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Chronotropic response and cognitive function in a cohort at risk for Alzheimer's disease

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Abstract

The objective of this study was to examine the association of chronotropic response (CR) and heart rate (HR) recovery—two indices of cardiovascular function within the context of a graded exercise test—with cognitive performance in a cognitively healthy, late-middle-aged cohort at risk for Alzheimer's disease (AD). Ninety participants (age=63.52±5.86 years; 65.6% female) from the Wisconsin Registry for Alzheimer's Prevention participated in this study. They underwent graded exercise testing and a comprehensive neuropsychological assessment that assessed the following four cognitive domains: Immediate Memory, Verbal & Learning Memory, Working Memory, and Speed & Flexibility. Regression analyses, adjusted for age, sex, and education, were used to examine the association between CR, HR recovery, and cognition. We found significant

associations between CR and cognitive performance in the domains of Immediate Memory, Verbal Learning & Memory, and Speed & Flexibility. In contrast, HR recovery was not significantly associated with cognitive function. The association between CR and cognition persisted even after controlling for HR recovery. Together, these findings indicate that, in a cognitively normal, late-middle-aged cohort, CR is a stronger correlate of cognitive performance than HR recovery. Overall, this study reinforces the idea that cardiovascular health plays an important role in cognitive function, specifically in a cohort at risk for AD; and that interventions that promote vascular health may be a viable pathway to preventing or slowing cognitive decline due to AD.

Keywords

Alzheimer disease; cognition; heart rate; cardiovascular health; cardiopulmonary exercise test

INTRODUCTION

Alzheimer's disease (AD) has become an increasingly critical public health concern, projected to affect 13.8 million Americans by 2050 (a tripling of current prevalence rate of 5.3 million) barring the development of curative or preventative therapeutics [1]. It has been hypothesized that the disease may have a vascular etiology [2]. More specifically, AD has been shown to share pathology with the global leading cause of death—cardiovascular disease (CVD) [3]. This may be a function of diminished perfusion, as decreased cerebral blood flow [4] and lower cardiac output [5, 6] have been associated with cognitive dysfunction and AD. Indeed, cerebral hypoperfusion has been linked to the development of white matter hyperintensities (WMHs) [7], a core feature of AD pathology [8]. Furthermore, cardiovascular risk factors, including hypertension [9], hypercholesterolemia [10], and atherosclerosis [11], are associated with worsened cognitive functioning and have been linked to risk of progression to AD. These connections between AD and vascular function merit additional investigation to further develop understanding of the vascular etiology of AD.

Previous studies of vascular function and AD have utilized measures such as cardiac output [5], aortic pulse wave velocity [12], and endothelial function [12, 13] to evaluate vascular health. However, two more easily obtained measures commonly used to assess cardiovascular functioning within the context of cardiopulmonary exercise testing are chronotropic response (CR) and heart rate (HR) recovery [14–16]. CR refers to the ability of the heart to raise its rate appropriately with increased demand and is largely under the control of the sympathetic nervous system [14]. An inadequate CR can negatively impact quality of life and lead to increased risk of severe cardiovascular outcomes, including coronary heart disease [15], cardiac death [17], and all-cause mortality [15, 17]. HR recovery refers to the change in HR following exercise or increased activity and is primarily controlled by the parasympathetic nervous system [18]. Insufficient HR recovery has also been associated with an increased risk of cardiovascular mortality [16] and all-cause mortality [18].

Although these measures have been studied previously, the vast majority of those reports have been conducted in relation to severe adverse outcomes such as mortality [15–18]. Investigations of the association between CR, HR recovery, and more intermediate outcomes, such as cognitive function, are limited. To date, only one study has assessed the relationship between HR recovery and cognition [19]. However, participants in that study were older adults with CVD. Therefore, it remains unknown (i) whether CR and HR recovery influence cognitive performance in the absence of manifest CVD and (ii) whether one measure is more sensitive to cognition than the other. Accordingly, the objective of this study was to investigate the univariate and differential influences of CR and HR recovery on cognitive function in an overall healthy late-middle-aged sample at risk for AD.

