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Resting-State Cardiac Workload in Preclinical Alzheimer's Disease

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RESTING-STATE CARDIAC WORKLOAD IN PRECLINICAL ALZHEIMER'S DISEASE

BY

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ABSTRACT

The objective of this thesis was to determine the association among a cardiac workload marker (the rate pressure product [RPP]), working memory, and cortical amyloid-β (Aβ) burden in 63 cognitively normal midlife adults (average age = 62.8 years-old) at risk for Alzheimer's disease (AD).

All subjects were recruited on the basis of reporting a first-degree family history of AD as well as significant subjective memory complains. Each subjects underwent ^{18}F-florbetapir PET imaging to measure neocortical Aβ aggregation. The PET standardized uptake values (SUV) of neocortical Aβ were summed and normalized to the whole cerebellum SUV, resulting in a region-to-cerebellum ratio (SUVr). Blood pressure and heart rate data were collected during an initial baseline visit with subjects at rest. All assessments occurred between 0800 and 0900. After the collection of these measures, all subjects completed the Groton Maze Learning Test (GMLT; www.cogstate.com). The GMLT is an iPad-administered hidden maze learning test that differentially measures both spatial working memory and reasoning/problem solving cognitive functions.

The results show a moderate positive correlation between cardiac workload (at rest) and cognitive impairment as measured by the GMLT; however, this result only holds for the 15 subjects with evidence of substantial neocortical amyloid aggregation (SUVr PET scan) (R^2 = 0.30; p = .034). By comparison, no such relationship was observed for the 48 subjects without any evidence of cortical Aβ plaque burden (R^2 = .02). With all 63 subjects considered together, there is a small-to-moderate

relationship between neocortical Aβ burden and RPP ($r = 0.261$, $\rho = .039$), with increasing cardiac workload at rest associated with greater neocortical amyloidosis. This relationship remained significant after statistical control for body mass index ($r = 0.262$, $\rho = .040$) and age ($r = .258$, $\rho = .043$).

These results show a small-to-moderate relationship between increasing myocardial oxygen use (at rest) and neocortical amyloidosis in individuals at the preclinical stage of AD.

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PREFACE

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TABLE OF CONTENTS

LIST OF TABLES

TABLE PAGE

LIST OF FIGURES

FIGURE PAGE

"Resting-State Cardiac Workload is Related to Both Increased Neocortical Aggregation of Amyloid-β and Relative Impairments in Spatial Working Memory in Pre-Clinical Alzheimer's Disease."

by

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CHAPTER 1

INTRODUCTION

Alzheimer's disease (AD) was first diagnosed more than 110 years ago and a disease modifying treatment has yet to be discovered (van Norden et al., 2012). The reason for the lack of treatment may be because the clinical symptoms, such as dementia, are the result of massive brain damage that is most likely irreversible by the time a patient presents with moderate-to-severe disease (Gottfries,1984; Filley 1995). Given the difficulties of treating AD once it has been clinically diagnosed, we have focused our research on the preclinical stage of AD. The preclinical stage of AD is believed to have its onset up to several decades prior to clinical diagnosis (Sperling et al., 2011), and it is now the stage of the disease targeted by several large secondary prevention trials (Sperling et al., 2014; Tarriot, 2016).

However, identification of the preclinical stage is problematic: behavioral presentations of cognitive impairments and functional status are heterogeneous across individuals. In addition, many individuals at the pre-clinical stage of AD are healthy older adults and routine neurologic and/or neuropsychological exams are typically unremarkable. Hence, any efforts to improve our ability to identify 'at-risk' individuals in the preclinical stage of AD, such as detecting subtle alterations in concomitant cardiovascular function, would be valuable.

Recent reports call into question the strength of the association between AD, cardiovascular and cerebrovascular diseases, despite the common knowledge that

these diseases affect the same at-risk population and share many of the same risk factors (Skoog et al., 1999; Martins et al., 2006; Profenno et al., 2009). Unfortunately, very little is known about the mechanism linking vascular changes with AD and even less is known about how early in the course of AD vascular changes can be detected.

Hence, to explore whether there is any evidence of cardiovascular change that may be related to preclinical AD we chose to obtain measurements for a well-known cardiac workload marker [rate pressure product (RPP)] at rest, and during a challenging cognitive task, in subjects with different levels of cortical Aβ. RPP has been previously shown to be associated with relative impairments in older adults, compared to a younger comparison group, in response to the presentation of a challenging cognitive task (Matthewson et al., 2011), providing evidence that healthy older adults demonstrate increased cardiac oxygen demands during their response to a mildly stressful cognitive task. In our study, we predicted that RPP would be increased for preclinical AD in comparison to healthy older adults, and that increased RPP would correlate with (impaired) performance on a spatial working memory test.

