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Long-term Caregiving is Associated with Impaired Cardiovagal Baroreflex

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Abstract

Objective—Caregiving stress is associated with increased risk of cardiovascular disease (CVD). Inability to adequately regulate blood pressure is a possible underlying mechanism explaining this risk. We examined the relationship between length of caregiving and cardiovagal baroreflex sensitivity (cBRS) to better understand the link between caregiving and CVD risk.

Methods—A total of 146 elderly individuals (> 55 years) participated in this study, of whom 96 were providing in-home care to a spouse with dementia and 50 were healthy controls married to a non-demented spouse (i.e., non-caregivers). Among the caregivers, 56 were short-term caregivers (caring < 4 years) and 40 were long-term caregivers (caring ≥ 4 years). A multiple linear regression model, with contrast codes comparing short and long-term caregivers with non-caregivers was used to understand relationships between chronic caregiving and cBRS.

Results—After controlling for relevant demographic and health characteristics, mean ± SE log transformed cBRS for non-caregivers was 0.971 ± 0.029 . Relative to non-caregivers, the long-term caregivers had significantly impaired cBRS (0.860 ± 0.033 ; $p = 0.013$). However, mean cBRS for short-term caregivers did not significantly differ from non-caregivers (0.911 ± 0.028 ; $p = 0.144$).

Conclusion—These results suggest that long-term caregiving stress is associated with an impaired cBRS. Accumulation of stress from years of caregiving could result in worse cBRS

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function, which could be a mechanistic explanation for the correlation between caregiving stress and the increased risk of CVD.

Keywords

cardiovascular disease; life stress; baroreceptor reflex; heart disease; Alzheimer's

1. Introduction

Caring for a spouse with dementia is often a burdensome life stressor with well-established links to psychological [1, 2] and physical health morbidity [3, 4]. Increased risk for cardiovascular disease (CVD) is believed to be one of the most likely health consequences resulting from the chronic stresses of caregiving. The link between caregiving stress and increased risk for coronary heart disease (CHD) [5, 6], borderline hypertension [7], and other cardiovascular diseases [8] has been well documented in the literature.

Although the biological pathways from stress to CVD are not fully understood, one important mechanism could involve an impaired baroreflex function. The baroreflex is the negative feedback mechanism that plays a central role in acute as well as chronic regulation of blood pressure by modulating parasympathetic outflow to heart and sympathetic outflow to blood vessels. Increases in blood pressure will stretch mechanoreceptors embedded in the adventitia of the carotid sinuses and aortic arch, which will send action potentials via afferent fibers in the glossopharyngeal and vagus nerve to the nucleus tractus solitarius in the medulla. In turn, baroreflex-mediated reciprocal changes are triggered in efferent vagal and sympathetic activity. Vagal response is quick, which allows beat-to-beat heart rate adjustment [9]. Cardiovascular baroreflex sensitivity (cBRS) was used in this study to assess the parasympathetic (i.e. cardiac) limb of the baroreflex. Because parasympathetic nerve endings are concentrated in atria and AV node, they are particularly important for the regulation of heart rate and rhythm. CVDs are associated with decreased parasympathetic nervous system (PNS) regulation [10]. Notably, patients with recent myocardial infarction tend to have a lower cBRS and higher risk of developing fatal arrhythmias [11]. Even without history of cardiac events, middle aged people with cBRS lower than 3ms/mmHg have nine times greater risk of cardiac death compared to those with cBRS > 3ms/mmHg [12, 13]. Given the studies that caregiving stress is associated with increased cardiovascular risk, a blunted cBRS may help explain higher risk of cardiovascular events in caregivers.

While caregiving is associated with increased psychological stress, the duration of exposure to the stress of caregiving may be associated with ever worsening cBRS. That is, the longer the individual is caregiving, the more blunted the cBRS becomes. Repeated exposure to stress has been shown to both accelerate atherosclerotic processes such as sympathetic reactivity [14, 15], coagulation [16, 17], and platelet activation [15] and induce frequent blood-pressure spikes [18] damaging the elastic fibers of the carotid arch and aortic sinus. These processes may reduce arterial compliance, thereby reducing distensibility of the vessels and reducing the baroreceptors' ability to detect changes in blood pressure [19–21]. Additionally, functional magnetic resonance imaging (fMRI) studies have demonstrated that repeated SNS activation by chronic stress can reduce the sensitivity of supramedullary

(cingulate cortex, insula, amygdala, and midbrain periaqueductal gray) control of the baroreflex [22]. Stress appears to dysregulate neural signals transmitted from these upper level brain structures to brainstem nuclei involved in autonomic cardiovascular control, thus blunting the cBRS. Therefore, it is reasonable to believe that long-term caregiver stress may lead to a blunted cBRS.

