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The Moderating Effect of Personal Mastery on the Relations Between Stress and Plasminogen Activator Inhibitor-1 (PAI-1) Antigen

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Objective: This study tested whether feelings of personal control over one's life circumstances (i.e., personal mastery) would attenuate the relations between stress (i.e., negative life events and caregiving distress) and Plasminogen Activator Inhibitor (PAI)-1 antigen, an inhibitor of fibrinolysis implicated in the development of cardiovascular disease. ***Design:*** Seventy-one spousal dementia caregivers were assessed for plasma levels of PAI-1 antigen, negative life events, caregiver distress, and feelings of personal mastery. Regression analysis was used to determine if personal mastery moderated the relations between stress (i.e., life stress and caregiving distress) and PAI-1 antigen levels. ***Main Outcome Measure:*** Plasminogen activator inhibitor (PAI)-1 antigen in plasma. ***Results:*** After controlling for other factors associated with PAI-1 antigen levels, negative life events were positively associated with plasma PAI-1 antigen concentrations in participants low in personal mastery ($\beta = .31$; $p = .050$) but not in individuals high in personal mastery ($\beta = -.22$; $p = .184$). The moderating effect of mastery on the relations between caregiving distress and PAI-1 antigen did not reach statistical significance ($p = .091$). ***Conclusions:*** These data suggest that mastery may protect individuals from some of the alterations in hemostatic factors that have been linked to cardiovascular risk.

Keywords: cardiovascular disease, fibrinolysis, dementia caregiving, stress, coping

For many elderly, the strain of providing long-term care for a disabled spouse (i.e., caregiving) can erode their psychological and physiological well-being, contributing to the development of cardiovascular morbidity. For example, caregivers who report elevated mental or emotional strain experience higher mortality rates compared to noncaregivers (Schulz & Beach, 1999), and spousal caregivers who provide significant amounts of care to their loved ones are at increased risk for coronary artery disease (Lee, Colditz, Berkman, & Kawachi, 2003). Although some studies have found that the stress of providing care for a disabled spouse is associated with an increased morbidity and mortality risk (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007; Schulz & Beach, 1999), others indicate that superimposed life stressors, which may not be related to caregiving, predict additional variance in caregiver burden (Russo & Vitaliano, 1995; von Känel, Dimsdale, Patterson, & Grant, 2003). Furthermore, caregivers who experience greater superimposed life stress have higher plasma norepinephrine levels than those who experience fewer life stressors (Mills et al., 1997), suggesting sympathoadrenal medullary arousal and a possible mechanism linking life stress to cardiovascular disease.

An impaired fibrinolytic capacity resulting in insufficient break down of blood clots may also contribute to the increased risk of coronary artery disease among caregivers. For example, increased plasma levels of plasminogen activator inhibitor (PAI)-1, the primary endogenous inhibitor of fibrinolysis, has been implicated in different types of atherothrombotic disorders (Kohler & Grant, 2000). Primarily, this effect is thought to be a consequence of an excess in circulating PAI-1 ultimately forming a complex with tissue-type plasminogen activator (t-PA; Vaughan, 2005). t-PA

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initiates fibrinolysis by converting plasminogen to fibrin-degrading plasmin bound to cross-linked fibrin chains of an arterial thrombus. Upon reaction and complex formation of active PAI-1 with t-PA, the latter becomes inactive thereby giving rise to a prothrombotic state. Consequently, relatively increased PAI-1 levels would be expected to increase the atherothrombotic risk due to accumulation of intramural fibrin deposits and subsequent formation of a coronary thrombus (Kohler & Grant, 2000). Elevated concentration of PAI-1, even within the normal range of a population, has been associated with prospective risk for first acute myocardial infarction (Thörgersen et al., 1998). In terms of coronary artery disease, previous research indeed showed that elevated plasma PAI-1 is associated with increased risk for reinfarction among individuals with a history of myocardial infarction (Hamsten et al., 1987) and in patients with stable angina (Held et al., 1997). Among young men with a history of myocardial infarction, elevated PAI-1 has been associated with progression of coronary artery disease (Båvenholm et al., 1998).