MATERIALS AND METHODS

Participants

This study consisted of 90 participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP). WRAP is a longitudinal cohort of approximately 1500 cognitively healthy, late-middle-aged adults between the ages of 40 and 65 at study entry [20]. Participants for the present analyses were selected based on completion of a graded exercise test (GXT) and comprehensive neuropsychological assessment. None of them were prescribed beta-blockers at the time they completed their GXT. Similar to the larger WRAP cohort, the sample was enriched with persons with a parental family history of AD (68.9%) and individuals carrying 1 apolipoprotein E ϵ 4 (APOE4) allele (42.2%). Table 1 displays the participants' relevant background characteristics. All study procedures were approved by the University of Wisconsin Institutional Review Board and each subject provided informed consent prior to participation.

Graded Exercise Testing

GXT was performed using a modified Balke protocol [21]. Comfortable brisk walking speeds were determined prior to testing as a safety precaution and to ensure a valid test. For participants who were capable of walking at 3.5 miles per hour comfortably, this speed was used throughout the test. For participants who found this walking speed uncomfortable, a slower speed was chosen. The grade of the treadmill was increased by 2.5% every two minutes until the participant reached volitional exhaustion. Oxygen uptake (VO_2), carbon dioxide production, minute ventilation, HR, and work rate were measured continuously using a metabolic cart and two-way non-rebreathing valve (TrueOne® 2400, Parvomedics, Sandy, UT). The system was calibrated 4 hours prior to each test using standard gases with known concentrations and with a calibrated three-liter syringe. In addition to continuous measurement of HR during exercise, we also measured HR at rest (in supine position) and over the course of a 3-minute cool-down at the end of the exercise test, with the treadmill set at a leisurely walking speed and 0% grade.

Chronotropic Response

CR was evaluated using two different methods: (1) percentage of age-predicted maximum HR (% APMHR) achieved and (2) percentage of HR reserve achieved. APMHR was calculated using the traditional formula defined for healthy populations, i.e. $(220 - \text{age})$ [22].

Thus, % APMHR was calculated using the following equation: $[\text{peak HR}/(220 - \text{age})] \times 100$, where peak HR was defined as the maximum HR achieved during the GXT [17, 23].

HR reserve is the difference between APMHR and resting HR [24, 25]. Thus, % HR reserve was calculated as follows: $((\text{peak HR} - \text{resting HR})/((220 - \text{age}) - \text{resting HR})) \times 100$ [17, 23, 24].

Results from the analyses completed using either measure of CR were largely identical. Therefore, we only present results using % HR reserve, hereafter referred to as CR, because this measure takes into account resting HR while % APMHR does not.

Heart Rate Recovery

HR recovery was defined as the difference between the peak HR achieved during GXT and the HR at 60 seconds after test termination [18].

Neuropsychological Assessment

Each participant completed a comprehensive neuropsychological battery [20] that included psychometric measures spanning conventional cognitive domains of memory, attention, executive function, language, and visuospatial ability. Previous factor analytic studies [26, 27] of these tests within the larger WRAP cohort found that they map onto six cognitive factors, i.e., Immediate Memory, Verbal Learning & Memory, Working Memory, Speed & Flexibility, Visuospatial Ability, and Verbal Ability. For this study, we only focused on the factors related to episodic memory and executive function due to the previously established association between these domains, aerobic fitness, and cardiovascular parameters [6, 28, 29]. Constituent tests for the selected factors are as follows: Immediate Memory: Rey Auditory Verbal Learning Test (RAVLT) learning trials 1 and 2 [30]; Verbal Learning & Memory: RAVLT learning trials 3, 4, 5, and Delayed Recall [30]; Working Memory: Digit Span and Letter-Number Sequencing subtests of the Wechsler Adult Intelligence Scale, 3rd edition [31]; and Speed & Flexibility: Stroop Color-Word Test Interference Trial [32] and Trail-Making Test A & B [33]. Scores were standardized into z-scores ($\sim N(0,1)$) using means and standard deviations from the entire baseline WRAP sample. The time interval between neuropsychological assessment and GXT was 0.88 ± 0.58 years.

Statistical Analyses

To address the primary aim of this study, i.e. an examination of the association between CR, HR recovery, and cognition, we fitted a series of covariate-adjusted linear regression models—one for each cognitive domain—that were controlled for age, sex, and education. In the first set of these covariate-adjusted models, CR and HR recovery were each examined in isolation with respect to their association with cognition. Then, to evaluate the relative (and unique) influence of CR vis-à-vis HR recovery on cognition, we fitted a model that contained both the CR and HR recovery variables.

All analyses were conducted using IBM SPSS, version 22.0. Only findings with $p < .05$ (2-tailed) were considered to be significant.