The aim of the current analysis was to evaluate the impact of the duration of stress exposure on cBRS function in three groups of elderly individuals: 1) long-term caregivers (≥ 4 years), 2) short-term caregivers (<4 years), and 3) non-caregiver controls. We used 4-years as our cutoff for short vs long-term caregivers for two reasons: a) epidemiologic national sampling reports show that the average length of caregiving is 4.0 years [23], and b) we wished to remain consistent with our previous study examining the relation between length of caregiving and endothelial function in caregivers [24], where longer-term caregiving was associated with worsened endothelial function in this population. Because repeated exposure to stress has previously been shown to accelerate the atherosclerotic process, we hypothesized that long-term dementia caregivers will demonstrate the greatest cBRS blunting relative to short-term caregivers and non-caregivers. Because short-term caregivers have not experienced the extended years of stress accumulation like long-term caregivers, our second hypothesis was that short-term caregivers would show preliminary evidence of blunted cBRS function, compared to non-caregiver controls.

2. Methods

2.1. Study Sample

One hundred forty-six elderly individuals participated in this study. These participants were enrolled between 2007 and 2012 into the University of California, San Diego (UCSD) “Alzheimer’s Caregiver Study”. The study protocol was approved by the UCSD Institutional Review Board (IRB). Participants were recruited through referrals, the UCSD Alzheimer’s Disease Research Center, support groups, senior care centers, and health fairs. Of these participants, 96 were providing care to a spouse with Alzheimer Disease (AD), and 50 were married to a non-demented, healthy spouse (i.e., non-caregivers). Among the caregiver sample, 56 had been providing care for fewer than 4 years (i.e., short-term caregivers), and 40 had been caring for ≥ 4 years (i.e., long-term caregivers). All participants provided formal written consent to participate in this study.

To be included in the study, caregivers were required to be providing in-home care to a spouse with dementia at the time of enrollment. Non-caregivers were required to be married to a healthy spouse free of any disease requiring care. All participants were required to be at least 55 years of age. Participants were asked to report all medications they were taking. These medications were reviewed and coded for whether or not they had anti-hypertensive properties (yes = 1, no = 0), since use of anti-hypertensives have been known to have effects on the cBRS. Participants were excluded if they were receiving current treatment for malignancies other than skin cancers or benign tumors, had severe chronic illnesses requiring ongoing medical treatment (e.g., heart failure, COPD, renal failure, or major psychiatric illnesses such as schizophrenia or bipolar disorder), used oral or parenteral steroids, had severe hypertension (>200/120 mmHg), or were receiving treatment with anti-

coagulant or beta-blocking medications. A diagnosis of major depressive disorder or use of non-dihydropyridine calcium channel blockers were not exclusion criteria.

Demographic and health characteristics of the participants, by caregiving group, are presented in Table 1. Statistical comparisons of the non-caregivers, short-term caregivers, and long-term caregivers indicated these groups did not significantly differ on any demographic or health characteristics except diastolic blood pressure ($F = 3.29$, $p = 0.04$), whereby Tukey's HSD post-hoc tests indicated that long-term caregivers had significantly higher DBP compared to non-caregivers ($p = 0.01$). Normality tests revealed that BMI and cBRS values were significantly positively skewed ($p = 0.001$). Both variables were transformed using log transformation which resulted in an approximately normal distribution.

We categorized antihypertensive medications into classes and summarized the frequency of participants who were taking each type of medication. The most common antihypertensive class taken by the current sample was diuretics ($n = 31$), followed by ACE inhibitors ($n = 16$) and then angiotensin II receptor antagonists ($n = 13$). Other classes (e.g., calcium channel blockers, hybrids) accounted for the remaining cases.

2.2. Measures

2.2.1. Health History—A research assistant recorded demographic information and administered our structured psychosocial assessment to the subjects to assess the psychological and physical health of the caregiver. Demographic information, such as the subject's self-reported age, race, ethnicity, education, weight, height, gender, number of years caregiving, smoking history, and medication list were recorded at this time. Participants were also asked to report any history of myocardial infarction, congestive heart failure, angina, or stroke/transient ischemic attack. Participants were coded as having a history of CVD if they answered 'yes' to any of these conditions. Body Mass Index (BMI) was computed from the self-reported weight and the height of the subject by dividing the subject's weight in kilograms by their height in meters squared.

