Published in final edited form as:
Arch Phys Med Rehabil. 2014 September ; 95(9): 1714–1718. doi:10.1016/j.apmr.2014.04.007.

Cardiopulmonary Exercise Testing Is Well-Tolerated in People with Alzheimer's-Related Cognitive Impairment

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Abstract

Objective—To retrospectively assess whether CPET would be well-tolerated in individuals with AD compared to a nondemented peer group.

Design—We retrospectively reviewed 575 CPET in individuals with and without cognitive impairment due to AD.

Setting—University medical center.

Participants—Exercise testing data was reviewed from non-demented individuals (n = 340) and those with Alzheimer's-related cognitive impairment (n = 235).

Interventions—Not applicable.

Main Outcome Measures—Main outcome measure for this study was reporting the reason for CPET termination. The hypothesis reported was formulated after data collection.

Results—We found that the CPET on cognitively impaired individuals were terminated as a result of fall risk more often but that overall test termination was infrequent, 5.5% vs 2.1% (p=0.04) in peers without cognitive impairment. We recorded 6 cardiovascular and 7 fall risk events in those with AD, compared to 7 cardiovascular and 0 fall risk events in those without cognitive impairment.

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Conclusions—Our findings support using CPET to assess peak VO_2 in older adults with cognitive impairment due to AD.

Keywords

graded exercise test; dementia; adverse event; treadmill

Increasing attention is being paid to the benefits of physical activity, specifically aerobic exercise, to support and maintain cognitive performance as we age,[1] and as a potential therapeutic intervention for those with cognitive impairment due to Alzheimer's disease (AD)[2]. Most of the guidelines for exercise testing and prescription for this clinical population are based on available literature for older adults.[3] As we move towards recommending and incorporating aerobic exercise for people with early AD, using the information generated from the cardiopulmonary exercise test (CPET) will provide useful information regarding cardiopulmonary fitness and guiding exercise prescription. The published data to date of those characterized with mild cognitive impairment likely related to AD and CPET[4–6] have not reported information regarding exercise testing termination criteria and whether CPET is well-tolerated in people with early AD. Recent reviews have noted the lack of CPET-based aerobic exercise prescription in clinical trials.[7]

When considering CPET for persons with cognitive impairment several concerns have been expressed, such as the reliability of the test for research or exercise prescription[3] and impaired communication and understanding during the CPET.[8] Additional concerns may include poor safety awareness and the potential for behavioral disturbance. In addition, we suspect there is a continued hesitance in the research[7] and clinical communities to perform CPET in this population, though there is little data to support these concerns.

To our knowledge, no data have been published regarding CPET tolerability, cardiovascular and fall risk adverse events in individuals with AD. The University of Kansas Alzheimer's Disease Center has performed 235 CPET on individuals with cognitive impairment related to possible and probable AD. Our goal was to retrospectively assess the whether individuals with AD had early CPET termination compared to a nondemented peer group.

METHODS

Participants

We reviewed source documentation for 575 tests on 326 unique individuals. This dataset included all CPET performed for 3 research studies between July 2005 and March 2013: the Brain Aging Project on which we have previously reported,[9] the Alzheimer's Disease Exercise Program Trial (NCT01128361)[9] and the Trial of Exercise for Aging and Memory (NCT01129115). The procedures used in this study were approved by the Institutional Review Board at Kansas University Medical Center. Written informed consent was obtained from all individuals or their legal representative prior to study participation. In cases where a legal representative consented for the participant, the participant provided informed assent. All participants, regardless of suspected cognitive impairment, underwent a semi-structured interview with a knowledgeable informant. Medications, past medical history, education,

demographic information, and family history were collected. We determined dementia status and probable etiology based on clinical evaluation. All participants included in the cognitive impairment cohort for this retrospective analysis were judged to have possible or probable AD. This evaluation method has a diagnostic accuracy for AD of 93%,[10] and are sensitive to detecting the earliest stages of AD.[11] Severity of dementia was characterized using the Clinical Dementia Rating (CDR) scale.[4] The CDR assesses impairment in multiple domains. An algorithm is used to generate a global dementia severity score (very mild=0.5, mild=1, moderate=2, severe=3), or the domains can be summed to create a more sensitive measure of (CDR Sum of Boxes, range 0–18).