Interestingly, stress has been associated with a sevenfold increase in PAI-1 antigen in mice (Yamamoto et al., 2002) and with increased PAI-1 in healthy middle-aged men (Räikkönen, Lassila, Keltikangas-Järvinen, & Hautanen, 1996). Vital exhaustion resulting from chronic psychological stress has been associated with elevated PAI-1 levels (Kop, Hamulyak, Pernot, & Appels, 1998), as has increased job strain (Brostedt, de Faire, Westerholm, Knutsson, & Alfredsson, 2004; Ishizaki et al., 1996).

Despite the general body of evidence that the chronic stress of caregiving is associated with morbidity, not all caregivers manifest substantial distress or negative health outcomes (Beach, Schulz, Yee, & Jackson, 2000), implying a need to understand variables that enhance or attenuate the impact of caregiving on health-related outcomes. One factor, a sense of personal mastery, may buffer individuals from the negative consequences of stressful life circumstances. Persons high in personal mastery retain a sense of control over their future and their life circumstances. That is, they have a general sense of control over things that happen to them and have greater confidence they can solve problems in their lives (Pearlin & Schooler, 1978). In contrast, those low in mastery feel helpless or powerless over such circumstances. Personal mastery overlaps to some extent with other positive psychological constructs, such as self-efficacy and perceived control (Skinner, 1996). Self-efficacy (Bandura, 1986, 1997; Carver et al., 2000) is differentiated from personal mastery by its emphasis on one's perceived ability to execute actions that are required to deal with specific circumstances (e.g., self-efficacy for managing disruptive patient behaviors). Mastery is therefore somewhat different from self-efficacy in that it reflects general expectations about personal coping resources versus confidence in performing specific behaviors. With regard to perceived control, mastery does involve a perception of personal control over one's life, but it also involves motivation to persist upon experiencing failure (Bandura, 1986; Carver et al., 2000). In the context of chronic life stress, personal mastery may promote specific, adaptive, goal-oriented behaviors, as well as maintenance of those behaviors, despite ongoing stresses experienced by the individual.

Previous research investigating the role of personal mastery in health outcomes indicates that reduced mastery may be related to depressive symptoms in individuals with severe arthritis (Penninx, van Tilburg, Deeg et al., 1997), reduced immune cell β2-adrenergic receptor sensitivity among dementia caregivers (Mausbach, Mills et al., 2007), and increased mortality risk in the elderly (Penninx, van Tilburg, Kriegsman et al., 1997). In contrast, a greater sense of mastery appears to moderate the relationship between stress and both health and well-being (Lachman & Weaver, 1998). Among caregivers, mastery appears to attenuate the relationship between both primary and secondary stress and psychological well-being (Mausbach et al., 2006). Despite evidence that mastery is associated with improved health outcomes, there has been no research to date exploring the moderating effect of personal mastery on the relationship between life stress and hemostatic indicators or cardiovascular risk markers. In this study, we examined the moderating effect of personal mastery on the relationship between both stressful life events (i.e., generalized stress) and caregiving distress and plasma levels of PAI-1 antigen in 71 spouse caregivers of patients with Alzheimer's disease (AD). Specifically, it was hypothesized that stress would be significantly associated with plasma concentration of PAI-1 antigen in caregivers with low mastery, but not for caregivers with high mastery. We further hypothesized that personal mastery would moderate the effects of caregiving distress on PAI-1 antigen levels. Note that PAI-1 antigen denotes the absolute concentration of PAI-1 bound to inactive t-PA (i.e., t-PA/PAI-1 complexes), whereas PAI-1 activity refers to the level of PAI-1 that has actually the opportunity to react with active t-PA (Vaughan, 2005). We did not measure activity of PAI-1 because PAI-1 activity and PAI-1 antigen are highly correlated (Declerck et al., 1988) and have both been associated with coronary artery disease (Vaughan, 2005).