2.2.2. Spontaneous cBRS measurement—Beat-to-beat systolic blood pressure (SBP) and heart rate (HR) were recorded for 5 minutes in supine position from the right middle finger by using finger photoplethysmography (FMS, Finapres Measurement Systems, Amsterdam, The Netherlands). We used the sequence method and custom made LabVIEW software to calculate spontaneous cardiovagal baroreflex sensitivity (cBRS) [25, 26]. Briefly, we calculated the slopes of the linear regression lines between the SBP and the subsequent RR interval for all recorded sequences where SBP and RR values synchronously either increased or decreased within 3 or more consecutive beats. Regression slopes were calculated only for sequences with at least a 1 mm Hg blood pressure change and 5 ms RR interval change between beats and $R^2 > 0.85$.

To control for the effect of respiration on spontaneous baroreflex, all recordings were made while the subjects were in a supine position at rest, with the subject instructed to maintain normal frequency and depth of respiration, unaltered from their normal respiration at rest. Length of individual RR-intervals does reflect PNS modulation of the RR-interval in the HF

respiratory band too. However, we previously confirmed that there is an agreement between spontaneous cardiovagal baroreflex determined in time domain with sequence technique and spontaneous BRS determined in LF frequency domain by correlating BP and RR oscillations in LF band (0.05Hz–0.15Hz) [26]. Therefore, cBRS values obtained with sequence method in time domain in our study are interchangeable with values obtained in the low frequency (LF) band.

2.2.3. Exercise—In order to assess the physical activity level of our subjects, we used the Rapid Assessment of Physical Activity (RAPA) questionnaire during the psychosocial assessment [27]. This questionnaire was designed to assess adequate physical activity for elderly (>50 years of age) subjects, based on Center for Disease Control (CDC) exercise guidelines, which recommends at least 30 minutes of moderate exercise on most days of the week. Subjects answered a series of “yes” or “no” questions that indicate their frequency and length of engagement in light, moderate, or heavy exercises. Pictures and descriptions of exercises that fit in each category were included in the questionnaire. From the RAPA data, participants were coded as to whether or not they met CDC-recommended guidelines for physical activity.

2.3. Statistical Analyses

Statistical analyses were performed via IBM® SPSS® Statistics, Version 24.0. Initial analyses compared groups on demographic and health characteristics using analysis of variance (ANOVA) and chi-square statistics for linear and dichotomous variables, respectively. In the case that the omnibus ANOVA was significant, post-hoc Tukey’s HSD tests were conducted to examine pairwise differences in group means. Normality of linear variables was checked by reviewing histograms and conducting Kolmogorov-Smirnov tests of normality. Variables with significant skew were transformed to achieve normal distribution prior to conducting our primary analysis. Linear regression was then used to examine our primary hypothesis that cBRS is impaired in caregivers versus non-caregivers. In this analysis, cBRS was the dependent variable, and two contrast variables (scored 1 if ‘yes’ and 0 if ‘no’) were created and used as the primary independent variables of interest. The first contrast variable denoted short-term caregivers (i.e. <4 years caregiving; N=56), and the second denoted long-term caregivers (i.e. ≥4 years caregiving, N=40), with non-caregivers (N = 50) serving as the reference group with whom the other groups were contrasted. Because older age [28], female gender [28, 29], higher body mass index (BMI) [30, 31], infrequent exercise [32], smoking history [33, 34], use of anti-hypertensive medications [35, 36], history of cardiovascular disease [37–40], and resting heart rate [41] have been associated with worsened cBRS, we included all of these variables as covariates in our regression model. To ensure multivariate normality, unstandardized residuals from the multivariate linear regression were tested via the Kolmogorov-Smirnov test. Multicollinearity of independent variables was tested via examination of Tolerance and VIF values. Tolerance and VIF values of < 0.2 and >10 seen as evidence of multicollinearity, respectively. A *P* value of < 0.05 was considered statistically significant.