CHAPTER 2

REVIEW OF LITERATURE

AD and CVD share important cardiometabolic and lifestyle risk factors that occur in middle-aged to elderly populations. Both AD and CVD are associated with increasing age, and both are among the leading causes of death in elderly populations. The primary causes of CVD are coronary heart disease (CHD), hypertension, stroke, and heart failure. These diseases are frequently interconnected and share an underlying pathology of atherosclerosis. All known risk factors for atherosclerosis have been the focus of studies to identify modifiable risk factors for AD. Researchers from the Framingham Heart Study (Dawber et al., 1951; Harrison et al., 2014) developed a composite measure of general cardiovascular risk, the Framingham Cardiovascular Risk Profile (FCRP), derived by evaluating a patient's age, gender, diabetes status, smoking behavior, treated and untreated systolic blood pressure (SBP), total cholesterol, and high density lipoprotein (HDL) cholesterol (Kanne et al., 1956).

Other scores developed from the Framingham Heart Study, the Framingham Stroke Risk Profile and the Framingham Coronary Heart Disease Risk Score, have been similarly associated with cognitive change over time, incident cognitive impairment, and dementia (Harrison et al., 2014;Viticchi et al., 2015; Laughlin et al., 2011; Dreagan et al., 2013; Kaffashian et al., 2011; Kaffashian et al., 2013; Unverzagt et al., 2006). These risk scores are similar to one developed specifically to assess dementia risk, i.e. the Cardiovascular Risk Factors Aging and Dementia (CAIDE) risk

score (Kivipelto et al., 2006; Virta et al., 2013; Exalto et al., 2013). Obesity, dyslipidemia, high blood pressure and metabolic syndromes are precursors to, or develop along with, atherosclerosis, diabetes, CVD, and an increased risk for AD (Martins et al., 2006).

In the Honolulu-Asia Aging Study (HAAS), results suggest that midlife elevated diastolic blood pressure may impair Aβ clearance, which can eventually lead to AD and cerebral amyloid angiopathy (Shah et al., 2012). It was also observed that raised systolic blood pressure increased the risk of AD in later life (Kivipelto et al., 2001; Atkinson et al., 2009).

Besides the complex relationship between AD and CVD, it has been shown that, in healthy older adults who are free of diagnosable cardiovascular diseases or dementia, a simple outpatient measure of cardiac workload, the rate pressure product (RPP), is associated with relative impairments in performance on a spatial working memory tests; this relationship is not observed in younger subjects (Matthewson et al., 2011). RPP (systolic blood pressure × heart rate/100) represents the maximum pressure in a structurally normal left ventricle when it is ejecting blood based on the number of beats per minute, providing an indirect assessment of myocardial oxygen consumption (Gobel et al., 1978). During the performance of challenging cognitive and/or physical tasks, such as exercise, psychological stress and every-day physical activity, RPP will increase to meet required metabolic demands (Fredericks et al., 2005; Atkinson et al., 2009). If RPP is high in the resting state, we may assume that myocardial oxygen use is already elevated in the absence of significant metabolic demands.

Although the relationship between increased cardiac workload and/or increased cardiac risk, and cognitive decline in older adults has been reasonably well-established (Jefferson et al., 2014; Jefferson et al., 2015), it is unclear just how strong the relationship is between cardiac function and biomarkers of prodromal disease in individuals without cardiovascular disease at high risk for preclinical AD. Given this gap in the literature, we sought to determine whether there was any association between cardiac workload, working memory and cortical Aβ burden in 63 cognitively normal older adults. We predicted that increased RPP at rest would be inversely related to performance on the spatial working memory test, but only for individuals with neuroimaging evidence of amyloid aggregation consistent with prodromal AD.

CHAPTER 3

METHODOLOGY

Subjects: Participants were recruited by serial referrals from two memory disorder centers in Rhode Island and from broad print advertising to the community. All subjects were cognitively normal midlife adults (N=63, M_{age}= 62.8; range = 55 to 75 years-old), with first-degree family histories of AD and with complaints of significant subjective memory impairment (SMI). All subjects presented with normal neurological exams, had MMSE scores > 27, no current Axis I or II psychopathology, no reported significant cardiovascular disease and no current alcohol or substance abuse. All subjects also performed well within normal limits on episodic memory testing, including a word-list learning test and computer-administered measures of working memory, concentration and attention (Lim et al., 2015). None of the subjects met NIA-AA diagnostic criteria for mild cognitive impairment (Albert et al., 2011). Although all subjects denied cardiologic conditions or diagnoses, we could not exclude the possibility of asymptomatic cardiologic conditions or the presence of occult cerebrovascular disease in some individuals.