Method

Participants and Research Design

Participants were 71 elderly individuals providing informal, in-home care for spouses with AD. All participants were part of a study of the biopsychosocial consequences of stress, and previous research from our lab has examined the effects of stress on coagulation markers D-dimer, interleukin (IL)-6, and C-reactive protein (von Känel, Dimsdale, Adler, Patterson, Mills, & Grant, 2005; von Känel, Dimsdale, Patterson, & Grant, 2003; von Känel et al., 2006). Caregivers were recruited through the University of California San Diego Alzheimer's Disease Research Center, community support groups, local senior centers and medical clinics, and senior service professionals. Prior to enrollment, participants were required to provide medical documentation of their loved-one's diagnosis of Alzheimer's disease. Furthermore, all participants were required to be 55 years of age or older. Exclusion criteria included the following: (a) taking β-blocking medication, (b) use of steroids, (c) a blood pressure greater than 200/120 mmHg, and (d) current treatment with anticoagulants.

All caregivers were evaluated in their homes by a research nurse and, after receiving an explanation of the protocol, provided written, informed consent. Following consent, the nurse administered all psychosocial and demographic questionnaires and obtained a blood pressure reading. Following this interview, a 22-gauge venous catheter was placed in the participant's nondominant forearm, and after a 15-min resting period, blood was drawn for assay.

Measures

PAI-1 antigen. After discarding the first 5 ml, 5 ml of venous blood were drawn into a plastic syringe and then dispensed into a glass tube containing CTAD anticoagulant. The samples were kept on ice and spun in a refrigerated centrifuge (4°–8 °C) at 1,250 g for 10 min. Obtained plasma was aliquoted and kept frozen at −80 °C until assayed. Plasma PAI-1 antigen level was measured using enzyme-linked immunosorbent assays (ELISA). Intra- and inter-assay coefficients of variation for PAI-1 antigen were $< 5\%$ each. It has previously been shown that PAI-1 antigen is highly stable both after blood drawing (Seljeflot, Haaland, & Arnesen, 1993) and in frozen plasma over time (Lewis, Callas, Jenny, & Tracy, 2001).

Stressful life events. A modified version of the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989; Grant et al., 1989) was used to assess for stressful life events. Caregivers underwent a semistructured interview to determine the total number of stressful life events they experienced in the 6 months prior to the interview, where they were asked to describe events they perceived to be stressful over the 6-month period. These perceived stressful life events included those related to caregiving (e.g., significant changes in cognitive functioning) and those not related to caregiving (e.g., death of a family member other than the Alzheimer's patient), thereby making this scale a measure of global stress rather than stress related specifically to caregiving. A total score was created by summing the number of stressful life events.

Caregiving distress. Participants were administered the Neuropsychiatric Inventory-Caregiver Distress Scale (NPI-D; Cummings, 1997). For this scale, caregivers rated the emotional or psychological distress they experienced in relation to 12 dementia-related disturbances (e.g., dysphoria, agitation, irritability). Responses for each item ranged from 0 (*not at all*) to 5 (*very severely or extremely*). A total distress score was calculated by summing responses to the 12 items (range = 0–60). Previous literature reports that the NPI-D has adequate reliability and validity (Kaufer et al., 1998).

Personal mastery. The Pearlin Mastery Scale (Pearlin & Schooler, 1978) was administered to each caregiver. This scale consists of seven items assessing the extent to which the caregivers believed their life circumstances were under their own control (e.g., *I have little control over the things that happen to me, What happens to me in the future mostly depends on me*). Responses were on a Likert scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). All items were summed, with higher scores indicating greater mastery.

Caregiver health/medications. We assessed a variety of health characteristics potentially associated with PAI-1 levels. We calculated each participant's body mass index (BMI) as the ratio of body weight in kilograms divided by the square of height in meters (kg/m^2). We assessed both systolic (SBP) and diastolic (DBP) blood pressure using a Critikon Dinamap 8,100 adult/pediatric noninvasive blood pressure monitor. After obtaining blood pressure measurements, participants' mean arterial pressure (MAP) was calculated as $([2 \times DBP] + SBP) \div 3$. Through a medical history questionnaire, we asked caregivers to indicate whether or not they had been diagnosed with diabetes and whether or not there was a current or past history of smoking behavior; both were coded as 1 (*yes*) and 0 (*no*).