3. Results

3.1. Relationship between length of caregiving and cBRS

The raw (unadjusted) mean cBRS (mean $\pm$ SE) for non-caregivers (N = 50) was 10.84 ± 0.72 , compared to 9.27 ± 0.81 for short-term caregivers and 8.41 ± 0.68 for long-term caregivers. Results of our multivariate linear regression are presented in Table 2 and covariate adjusted values are presented in Figure 1. The covariate-adjusted log-transformed cBRS values (mean $\pm$ SE) was 0.971 ± 0.029 for non-caregivers, 0.911 ± 0.028 for short-term caregivers, and 0.860 ± 0.033 for long-term caregivers (see Figure 1). Table 2 presents results for the overall model predicting cBRS. As seen, our overall model accounted for 32.2% of the variance in cBRS (adjusted R squared = 27.2%). Significant differences in cBRS were observed between the long-term caregiver and non-caregiver groups ($t = -2.53$, $df = 135$, $p = 0.013$). Computation of Cohen's d effect size resulted in a value of 0.54, considered a moderate effect size. In contrast, no significant difference in cBRS was observed between the short-term caregivers and non-caregivers ($t = -1.47$, $df = 135$, $p = 0.14$; Cohen's d = 0.29). Comparison of the short-term and long-term caregivers indicated no significant cBRS differences between these groups ($t = -1.18$, $df = 135$, $p = 0.24$; Cohen's d = 0.25).

4. Discussion

Our study of elderly caregivers and non-caregivers suggests long-term caring, but not short-term caring, is associated with decreased cBRS independent of age, gender, BMI, smoking history, use of blood pressure medication, and exercise. Although our results are promising, we caution causal interpretation of this data. However, if confirmed, these results may suggest that the stress associated with long term caregiving diminishes caregivers' ability to maintain blood pressure homeostasis and provide one possible link between stressful caregiving and increased risk of cardiovascular disease.

The results of our study are consistent with those of Lucini and colleagues [42] who reported evidence of autonomic dysregulation in cancer caregivers. Our study adds to this body of information through observation of a group of older caregivers, whereby the participants in the Lucini study were in their 40s, and those in our study in their 70s. Further, our study examined a group of caregivers whose caregiving extended much longer in time (i.e., > 4 yrs in our chronic stress group vs. approximately 1 year in the cancer caregivers).

Although short-term caregivers also had lower cBRS compared to non-caregivers, this difference was not statistically significant. We conceptualize that these caregivers have not experienced the chronic accumulation of stress and therefore have less dysfunction than long-term caregivers who have multiple years of caregiving. This appears consistent with the extant literature. Specifically, similar trends have been found in endothelial function in dementia caregivers [43], whereby brachial artery flow mediated dilation (FMD) in long-term caregivers was significantly worse than non-caregivers, but not for short-term caregivers (<4 years caring).

Clinically, this possible link emphasizes the importance of appropriately treating caregiver-related stress not only to reduce psychological distress but also to potentially mitigate the increased risk of CVD in this population. Evidence-based treatments such as psychoeducational programs, psychotherapy, and multicomponent interventions have been shown to be effective in reducing caregiver distress for older adults [44]. Furthermore, morbidity in caregivers has been linked to care-recipient behavioral problems [3], and behavioral problem-solving therapies have been shown to modify these problems effectively [45]. Evidence-based therapies for stressed caregivers should ultimately reduce their long-term risk for CVD in addition to improved psychological health and well-being. However, more research is needed to specifically document improved cardiovascular health outcomes as a result of these treatments.

This study has several limitations. First, the caregiver population we used was a racially homogenous (92.5% white) and elderly (>55 years or older) population, limiting the generalizability of our study. Second, our participant population was relatively healthy. Our inclusion/exclusion criteria limited the caregivers to those without a history of serious/major ongoing illnesses (i.e. cancer, heart failure, severe hypertension, etc.). In addition, small group sizes, the possible effects of acute altered mental health, and lack of a more tangible method of measuring chronic caregiver stress (aside from “years caregiving”) are limitations to our study that should be addressed in future research. Our naturalistic approach to our caregiver sample was both a help and a hindrance to our study. For instance, our method of minimizing medication exclusionary factors was helpful because older individuals are more likely to be taking multiple medications. If we eliminated these individuals from our study, it would jeopardize the generalizability of our study. However, it is possible that some confounds were thereby introduced. Certainly, replication of our study would be important so that such confounds would be minimized. And finally, due to the cross-sectional nature of this study, caution should be taken in interpreting within subject effects from between subject observations. This limitation hinders us from understanding mechanistic pathways in the blunting of cBRS, but we theorize that peripheral baroreceptor resetting due to reduced arterial compliance [19] and central resetting may have a role in this process. Longitudinal analyses will be necessary to confirm this relationship.