Subjects were separated into two groups based on PET amyloid imaging results with 15 subjects having Florbetapir uptake SUVr scores $\geq$ 1.10, and 48 subjects having SUVr scores < 1.10. Additionally, all 15 subjects with evidence of significant neocortical amyloid aggregation failed a micro-dose scopolamine “cognitive stress

test" (Lim et al., 2015; Snyder et al., 2014) suggesting the presence of prodromal cholinergic tone disruption and supporting the prediction of preclinical AD.

With respect to genetic risk for AD, eight of the 15 individuals (53%) in the amyloid positive group (SUVr scores $\geq$ 1.10) had at least one copy of the APOE ε4 allele, whereas 20 of 45 individuals (45%) in the amyloid negative group (SUVr scores < 1.10) had at least one copy of the APOE ε4 allele. Roughly half of the subjects in each group presented with this additional risk factor for AD, but due to small sample sizes we were not able to further evaluate the specific effect of APOE genetic risk on the relationship between RPP and cognitive performance. Subject demographics are provided in Table 1.

Table 1. Demographic Characteristics

	Main Outcome	Full sample (n = 63)	Aβ+ (n = 15)	Aβ- (n = 48)		
		N (%)	N (%)	N (%)	*p*	*Cohen's d*
Sex	No. of female	39 (61.9%)	11 (73.3%)	28 (58.3%)	.296	-
Age	No. of years	62.79 (5.35)	63.93 (6.31)	62.44 (5.04)	.349	0.28
Education	No. of years	17.21 (2.77)	17.47 (3.46)	17.14 (2.55)	.689	0.12
Florbetapir PET SUVr	Standardized Uptake Value ratio	**1.04 (0.19)**	**1.30 (0.20)**	**0.95 (0.08)**	**.000**	**2.95**
GDS	Total Score	1.86 (2.16)	1.60 (1.45)	1.94 (2.35)	.602	-0.16
DASS Depression Subscale	Total Depression Subscale Score	3.56 (6.70)	2.60 (2.59)	3.87 (7.56)	.526	-0.19
DASS Anxiety Subscale	Total Anxiety Subscale Score	2.73 (4.53)	2.40 (3.58)	2.83 (4.83)	.752	-0.09
DASS Stress Subscale	Total Stress Subscale Score	6.73 (6.77)	6.67 (4.55)	6.74 (7.38)	.969	-0.01
Body Mass Index	Body Mass Index	26.69 (5.50)	28.66 (7.95)	26.07 (4.41)	.113	0.48
MMSE	Total Score	29.05 (1.02)	28.93 (1.16)	29.08 (0.99)	.624	-0.15
ISLT Total Recall	Total words recalled	25.59 (4.22)	24.73 (4.46)	25.85 (4.16)	.374	-0.26

*Note: SUVr = standardized uptake value ratio; GDS = Geriatric Depression Scale; DASS Depression, Anxiety, and Stress Scale; MMSE = Mini Mental State Examination; ISLT = International Shopping List Test; bolded value is significant at the $p<.001$ level.

Neuroimaging: A 370MBq (10 mCi +/- 10%) bolus injection of F-florbetapir was administered intravenously [21]. Approximately 50 minutes post-injection, a 20-minute PET scan was performed with head CT scan for attenuation correction purposes. Because this is a study of relatively healthy midlife adults for whom only a minority of subjects present in the preclinical stage of AD, we had no reason to suspect generalized neocortical amyloid deposition and instead focused our attention on the anterior cingulate region-of-interest (ROI) (Lim et al., 2015). The PET standardized uptake value (SUV) for the anterior cingulate (ACC) region was summed and normalized to the whole cerebellum SUV, resulting in an ACC-to-cerebellum ratio termed SUV ratio (SUVr). An ACC SUVr threshold of ≥1.1 was used to discriminate between Aβ- and Aβ+; both the rationale for selection of this specific ROI, and these methods, are described by Lim et al (2015) (Lim et al., 2015). For all cases, Aβ positivity was confirmed by consensus over-read by two board-certified radiologists who were also board-certified in Nuclear Medicine.