Caregivers were also asked to provide a list of medications they were currently taking. All medications were coded according to whether or not they were taken for cardiovascular purposes, 1 (*yes*) and 0 (*no*). Examples of cardiovascular medications in the present sample included angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, enalapril), diuretics (e.g., amiloride, bumetanide), sympathetic nerve inhibitors (e.g., clonidine), Antilipemics (e.g., statins and fibrates), and antiarrhythmics (e.g., diltiazem). No participants were taking anticoagulation medications (e.g., warfarin).

Depressive symptoms. The depression subscale of the Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983) was used to assess depressive symptoms. Participants were asked to rate each of six items using a 5-point Likert scale ranging from 0 (*not at all*) to 5 (*extremely*). The average of the six items was used to calculate an overall score. The BSI depression subscale has similar accuracy as the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HDRS) for detecting cases of depression in the elderly (Stukenberg, Dura, & Kiecolt-Glaser, 1990).

Statistical Analysis

Prior to conducting any analyses, the distribution of all variables was examined for normality. Inspection of variables indicated that PAI-1 was positively skewed. Because PAI-1 was positively skewed, it was normalized using a square root transformation. No other variables required transformation. We used Holmbeck's (1997) regression approach to test the moderating effect of personal mastery on the relations between our primary stress variables (i.e., stressful life events and caregiver distress) and PAI-1. In this approach, the predictor (e.g., stressful life events) and moderator (i.e., personal mastery) main effects are entered into the model first along with any covariates, followed by the interaction of the predictor and the moderator. Because literature suggests that a number of health factors are predictive of PAI-1 levels, most notably those related to the metabolic syndrome (i.e., adiposity, diabetes, blood pressure), and history of Coronary Artery Disease (CAD; Kohler & Grant, 2000; Vaughan, 2005), we controlled for these factors in our multiple regression analysis. Overall, our regression entered the following variables as predictors of (square root) PAI-1 antigen: (a) BMI, (b) hypertensive status, (c) diabetic status, (d) caregiver age, (e) stress/distress, (f) personal mastery, and (g) the interaction between stressful life events and personal mastery. To reduce potential problems resulting from multicollinearity, all predictor variables were centered, with linear variables centered at their means (Cohen, Cohen, West, & Aiken, 2003). Using this approach, a statistically significant interaction indicates a potential moderator effect, which could be interpreted by plotting simple slopes for high and low values of mastery (Holmbeck, 1997, 2002).

Results

Characteristics of the Sample

Table 1 presents the demographic and health characteristics of our sample (mean age = 73.5 ± 9 years); the majority of participants were female (63%), Caucasian (93%), and had at least some

Table 1
Demographic Characteristics of the Sample

Variable	*M (SD)*	*n* (%)
Caregiver age in years	73.5 (9.0)	
Gender		
Male		26 (36.6)
Female		45 (63.4)
Caregiver race		
Caucasian		66 (93.0)
Other		5 (7.0)
Years of education		
High school		15 (21.1)
Some college		18 (25.4)
College or above		38 (53.5)
Yearly household income[a]		
Less than $43,000		30 (52.6)
$43,000 and above		27 (47.4)
History of CAD		5 (6.9)
Use of cardiovascular medication		30 (41.7)
Caregiver PAI-1 (mg/dl)	45.0 (32.9)	
Stressful life events	3.2 (1.7)	
Caregiver distress (NPI-D scores)	11.0 (9.5)	
Personal mastery	19.1 (3.1)	
Caregiver BMI (kg/m^2)	24.9 (3.8)	
Caregiver MAP	87.7 (11.7)	
Caregiver diabetes		
Yes		3 (4.2)
No		68 (95.8)
Former or current smoker		
Yes		38 (53.5)
No		33 (46.5)
Care recipient CDR score	2.5 (0.9)	

Note. PAI-1 = Plasminogen Activator Inhibitor-1; NPI-D = Neuropsychiatric Inventory-Distress Scale; BMI = Body Mass Index; MAP = Mean Arterial Pressure; CDR = Clinical Dementia Rating; CAD = Coronary Artery Disease.
[a] 14 participants refused to provide income data.

college education (79%). Thirty-eight caregivers (54.5%) reported being a former or current smoker, and three (4.2%) reported having a diagnosis of diabetes.