To summarize, our data shows that long-term dementia caregivers may have a more blunted cBRS. Since both a blunted cBRS [11] and chronic caregiving stress [5, 6, 8] has been associated with increased risk for CVD, our findings suggest an important role of blunted cBRS in the etiology of cardiovascular disease of caregivers. Further longitudinal studies should be conducted to examine the pathophysiological mechanism of this blunted cBRS and investigate relationship of the cBRS in caregivers and to overcome limitations of our cross-sectional study. Clinically, appropriate treatments to address caregiver distress should also decrease long-term cardiovascular disease risk in caregivers.

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Highlights

- Impaired cBRS function may have a role in poor CV outcomes of stressed caregivers.
- We compared cBRS of long-term caregivers, short-term caregivers, and controls.
- Long-term caregivers have a significantly blunted cBRS compared to controls.
- cBRS of short-term caregivers did not differ significantly from controls.
- Chronic caregiver stress may impair cBRS in a cumulative manner over time.

Figure 1.

Covariate-adjusted (log) cBRS by caregiver status.

Note. Bars represent mean $\pm$ SEM. P-values represent comparison to non-caregiver group.

Table 1

Demographic and health characteristics of the study participants.

Variables	Non-caregivers (N = 50)	Short-term Caregivers (N = 56)	Long-term Caregivers (N = 40)	F	χ^2	p
Age in Years, mean $\pm$ SD	74.3 $\pm$ 5.9	72.9 $\pm$ 7.8	74.4 $\pm$ 8.2	0.63		0.53
Female, n (%)	36 (72.0)	43 (76.8)	31 (77.5)		0.46	0.79
Race					2.01	0.37
White Non-Hispanic, n (%)	40 (80.0)	50 (89.3)	35 (87.5)			
Other, n (%)	10 (20.0)	6 (10.7)	5 (12.5)			
Years of Education, mean $\pm$ SD	15.8 $\pm$ 2.9	14.9 $\pm$ 3.1	15.3 $\pm$ 3.1	1.12		0.33
Body Mass Index, (kg/m ²) mean $\pm$ SD	26.0 $\pm$ 6.2	26.9 $\pm$ 4.8	25.8 $\pm$ 4.9	0.58		0.56
Taking anti-hypertensive meds, n (%)	26 (52.0)	30 (53.6)	23 (57.5)		0.28	0.87
Ever smoked, n (%)	20 (40.0)	28 (50.0)	15 (37.5)		1.79	0.41
CDC-recommended Exercise, n (%)	23 (46.0)	16 (28.1)	14 (34.2)		3.79	0.15
History of CVD, n (%)	3 (6.0)	8 (14.3)	8 (20.0)			0.13*
Resting heart rate, (BPM) mean $\pm$ SD	65.1 $\pm$ 9.6	67.7 $\pm$ 9.2	64.4 $\pm$ 9.5	1.69		0.19
Systolic Blood Pressure (mmHg), mean $\pm$ SD	133.1 $\pm$ 16.3	132.4 $\pm$ 15.4	137.8 $\pm$ 16.1	1.47		0.23
Diastolic Blood Pressure (mmHg), mean $\pm$ SD	72.3 $\pm$ 10.8	75.0 $\pm$ 8.3	77.5 $\pm$ 9.1	3.29		0.04

* Fisher's exact test.

Table 2
Multiple linear regression model predicting (log) spontaneous baroreflex sensitivity (BRS)

Variable	B	SE	B	t	p
Age	0.004	0.003	0.12	1.54	0.13
Female	0.002	0.040	0.00	0.06	0.95
(log) Body Mass Index	-0.178	0.246	-0.06	-0.72	0.47
CDC-recommended exercise	0.082	0.037	0.16	2.20	0.03
Ever smoked	-0.047	0.036	-0.10	-1.31	0.19
Taking anti-hypertensive medications	-0.100	0.039	-0.21	-2.59	0.01
History of CVD	0.100	0.053	0.14	1.90	0.06
Resting heart rate	-0.010	0.002	-0.38	-5.03	<0.01
Short Term Caregivers	-0.060	0.041	-0.12	-1.47	0.14
Long Term Caregivers	-0.112	0.044	-0.21	-2.53	0.01
R ²	32.2%				
Adjusted R ²	27.2%				