Cardiac Measures and Cognitive Assessment: Blood pressure and heart rate data were collected while subjects were at rest, with all assessments occurring between 0800 and 0900. Subsequent to the collection of these measures, all subjects completed the Groton Maze Learning Test (GMLT; www.cogstate.com). The GMLT is a computer-administered hidden maze test that differentially measures both spatial working memory and reasoning/problem solving cognitive functions (Thomas et al., 2014). For the purpose of this study, the total errors score was relied on as the principal measure of spatial working memory. In addition, the number of rule-break

errors was obtained as an additional measure of executive functioning (Papp et al., 2011). Rule-break errors are made when subjects fail to adhere to any of three very simple rules (e.g., not to move diagonally) that, when followed, facilitate performance on the test. Finally, we chose to also look at the timed chase test of the GMLT (Snyder et al., 2005; Thomas et al., 2008), as a measure of simple visuomotor speed. The GMLT, and these three component scores, has been described previously both in terms of performance within the context of studies with healthy elderly adults (Snyder et al., 2005; Thomas et al., 2008; Pietrzak et al., 2007; Chen et al., 2010), as well as in mild cognitive impairment (MCI) (Papp et al., 2011). All subjects completed an initial practice run of the GMLT to allow for initial task familiarity; after a 10 minute break all subjects repeated the GMLT as a baseline assessment.

CHAPTER 4

FINDINGS

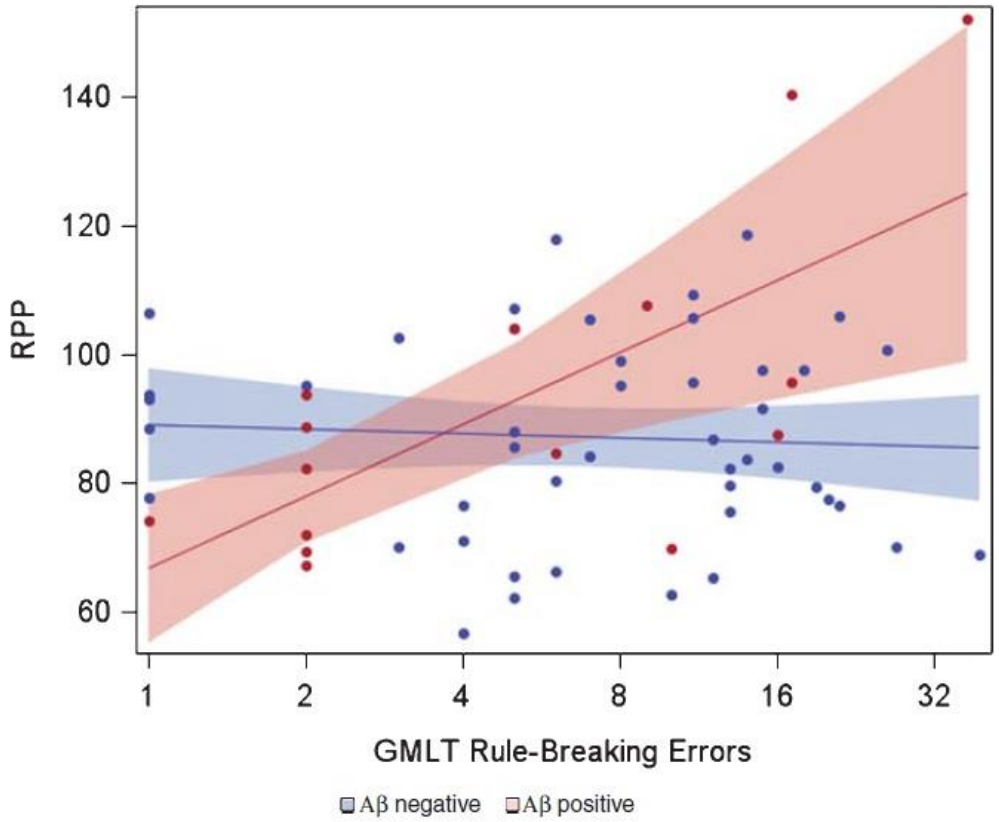
A moderate relationship was found between increasing cardiac workload (at rest) and increasing impairments on the GMLT measure of spatial working memory (total errors score) for the 15 subjects with evidence of substantial neocortical amyloid aggregation (Florbetapir PET imaging); however, after adjustment for multiple comparisons, the effect was not statistically significant (p=0.0429, adj p=0.0858). This association was nonetheless significantly different than that observed for the other 48 subjects (interaction p=0.0307), in whom no association was evident (p=0.3974, adj. p=0.3974). This relationship remained significant after statistical control for education (p=0.0354), sex (p=0.4708), body mass index (p=0.3668) and age (p = 0.9425).