Caregivers reported a wide variety of stressful life events. All caregivers reported at least one caregiving-related stressor over the past 6 months (e.g., *significant changes to the care receiver's cognitive functioning, emotional outbursts from the care recipient*). Extracaregiving events included school-related events (e.g., started training program), those related to work (e.g., changed jobs), relationships (e.g., got a divorce), health (e.g., sustained a major injury, hospitalization), legal difficulties (e.g., jailed), finances (e.g., went on welfare), and personal problems (e.g., moved, pet died, funeral).

Prediction of Plasma PAI-1 Antigen

Results of the regression model predicting PAI-1 antigen levels (see Table 2) indicated a main effect for BMI ($\beta = .24$; $t[59] = 2.08$, $p = .042$), MAP ($\beta = .26$; $t[59] = 2.13$, $p = .037$), and diabetic status ($\beta = .26$; $t[59] = 2.39$, $p = .020$). No main effects were observed for caregiver age ($\beta = -.14$; $t[59] = -1.12$, $p = .269$), gender ($\beta = .08$; $t[59] = 0.70$, $p = .487$), smoking history ($\beta = -.08$; $t[59] = -0.68$, $p = .502$), history of CAD ($\beta = -.10$; $t[59] = -0.88$, $p = .383$, use of CVD medication ($\beta = -.04$; $t[59] = -0.31$, $p = .757$), stressful life events ($\beta = .04$; $t[59] = 0.35$, $p = .725$), or personal mastery ($\beta = -.18$; $t[59] = -1.63$, $p = .108$). However, there was a significant interaction between stressful life events and personal mastery, $t(59) = -2.46$, $p = .017$, indicating a potentially moderating effect of personal mastery on the relations between stress and PAI-1 antigen. Examination of tolerance and VIF statistics for the main effects of stressful life events (0.79 tolerance, 1.26 VIF) and personal mastery (0.88 tolerance, 1.13 VIF) indicated acceptable values for each. For our interaction term, tolerance was 0.86, and VIF was 1.16. Overall, our model predicted approximately 35% of the variance in PAI-1 antigen levels.

As recommended by Holmbeck (2002), post hoc analyses were conducted to determine the nature of this significant interaction. Prior to these analyses, we created a high mastery (i.e., centered mastery – 1 *SD*) and low mastery variable (i.e., centered mastery + 1 *SD*) (Aiken & West, 1991). Each of these variables was then multiplied by the (centered) stressful life events variable to create interaction terms. With these variables, we conducted two regression analyses, each of which included the main effect for stressful life events, one of the conditional mastery variables (high mastery or low mastery), and the interaction of the stress and mastery variable, thereby producing the slope for the high and low mastery conditions. Results of the regression for low mastery indicated that number of stressful life events was significantly associated with

Table 2
Regression Model Predicting (Square Root) PAI-1

	B	*SE*	β	*t*	*p*	Toler	VIF
Body mass index	0.13	0.06	.24	2.08	.042	0.85	1.18
Mean arterial pressure	0.05	0.02	.26	2.13	.037	0.76	1.32
Diabetic status	2.78	1.15	.26	2.39	.020	0.92	1.08
Caregiver age	−0.03	0.03	−.14	−1.12	.269	0.74	1.35
Male	0.36	0.51	.08	0.70	.487	0.83	1.20
Current or previous smoker	−0.32	0.48	−.08	−0.68	.502	0.89	1.12
History of CAD	−0.82	0.94	−.10	−0.88	.383	0.88	1.14
Use of cardiovascular medication	−0.16	0.52	−.04	−0.31	.757	0.78	1.28
Negative stressful life events	0.05	0.15	.04	0.35	.725	0.79	1.26
Mastery	−0.13	0.08	−.18	−1.63	.108	0.88	1.13
Stress × mastery	−0.11	0.04	−.28	−2.46	.017	0.86	1.16

Note. $df = 11, 59$; $R^2 = 0.350$; CAD = Coronary Artery Disease; Toler = Tolerance.