RESULTS

Participant Characteristics

Table 1 details the relevant background characteristics of the participants. The average age of the sample was 63.52 ± 5.86 years and women constituted the majority of the sample (65.6%). 68.9% of the sample had a parental family history of AD and 42.2% were APOE4 positive. The sample was well educated, with an average of 16.52 ± 2.32 years of education. 4.4% of participants failed to meet 80% HR reserve [14] and 11.1% exhibited abnormal HR recovery (i.e., <13 beats per minute) [18]. The average body mass index (BMI) of the sample was 27.67 ± 5.19 kilograms/meters². Other relevant vascular risk factors are reported in Table 1.

Individuals with improved CR were more fit (i.e., had greater VO₂ peak) ($r=.358$, $p=.001$). Those with higher HR recovery were also more fit ($r=.353$, $p=.001$) and had lower resting HR ($r=-.292$, $p=.005$) and lower BMI ($r=-.346$, $p=.001$). However, there was no significant correlation between CR and HR recovery ($r=.019$, $p=.858$). In addition, neither HR measure was associated with age or gender.

Univariate Associations between CR, HR Recovery, and Cognition

There were significant positive associations between CR and cognition for the domains of Immediate Memory ($p=.044$), Verbal Learning & Memory ($p=.044$), and Speed & Flexibility ($p=.036$) (Table 2, Figure 1). In contrast, no significant relationship was found between HR recovery and cognition (Table 2).

To ensure the results were not confounded by BMI, the analyses were repeated while additionally controlling for BMI. The association between CR and cognition remained significant for the domains of Immediate Memory (β (SE)=.02 (.01), $p=.035$); Verbal Learning & Memory (β (SE)=.02 (.01), $p=.021$); and Speed & Flexibility (β (SE)=.01 (.01), $p=.031$). Similarly, the results for HR recovery remained unchanged (i.e. no significant relationships).

In addition, the analyses were repeated while controlling for VO₂ peak to verify the results were not confounded by exercise capacity. Again, there were significant positive relationships between CR and cognition for the domains of Immediate Memory (β (SE)=.02 (.01), $p=.049$) and Verbal Learning & Memory (β (SE)=.02 (.01), $p=.046$). However, the significant relationship between CR and Speed & Flexibility was lost (β (SE)=.01 (.01), $p=.122$). The associations for HR recovery remained nonsignificant.

Relative Influence of CR vs. HR Recovery on Cognition

When both CR and HR recovery were included in a single model, significant positive associations were detected between CR and Immediate Memory ($p=.045$), Verbal Learning & Memory ($p=.045$), and Speed & Flexibility ($p=.035$) (Table 3). Again, HR recovery did not exhibit any significant association with cognition. The close similarity between these sets of findings and the findings from the univariate analyses suggest that the influences of

CR and HR recovery on cognition are largely independent, with CR exerting a relatively stronger effect.

Supplementary Analyses

In order to further investigate the null findings for HR recovery, we conducted additional analyses specifically to uncover potential effect modifiers. Previous studies have found age and BMI to be closely related to HR recovery, such that abnormal HR recovery is more common in older age [16, 18, 34] and at higher BMI [35–37]. In addition, poorer cognition is also associated with older age [38] and increased BMI [39, 40].

We examined the possibility that the relationship between HR recovery and cognition varied as a function of age and BMI, re-fitting our original models to include—in two separate runs—interaction terms between (a) age and HR recovery and (b) BMI and HR recovery. We did not observe any significant age*HR recovery effects, indicating that age did not moderate the relationship between HR recovery and cognition. In contrast, we found significant BMI*HR recovery interactions for Immediate Memory (β (SE)=.01 (.01), $p=.001$) and Verbal Learning & Memory (β (SE)=.01 (.01), $p=.003$). Simple main effects analyses revealed that increased HR recovery was strongly associated with better scores on Immediate Memory ($p=.013$) and Verbal Learning & Memory ($p=.014$) among those with high BMI (i.e., 1 SD above the mean) but not as strongly among those with low BMI, i.e., –1 SD (p 's=.046 and .122, respectively). This suggests that a favorable HR recovery is more beneficial for cognition in the context of higher body composition, as compared to when body composition is healthy.

DISCUSSION

This study found that in a cognitively-normal late-middle-aged cohort at risk of AD, CR (indexed by % HR reserve) was significantly related to cognitive function, particularly in the domains of Immediate Memory, Verbal Learning & Memory, and Speed & Flexibility. In contrast, HR recovery was not associated with cognitive function. CR continued to exhibit a strong relationship with cognitive function even when controlling for HR recovery.