Cardiopulmonary Exercise Test

Our CPET methodology has been previously published.[12] Briefly, we conducted a medical screen to determine cardiac risk and whether any an absolute or relative contraindications to exercise testing were present.[13, 14] We employed a modified Cornell Bruce protocol on a treadmill. Speed and incline changes were pre-set and controlled by the metabolic analysis software (ParvoMedics, Sandy UT). Expired gases were captured using a nose clip, mouthpiece and 2-way non-rebreathing valve (Hans Rudolph, Shawnee, KS). Participants were oriented to the Borg Rating of Perceived Exertion (RPE) 6–20 scale prior to beginning the CPET. The exercise physiologist would point to the number on the RPE scale and to determine perceived exertion level, the participant communicated by head nodding (yes) or shaking left to right (no). Thirty seconds prior to the beginning of the next stage, the exercise physiologist reminded the participant of their previous level and asked them about subsequently greater levels until the participant indicated “yes”. Participants could elect to end the test by raising their hand. Our staff exercise physiologist led the test, while a nurse took blood pressures on the opposite side of the exercise physiologist. For safety, a spotter stood behind and to the side of the participant, and a medical monitor (physician or nurse practitioner) observed real time electrocardiography (ECG). We used American College of Sports Medicine (ACSM) recommendations for absolute and relative indications for terminating tests.[13]

We recorded any instance of early termination of the CPET by the medical monitor due to cardiovascular or fall risk concerns (i.e. unsteady gait) or by the study participant. We followed guidelines for indications for termination of exercise testing.[13, 14] Absolute indications for test termination were: drop in SBP of ≥10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia; moderate to severe angina; increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope); signs of poor perfusion (cyanosis or pallor); sustained ventricular tachycardia or other arrhythmia including second- or third-degree atrioventricular block that interferes with cardiac output during exercise; ST segment elevation (≥1.0 mm in leads without diagnostic Q-waves, other than V1 or aVR). Relative indications for early test termination were: ST or QRS changes such as excessive ST depression (>2 mm horizontal or down sloping ST segment depression) or marked axis shift; arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block or bradyarrhythmias; unusual shortness of breath, wheezing, leg cramps, or claudication; development of bundle branch block or intraventricular conduction

delay that could not be distinguished from ventricular tachycardia; increasing chest pain; hypertensive response (SPB>250 mmHg and or a DBP>115 mmHg).

The remaining CPET were terminated either volitionally by the participant (peak exercise test) or by the exercise physiologist if balance was compromised or when 3 of 4 of the following maximal effort criteria were met.[15] 1) plateau in VO_2 with additional load (< 100mL increase over last 1 minute mean of prior stage); 2) HR > 90% of age predicted maximum; 3) RER > 1.1; 4) RPE >=17.

Statistical Analysis

Group differences between those with and without cognitive impairment were tested using parametric or non-parametric tests as appropriate. Differences in early test termination between those with and without cognitive impairment were evaluated using Fisher's Exact Test. For exercise test values, only those tests that were not terminated early by the testing staff were included in analyses. Analyses were conducted using R (v. 2.15.3; R Foundation, Vienna, Austria).

RESULTS

Participant Characteristics

Table 1 provides summary demographic and testing information. The group with cognitive impairment had fewer females but was otherwise demographically similar to the nondemented group. Severity of dementia was general very mild to mild, with 172 individuals rated as CDR 0.5 (very mild), 57 rated CDR 1 (mild), 4 rated CDR 2 (moderate), and 1 rated CDR 3 (severe). Of the nondemented participants, 117 were classified as high cardiac risk at the time of testing according to ACSM guidelines and the remaining 223 were classified as moderate cardiac risk. Of the individuals with cognitive impairment, 95 were classified as high cardiac risk according to ACSM guidelines, and the remaining 140 classified as moderate cardiac risk. For participants who were tested twice as part of intervention or observational studies, no early termination due to an adverse event was repeated.