PAI-1 antigen, $\beta = .31$; $t(59) = 2.00$, $p = .050$. In contrast, results of the regression for high mastery indicated that number of stressful life events was not significantly associated with PAI-1 antigen, $\beta = -.22$; $t(59) = -1.34$, $p = .184$. Regression lines depicting raw PAI-1 antigen levels for high and low mastery are plotted in Figure 1.

Because past research suggests that depressive symptoms may be associated with cardiovascular risk (Shaw et al., 1999; Vitaliano et al., 2002), and that socioeconomic status factors may be associated with hemostatic alterations (Myllykangas et al., 1995; Wamala et al., 1999), we conducted a secondary regression analysis to determine if these factors significantly contributed to PAI-1 antigen levels. For this analysis, we replicated our primary regression while adding control for depressive symptoms and both income and education. Results of this analysis were similar to our original model (i.e., stressful life events were associated with PAI-1 antigen when mastery was low but not when mastery was high). Because income and education are often highly correlated, we conducted separate regression analyses using each as a covariate. In these regressions, income was not significantly associated with PAI-1 antigen level ($p = .786$), nor was education ($p = .827$),

Our next analysis examined whether personal mastery moderated the relationship between caregiving distress (i.e., upset from care receiver problem behaviors) on PAI-1 antigen levels. Results of this analysis indicated no significant main effect of mastery, $t(59) = -1.93$, $p = .059$, distress, $t(59) = -0.34$, $p = .732$, or distress-by-mastery interaction, $t(59) = -1.72$, $p = .091$. Post hoc analyses indicated that caregiving distress had a positive association with PAI-1 antigen when mastery was low ($\beta = .12$), but a negative association when mastery was high ($\beta = -.24$). However, neither of these slopes was significant ($p > .05$).

Discussion

Providing care for a loved one suffering from dementia has been implicated in a number of health consequences, including risk for coronary artery disease (Lee et al., 2003; Mausbach, Patterson, et al., 2007) and mortality (Schulz & Beach, 1999). However, not all caregivers experience negative health consequences, thereby prompting research targeting factors that may protect caregivers from these outcomes. The purpose of this study was to determine whether personal mastery might buffer the relations between stress/distress and an indicator of altered clotting environment (plasma concentrations of PAI-1) which may be associated with enhanced atherorthrombotic risk in caregivers of patients with Alzheimer's. Our results indicated that greater experience of stressful life events was associated with elevated plasma PAI-1 antigen among caregivers who felt a reduced sense of control over their life circumstances. In contrast, caregivers who retained a sense of control appeared to be protected from the negative sequelae of stress. This interaction remained significant even after factors associated with elevated PAI-1 concentration had been adjusted for in the model. Our study expands upon past research indicating that stress is associated with elevated plasma PAI-1 (Brostedt et al., 2004; Ishizaki et al., 1996) by providing specific circumstances under which stressful life circumstances may lead to this particular outcome. These results also build upon emerging evidence that life stress among caregivers can be associated with changes in biological indicators which themselves have been linked to cardiovascular disease. For example, previous work indicates that greater experience of life stress among caregivers is associated with elevated fibrin D-dimer, which has a supposed role in hypercoagulability (von Känel et al., 2003). The present data indicate that part of the shift toward hypercoagulability may be due to the effect of life stress, in the context of low mastery, on PAI-1 antigen, compatible with decreased fibrinolytic activity.

