exercise were still lower in our subset of participants ($n = 45$) who met ACSM criteria for VO_2 max compared to historical averages of healthy older adults [16] (▶ **Table 2**). There are several physiologic systems that could potentially contribute to low VO_{2peak} seen in this sample including reduced cardiac and pulmonary function as indicated by lower O_2 $pulse_{peak}$ and $V_{E\,Peak}$, respectively. Although, it should also be noted that other AD studies have shown reduced skeletal muscle atrophy [29], which could also negatively affect aerobic exercise performance via associated reductions in mitochondria content.

This study is the first to attempt to establish CRF reference parameters stratified by sex and CVD in persons with AD. Furthermore, this study provides an established CPET protocol that can be employed by future studies that existing studies in AD often fail to clearly describe. Lastly, this study fully reports the majority of relevant output from the metabolic cart and provides a thorough description and breakdown of both subjective and objective data to

allow the reader to gauge the quality of the CPET. This study was limited by its sample size. Although this is one of the largest sample sizes to date reporting CRF parameters in persons with AD, longitudinal studies investigating CRF values in older populations without AD and across the lifespan have used substantially larger samples [28]. Nonetheless, it is well known that recruiting persons with AD is very challenging and this study may provide a model to explore CRF norms in older adults with mild to moderate AD. Another limitation was the single group (AD only) design without the use of a cognitively healthy, aged-matched control group. This was outside the scope of the parent randomized, controlled trial (The FIT-AD Trial) and therefore we relied on historical controls for comparison purposes. Lastly, the use of some CRF parameters such as O_2 pulse and VO_2/work rate ratio have limitations pertaining to use as surrogate markers of stroke volume and muscle O_2 extraction capacity.

Future research is needed to further augment the establishment of normative values of CRF using peak cycle-ergometer exercise tests in persons with AD. Such studies are essential to unveil the mechanisms of aerobic exercise in AD by establishing whether an improvement in CRF is essential for any therapeutic effects of aerobic exercise in AD and for determining dose-response relationships. Establishing normative values obtained during CPET will also help elucidate changes in metabolic, cardiovascular, and ventilatory function seen as AD develops and progresses.

Conclusion

Our study established the initial reference values for CRF in older adults with mild to moderate AD within sex and the presence of CVD. These data provide a frame of reference for assessing the normalcy of the response profiles for standard indices of metabolic, cardiovascular, and ventilatory function during CPET performed on a cycle ergometer. Older adults with mild to moderate AD achieved VO_{2peak} values that are 10–20 % lower than those achieved in treadmill tests and appear to have reduced CRF parameters (including VO_{2peak}) compared to peers without AD. Because epidemiological studies have shown that reduced physical activity and exercise in midlife contributes to AD onset, it will be important for future studies to examine if reduced VO_{2peak} is the underlying physiological mechanism.

Conflict of Interest

The authors declare that they have no conflict of interest.

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