CPET performance is summarized in Table 1. On average, individuals with cognitive impairment performed well on the CPET. However, these individuals had shorter tests, achieved lower peak heart rates and had lower peak oxygen uptake. We found that 52% of the group with cognitive impairment and 64% of the non-demented group met 3 of the 4 criteria considered maximal effort. The number of early test terminations due to adverse events was significantly greater (p=0.04) in the group with cognitive impairment (5.5%) versus the group with normal cognition (2.1%) (see Table 2). This was specifically due to the 7 terminations due to fall risk concerns all in the cognitive impairment group; 1 test was terminated because the participant became agitated and failed to follow directions with regard to walking safely on the treadmill (this person had very mild dementia, CDR 0.5), and 6 tests were terminated because individuals could not keep pace with the treadmill (2 with CDR 0.5, 3 with CDR 1, and 1 with CDR 2). The frequency of cardiac adverse events was not different between those with and without cognitive impairment (p=0.77). Nine of

the individuals who had a cardiac adverse event were considered moderate cardiac risk[13] prior to CPET. The remaining 4 individuals who had a had a cardiac adverse event were considered high risk[13] prior to CPET.

DISCUSSION

Our results indicate that conducting CPET in individuals with cognitive impairment is associated with significantly higher early termination of tests. However, the overall percentage of early test termination by staff due to a cardiovascular or fall risk concern was very low (5.5%). In general, our cohort of individuals with cognitive impairment was able to successfully complete CPET for research purposes. We report that those with cognitive impairment tolerated the using the Cornell protocol, which is a graded treadmill test. Since the CPET requires individuals to don headgear, a nose clip and mouthpiece, it is important to note that only one participant became agitated during the CPET. No other participants became agitated and all followed commands during the CPET. This is encouraging for those physicians or healthcare professionals interested in using CPET to determine cardiopulmonary fitness in people with early cognitive impairment.

We have previously noted lower peak oxygen uptake capacity, lower peak heart rates and shorter tests in those with cognitive impairment.[12] Several factors likely contribute to these differences. First, acetylcholinesterase inhibitors are known bradycardic agents and likely depress heart rate response to effort. Second, individuals with AD may have given less effort or had increased apathy towards the test.[16] In addition, systemic changes, such as lean mass loss,[17] in individuals with AD may contribute to reductions in measured VO_2 peak.

Despite greater occurrence of early test termination in those with cognitive impairment, these results support the overall CPET was well-tolerated for those with cognitive impairment. We have demonstrated that with adequate instruction and supervision, individuals with early AD can complete a peak exercise test. Based on our experience, we have implemented several strategies to maximize safety for these individuals. First, we conduct a thorough cardiac risk screen and ask for medical records release of any clinical stress testing in the preceding 2 years. Second, we provide a clear and concise explanation of the CPET and RPE scale from a general script prior to testing by the exercise physiologist. We repeat the instructions for the CPET, RPE and terminating the test until the participant can summarize the procedure. This encourages full understanding of the test to be performed as well as an opportunity for the participant to ask questions or express concerns prior to testing. Although it is recommended that individuals with AD have multiple visits with several practice sessions,[3] we believe our methodology for understanding the CPET procedure eliminates extra visits, reduces caregiver burden related to travel and possible confusion on behalf of the person with early AD. Third, we recommend the use of an additional spotter for tests. This provides extra reassurance to the individual before we begin testing and also additional safety support if the participant experiences difficulty with balance. It is important to note that we do not touch or hold on to the participant. Rather, should a loss of balance occur during testing, the spotter is present as an added safety measure. In our testing experience, our exercise physiologist has terminated CPET when the individual’s balance is compromised in advance of a potential fall. Despite the generally low

occurrence of treadmill difficulty (only 7 individuals with AD were unable to keep pace with the treadmill or became agitated during testing), a brief practice session on the treadmill would be beneficial. Fourth, we recommend that only one individual, in our case, the exercise physiologist, speak to and encourage the participant during the test. This reduces environmental stimulation and improves uniformity in testing.

Study Limitations

Although we did assess overground walking prior to the exercise test, it may be insufficient to determine how an individual with AD will perform on a treadmill. Overground walking is a daily occurrence, whereas treadmill walking is unfamiliar to many individuals. Though we did not measure this directly, our general experience has been that more apraxic individuals have greater difficulty with the treadmill. Future work should screen for apraxia or having a practice trial on the treadmill prior to the exercise test. This would allow those individuals to conduct an exercise test on another type of exercise modality such as a cycle ergometer or a recumbent stepper if treadmill testing is not appropriate due to balance concerns.