Because CR is a measure of the heart's ability to adequately respond to increased activity, it is closely tied with cardiac output [14]. An appropriate CR is necessary to produce sufficient cardiac output to meet the body's metabolic demands [14]. Thus, our finding of a strong association between CR and cognition is deemed to be in line with previous studies that found cardiac output to be associated with improved cognitive performance, such that decreased cardiac output is related to a decreased cognitive flexibility [41], reduced executive function performance [5], and a faster rate of cognitive decline [6].

One possible mechanism for this association between CR and cognition is through alterations in brain structure and function. Inadequate CR often occurs in individuals with CVD and heart failure (HF) [14]. Previous studies have shown these conditions to be associated with important structural brain changes, such as brain atrophy and white matter microstructural changes [42, 43], which may be related to cognitive dysfunction [44–46]. In their study, Vogels et al. [43] found participants with HF to have significantly more total

WMHs and more atrophy in the medial temporal lobe than healthy controls. Similarly, in their review, Alosco & Hayes [42] found HF patients exhibited more adverse changes in white matter microstructure and neural atrophy in key AD-related areas. In addition to structural brain changes, alterations in brain function may occur as a result of HF. Park et al. [47] found altered functional connectivity in the brains of HF patients, possibly resulting in brain dysfunction. Taken together, these studies indicate the close relationship between cardiac dysfunction and adverse structural and functional brain changes. These brain alterations have been implicated in poor cognitive function [44–46] and AD development [8, 48, 49]. Thus, it is possible that CR, a measure of vascular health, may influence cognition via adverse brain alterations. Additional study is required to explicitly test this hypothesis.

Prior studies of HR recovery have primarily focused on its association with severe outcomes, such as cardiovascular or all-cause mortality [16, 18]. Only one previous study has shown HR recovery to be positively associated with cognitive function, such that reduced HR recovery was correlated with poorer cognitive performance [19]. However, that study focused on older adults with CVD while our sample was overall healthy with no serious cardiovascular problems, possibly attenuating our HR recovery effects. Furthermore, the relationship between HR recovery and cognition may be more nuanced than a simple direct association. As our supplementary analyses revealed, the relationship between HR recovery and cognition for the domains of Immediate Memory and Verbal Learning & Memory is dependent on BMI. Further study of HR recovery, possible moderators, and cognition in both healthy and diseased populations is needed to better characterize this association.

Regarding the relative utility of CR versus HR recovery in predicting cognitive function, this study found CR to be significantly associated with cognition while HR recovery was not. Few previous studies have investigated both CR and HR recovery in the same model and their findings are conflicting. A study by Myers et al. [16] investigated the relative utility of CR (measured as % HR reserve) versus 2-minute HR recovery in predicting cardiovascular mortality. Similar to our study, they found CR to be a more powerful predictor than HR recovery, though both measures independently predicted cardiovascular mortality. Jouven et al. [50] conducted a similar study investigating the association between HR profiles and sudden death. Although they excluded participants with abnormal CR, the researchers used a measure of HR increase during exercise, which is comparable to CR, as well as resting HR and HR recovery, to predict risk of sudden death by myocardial infarction (MI). They found that an attenuated increase in HR (failure to increase HR at least 89 beats per minute during exercise) was the most powerful predictor of sudden death from MI. Although resting HR and HR recovery were also found to be independent risk factors for sudden death from MI, only CR continued to be a significant predictor when all measures were included in a single model. In contrast with these reports, other studies have found HR recovery to be a stronger risk factor for adverse outcomes [18, 34]. Taken together with our findings, it appears that CR and HR recovery are largely independent, capturing different aspects of the broad sphere of vascular health.

Even so, it is not entirely clear why CR appears to be a stronger correlate of cognitive function than HR recovery within our cohort. The two measures are largely under the control of two complementary systems: the sympathetic and parasympathetic nervous systems. In

general, HR recovery is regulated by activation of the parasympathetic system while CR is controlled by activation of the sympathetic nervous system and withdrawal of the parasympathetic [14]. These differences in underlying control mechanisms may be the reason for the contrasting results we obtained wherein CR is more consistently and strongly associated with cognition than HR recovery. Further study of these variables and their relation with cognition and other intermediate outcomes is warranted.