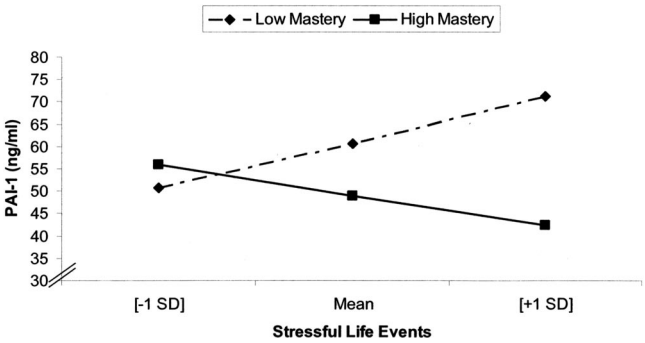

Figure 1. Regression lines for relations between stressful life events and PAI-1 for high and low levels of personal mastery. The slope for stressful life events was significant when personal mastery was low ($\beta = .31$; $p = .050$), but not significant when personal mastery was high ($\beta = -.22$; $p = .184$).

Even though findings from our study are preliminary, these results may have implications for the health and treatment of dementia caregivers. In particular, negative life events may contribute to elevated plasma PAI-1 antigen among caregivers who have a decreased sense of personal mastery. Although we did not test this in the current study, the existing evidence suggests that elevated PAI-1 concentration is associated with risk of experiencing a variety of thrombotic disorders (Kohler & Grant, 2000) and for developing myocardial infarction (Teger-Nilsson, Larsson, Hjemdahl, & Olsson, 1991). This raises the possibility that the combined effect of low mastery and stressful life events on plasma PAI-1 antigen levels could confer an increased risk for cardiovascular disease among elderly caregivers.

If this relationship is confirmed, it is possible that interventions targeting caregivers' sense of personal mastery may help reduce their PAI-1 concentration and consequently their cardiovascular risks. Such interventions might include skills-building components in which caregivers can learn and practice methods of managing stressful life circumstances, such as those associated with caregiving. Indeed, interventions which teach caregivers specific skills have been shown to significantly improve a number of psychiatric outcomes including caregiver burden (Gallagher-Thompson et al., 2000) and depressive symptoms (Gallagher-Thompson et al., 2003, 2000), and others have reported that change in mastery mediates change in depressive symptoms (Coon, Thompson, Steffen, Sorocco, & Gallagher-Thompson, 2003). In future studies, it will be useful to examine whether skills-based interventions are accompanied by reduced PAI-1 antigen levels, and whether such changes are related to increases in personal mastery.

Although we did not find a significant moderating effect of mastery on the relations between caregiving distress (conceptualized as feeling upset by a care receiver's problem behaviors) and PAI-1 antigen levels, we did find that slopes for caregiving distress

at low and high mastery were similar to those of life event stress. Nonetheless, this nonsignificant interaction may indicate that distress associated with one aspect of caregiving (i.e., problem behaviors) does not adequately capture the multiple life areas in which caregivers experience distress (e.g., physical strains, poor sleep, lack of recreation, etc.). Indeed, it may be caregivers' perceived stress associated with caregiving and noncaregiving related stressors is more suggestive of negative health outcomes. However, because we did not specifically assess appraisals associated with caregivers' life events (e.g., *How upset or bothered were you by life stressors?*), this hypothesis is beyond the scope of our current study. As such, we recommend future research examine the moderating effect of mastery on the relations between life event stress appraisals and PAI-1 antigen.

It is also possible that the buffering effects of personal mastery are extended only to general life stress and not to specific distresses that are associated with caregiving. Indeed, personal mastery is conceptualized as one's sense of control over life in general rather than specific stressors (e.g., care receiver problem behaviors). It is possible that a high sense of self-efficacy for controlling disruptive behaviors (Steffen, McKibbin, Zeiss, Gallagher-Thompson, & Bandura, 2002) is needed to buffer the effects of distress associated with problem behaviors on PAI-1 antigen levels or other health outcomes. For example, there is evidence that greater feelings of self-efficacy are associated with self-reported physical outcomes. In studies of patients with persistent physical pain, those with higher self-efficacy for controlling their pain reported both a reduced experience of pain and reduced emotional distress associated with pain compared to those with lower self-efficacy (Keefe, Rumble, Scipio, Giordano, & Perri, 2004). Steffen et al. (2002) describe three domains specific to caregiving in which caregivers may experience various levels of control or mastery. These domains encompass one's belief he or she can (a) obtain respite, (b) successfully respond to disruptive behaviors, and (c) control upsetting thoughts about caregiving. It may be that caregivers feel a differential sense of control over each these domains and future researchers may wish to examine the protective role of self-efficacy for each of these caregiving areas.