CONCLUSIONS

A greater percentage of people in the non-demented group met the pre-determined criteria for maximal “effort” during the CPET. Although only half of the participants with early AD met the criteria, a CPET using an already established treadmill protocol is feasible and safe to conduct in this clinical population. We can use the results of the peak exercise test to guide exercise prescription and integrate physical activity into their daily routine. These data provide important information regarding exercise test performance and serves as a guide for physicians, healthcare professionals and those interested in conducting exercise tests in people with early AD.

Peak exercise testing continues to be the gold standard for measuring cardiorespiratory fitness. We believe that with adequate screening for cardiac risk and the necessary safety precautions are followed, individuals with early AD can participate in peak exercise testing using a treadmill. We conclude that conducting CPET in this clinical population is well-tolerated for individuals with cognitive impairment.

Acknowledgments

Conflicts of Interest and Source of Funding

This data was collected as part of projects funded by R03AG026374, R21AG029615, R01AG034614 and R01AG033673 through the National Institutes of Aging, and K23NS058252 from the National Institute on Neurological Disorders and Stroke. The University of Kansas General Clinical Research Center (M01RR023940) and the Clinical and Translational Science Unit (UL1 TR000001) provided essential space, expertise, and nursing support. Dr. Burns and Vidoni are supported by the University of Kansas Alzheimer's Disease Center (P30AG035982). Dr. Vidoni is supported by the Heartland Institute for Clinical & Translational Research, University of Kansas Medical Center’s CTSA, KL2 TR000119. Sandra A. Billinger was supported in part by K01HD067318 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Anna E. Mattlage was supported in part by T32HD057850 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development or the National Institutes of Health.

Abbreviations

CPET	cardiopulmonary exercise test
AD	Alzheimer's disease
CDR	Clinical Dementia Rating
RPE	Borg Rating of Perceived Exertion
ACSM	American College of Sports Medicine

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Table 1

Participant demographics and performance on graded exercise tests.

	Nondemented (n= 340)	Cognitive Impairment (n=235)	p value
Age (y)	74.0 (6.2)	75.0 (6.7)	0.09
CDR Global	0.0 (0.0)	0.7 (0.3)	
CDR Sum of Boxes	0.0 (0.1)	3.5 (2.4)	
Sex (% female)	60.6	49.8	0.01
Maximal HR (bpm)	148.0 (14.7)	138.5 (19.5)	<0.001
Peak Rating of Perceived Exertion (RPE)	17.2 (1.9)	16.9 (2.7)	0.06
Exercise Duration (s)	645.6 (195.0)	570.5 (191.0)	<0.001
Peak oxygen consumption ($ml*kg^{-1}*min^{-1}$)	21.9 (5.2)	20.2 (4.4)	<0.001
RER at peak oxygen consumption	1.10 (0.1)	1.09 (0.1)	0.20
BMI ($kg*m^{-2}$)	27.0 (4.3)	26.6 (4.6)	0.32
# achieving 3 of 4 criteria	n=219	n= 122	<0.01
Any Early Termination Due to Adverse Event	n= 7	n= 13	0.03

Values are means (standard deviation) unless otherwise noted. Abbreviations: CDR = Clinical Dementia Rating, bpm = beats per minute, s = seconds

Table 2

Reasons for early test termination due to adverse event (AE).

	Nondemented	Cognitive Impairment	p value
Cardiovascular AE	n=7	n=6	0.78
HTN response	n=3		
(SBP > 250 mmHg or DBP > 115 mmHg)			
Supraventricular tach.	n=1		
Atrial fibrillation with RVR*	n=1		
Widening ST segment and tach.	n=1		
Unusual shortness of breath	n=1		
Ventricular ectopy		n=1	
Left BBB		n=1	
Right BBB*		n=2	
HTN response		n=1	
(SBP > 250 mmHg or DBP > 115 mmHg)			
Type II heart block		n=1	
Chest pain*		n=1	
Fall Risk AE	n=0	n=7	0.002
Unable to keep pace with treadmill		n=6	
Became agitated during test		n=1	

*One individual reported chest pain during the CPET and concomittant right BBB. This is reported as a separate sign and symptom for this table but counted as a single early termination for analysis purposes. Abbreviations: RVR= rapid ventricular rate, BBB = bundle branch block, HTN = hypertension, SBP = systolic blood pressure, DBP = diastolic blood pressure, CDR = Clinical Dementia Rating, tach. = tachycardia