Our study is not without limitations, with the principal one being its cross-sectional design. Consequently, our ability to establish a causal relationship between CR and cognitive performance is restricted. A similar study within the context of a prospective design would be beneficial for further verifying the findings from our study. In addition, our sample was relatively homogenous in regards to race and education. Specifically, the majority of participants were non-Hispanic whites and well-educated, limiting the generalizability of our results to the larger United States population. Lastly, the effects we found are modest, supporting the notion that cognition is influenced by a variety of factors, with CR only accounting for a portion of this variability.

In conclusion, this study found CR to be positively associated with cognitive function, such that those with increased CR had better cognitive performance. In addition, we found CR to be more strongly associated with cognition than HR recovery. Importantly, these inter-individual differences in cognition as a function of vascular health were detected in a cognitively healthy sample, indicating these subtle changes in cognitive function may be discernable long before diagnosis of AD. In clinical settings, this suggests that protecting vascular health early may be a viable pathway to preventing or slowing cognitive decline due to AD. However, given the novelty of our study design (i.e., we tested both CR and HR recovery in a healthy, late-middle-aged, at-risk cohort), additional studies are needed to further validate our findings.

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Figure 1. Association between chronotropic response and cognitive performance

These graphs show the positive relationships between % HR reserve, a measure of chronotropic response, and cognition in the domains of (A) Immediate Memory, (B) Verbal Learning & Memory, and (C) Speed & Flexibility. The points on the scatterplot were residualized for age, sex, and education.

HR=heart rate; a.u.=arbitrary units

Table 1**Participant Characteristics (N=90)**

Characteristic	Value[*]
Demographics	
Age, years	63.52 (5.86)
Female, %	65.6
Education, years	16.52 (2.32)
Family history positive, %	68.9
APOE4 positive, %	42.2
Cognitive and HR Measures	
MMSE	29.36 (1.05)
% APMHR	101.07 (7.49)
% HR reserve	102.84 (12.50)
HR recovery, bpm	21.13 (6.74)
Resting HR, bpm	60.97 (10.26)
Abnormal % HR reserve, %	4.4
Abnormal HR recovery, %	11.1
Vascular Risk Indices	
Body mass index, kg/m ²	27.67 (5.19)
Total cholesterol, mg/dL	202.08 (40.55)
HDL cholesterol, mg/dL	65.67 (18.67)
Systolic blood pressure, mmHg	125.98 (18.12)
Diastolic blood pressure, mmHg	75.41 (9.73)
Hypertension, %	22.2
Diabetes, %	2.2
Smoker (ever), %	40.0

* Values indicate mean and standard deviation, unless otherwise indicated.

APOE4=ε4 allele of apolipoprotein E gene; MMSE=Mini-Mental State Examination; APMHR=age-predicted maximum heart rate; HR=heart rate; bpm=beats per minute; Abnormal % HR reserve = less than 80% HR reserve; Abnormal HR recovery = less than 13 beats per minute

Table 2

Univariate Influence of Chronotropic Response and HR Recovery on Cognition

Domain	Chronotropic Response				HR Recovery			
	β (SE)	F	p	R ²	β (SE)	F	p	R ²
Immediate Memory	.02 (.01)	4.186	.044	.047	-.01 (.02)	.022	.882	.001
Verbal Learning & Memory	.02 (.01)	4.190	.044	.047	-.01 (.01)	.072	.789	.001
Working Memory	.01 (.01)	.033	.855	.001	-.02 (.02)	.994	.322	.011
Speed & Flexibility	.01 (.01)	4.545	.036	.050	.02 (.01)	2.002	.161	.017

HR=heart rate; β =regression estimate; SE=standard error
Covariates included in the statistical models were age, sex, and education.

Table 3

Relative Influence of Chronotropic Response and HR Recovery on Cognition

Domain	Chronotropic Response				HR Recovery			
	β (SE)	F	p	R ²	β (SE)	F	p	R ²
Immediate Memory	.02 (.01)	7.469	.045	.058	-.01 (.02)	.104	.880	.001
Verbal Learning & Memory	.02 (.01)	3.799	.045	.027	-.01 (.01)	.329	.785	.002
Working Memory	.01 (.01)	.235	.855	.002	-.02 (.02)	.073	.324	.001
Speed & Flexibility	.01 (.01)	8.726	.035	.057	.02 (.01)	3.400	.153	.022

HR=heart rate; β =regression estimate; SE=standard error

Terms included in the statistical model were % HR Reserve, HR Recovery, age, sex, and education.