We did not assess for genetic factors, which are potentially associated with hemostasis and cardiovascular mortality. For instance, previous research has demonstrated that subjects with the 4G allele of the PAI-1 4G/5G polymorphism have an increased risk of myocardial infarction (Iacoviello et al., 1998). In subjects homozygous for the 4G allele, plasma PAI-1 levels are approximately 25% higher than in subjects homozygous for the 5G allele (Lane & Grant, 2000). Moreover, the 4G/5G promoter site is thought to confer genotype-specific responses to tryiglycerides such that highest levels of PAI-1 among 4G/4G individuals are found in those with elevated serum triglycerides (Lane & Grant, 2000). The implication of such studies is that certain individuals may possess a particular genetic vulnerability when placed in circumstances where they are exposed to high stress and have low mastery. Future studies examining PAI-1 levels and cardiovascular risk in relation to chronic stress and mastery of stressful situations may wish to consider these factors in their model.

Because of our relatively small sample, our analysis examined the general effects of taking cardiovascular medications rather than the effects of specific types of medications (e.g., antihypertensives, antilipemics, or antiarrhythmics). Indeed, there is a possibility that individuals with blood pressure in the normal range were hypertensives on medications, thereby increasing their risk of CVD. A further limitation is that hydration level prior to the blood draw may influence the blood concentration of the nondiffusible PAI-1. However, due to technical difficulties, we did not have hematocrit data for all participants to control for hemoconcentration. Future studies may therefore wish to replicate these effects and account for the effects of specific classes of cardiovascular medications and examine the influence of dilution effects.

While these results may be applicable to caregivers of people with Alzheimer's, it is unclear how they generalize to other populations, including noncaregivers. Although past research with noncaregiving populations indicates that stress is positively associated with PAI-1 levels (Brostedt et al., 2004; Ishizaki et al., 1996; Johnson & Hall, 1988; Räikkönen et al., 1996; Schnall, Landsbergis, & Baker, 1994), we do not know how increased feelings of mastery affect this relationship. Furthermore, our research consisted of a predominately Caucasian sample, making it unclear as to the generalizability of the current results to minority populations. Others should replicate the present findings in these populations to determine whether they are generalizable.

A large subset of caregivers experience physical challenges associated with caring for their loved-ones (Bookwala & Schulz, 2000; Covinsky et al., 2003). These physical challenges may involve lifting and turning, such as aiding a care recipient from a bed to a chair and, if chronic, may result in vital exhaustion. In conjunction with the psychological stresses of caregiving, these physical demands may exacerbate physiologic alterations that potentially influence the hemostatic and fibrinolytic pathways. For example, physical challenges are known to produce sympathetic responses (Roy, Guthrie, Pickar, & Linnoila, 1987), and this response appears exaggerated in those experiencing psychological distress (Rudorfer, Ross, Linnoila, Sherer, & Potter, 1985). Sympathetic activation induces increased activities of blood clotting factors, fibrinolytic enzymes, and platelets (el-Sayed, 1996; Jern et al., 1989). The effects of physical demands on altered hemostasis is therefore important because it suggests that interventions for caregivers may also need to reduce both physical and psychological stresses.

In conclusion, we found evidence that an increased sense of personal mastery may protect caregivers of people with Alzheimer's from the effects of chronic stress on changes in an antifibrinolytic factor that has previously been linked to different types of atherothrombotic diseases and coronary artery disease in particular. If these findings are corroborated by future research, they suggest the possibility that psychological interventions for increasing feelings of mastery in caregivers of people with Alzheimer's might result in changes in the coagulation environment, such as reduction in plasma PAI-1 levels. This, in turn, might reduce one of the risks for cardiovascular disease among elderly caregivers.

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