The effect of Aβ moderation was more apparent with regards to the relationship between RPP and increasing impairments on the GMLT measure of reasoning/problem-solving (rule-break errors score). Here, RPP increased by approximately 11.2 mmHg*bpm (95%, CI 3.5-18.8 mmHg*bpm; p=0.0014, adj. p=0.0028) for the 15 Aβ positive subjects (see Figure 1). This relationship was significantly stronger than for the 48 subjects (interaction p=0.0017) without any evidence of cortical Aβ plaque burden, in whom no association was evident (p=0.6230, adj. p=0.6230). This relationship remained significant, after statistical control for education (p=0.0256), sex (p=0.9586), body mass index (p=0.3999) and age (p = 0.9727). By comparison, the correlation between systolic blood pressure

alone and the GMLT rule-break errors score for the Aβ positive group was comparatively modest but still significant (Adj. R^2 = 0.21, p <0.05), and there was no such correlation observed for the Aβ negative group (Adj. R^2 = -0.02, NS).

Finally, no significant relationship between RPP and the GMLT measure of simple visuomotor speed (timed chase test) were observed, regardless of Aβ status.

FIGURE 1. Increasing impairment on the Reasoning/Problem-Solving measure of the Groton Maze Learning Test (GMLT). In Healthy Midlife Adults who present with evidence of elevated neocortical Aβ aggregation (PET Florbetapir anterior cingulate SUVr ratio ≥ 1.10; N = 15), the Rate Pressure Product (RPP) increased by approximately 11.2 mmHg*bpm (95%, CI 4.5-17.8 mmHg*bpm; adj. p=0.0028) for every doubling in the total number of rule-break errors over the 5 learning trials. This association was significantly different (interaction p=0.0017) than was seen for individuals without such neuroimaging evidence of preclinical AD (N = 48), in whom no association was evident (adj. p=0.6263).



With all 63 subjects considered together, there is a small-to-moderate relationship between neocortical Aβ burden and RPP ($p = 0.0329$), with increasing cardiac workload at rest associated with greater neocortical amyloidosis. This relationship remained significant, after statistical control for education ($p = 0.2011$), gender ($p = 0.0476$), body mass index ($p = 0.1846$), and age ($p = 0.8548$).

CHAPTER 5

CONCLUSION

This study may be the first to demonstrate that increased cardiac workload, as a surrogate of myocardial oxygen use at rest, has a small to moderate correlation with neocortical amyloidosis in midlife adults with preclinical AD. Approximately one-quarter of the sample (N=15) met neuroimaging criteria for pre-clinical stage of the disease. This relationship is modest, and RPP does not have the potential to serve as a biomarker of cortical Aβ burden in preclinical AD. Rather, we were impressed that a significant relationship even existed given that our study subjects are all relatively young, healthy, living independently and free of any diagnosable cardiological or neurological diseases. Limitations of this current study and report include the small sample sizes (particularly for the amyloid positive group, N = 15) and the cross-sectional design of these planned comparisons.

We have shown previously that, in older adults, elevated resting state RPP is associated with relatively poor cognitive performance on a modified version of the GMLT, but this prior cohort was not specifically screened for possible occult disease (Mathewson et al., 2011). The results presented here corroborate that initial report as we observed a strong linear correlation between RPP and performance on both the spatial working memory and reasoning/problem-solving measures of the GMLT, with increasing cardiac workload at rest associated with greater impairment on the spatial working memory measure of this test, but only for those subjects with PET amyloid

imaging evidence of likely preclinical AD. By comparison, this association was not observed for the GMLT measure of simple visuomotor speed, suggesting that this relationship might only be observed for cognitive measures that require executive functions (including working memory).

Taken together, these results support a relationship between at least one major neuropathologic pathway for the disease (the aggregation of Aβ protein plaques in the neocortex) and less efficient myocardial oxygen use in the absence of significant metabolic demands, which appears related to a relative decrement in cognitive function. We are currently re-evaluating the subject cohort described in this report to determine whether indices of phasic vagal cardiac control, such as their resting sinus arrhythmia (RSA) and heart rate variability (HRV) measures, are also related to cortical amyloidosis in preclinical AD since both cardiac phenomena are directly modulated by muscarinic and nicotinic cholinergic autonomic neurotransmission.

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