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Association of vital exhaustion and depressive symptoms with changes in fibrin D-dimer to acute psychosocial stress

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Abstract

Objective: Vital exhaustion and depression are psychosocial risk factors of coronary artery disease. A hypercoagulable state in response to acute psychosocial stress contributes to atherothrombotic events. We aimed to investigate the hypothesis that vital exhaustion and depression correlate with stress-induced changes in the hypercoagulability marker D-dimer. **Methods:** Thirty-eight healthy and nonsmoking school teachers (mean age 50±8 years, 55% women) completed the nine-item Maastricht Vital Exhaustion Questionnaire and the seven-item depression subscale of the Hospital Anxiety and Depression Scale. Within 1 week, subjects twice underwent the Trier Social Stress Test (i.e., preparation phase, mock job interview, and mental arithmetic that totaled 13 min). Plasma D-dimer levels were determined at five time points during the protocol. **Results:** Vital exhaustion (P=.022; η^2=.080) and depressive symptoms (P=.011; η^2=.090) were associated with stress-induced changes in D-dimer levels over time controlling for sex and age. Elevated levels of vital exhaustion (r=−.46, P=.005) and of depression (r=−.51, P=.002) correlated with reduced D-dimer increase from pre-stress to immediately post-stress. Also, elevated vital exhaustion (r=.34, P=.044) and depression (r=.41, P=.013) were associated with increase (i.e., attenuated recovery) of D-dimer levels between 20 and 45 min post-stress. Controlling for stress hormone and blood pressure reactivity did not substantially alter these results. **Conclusion:** The findings suggest an attenuated immediate D-dimer stress response and delayed recovery of D-dimer levels post-stress with elevated vital exhaustion and depressive symptoms. In particular, the prolonged hypercoagulability after stress cessation might contribute to the atherothrombotic risk previously observed with vital exhaustion and depression, even at subclinical levels.

Keywords: Blood coagulation; Cardiovascular disease; Depression; Psychological stress

Introduction

Psychosocial factors such as vital exhaustion (VE) and depression are associated with an increased risk of coronary artery disease (CAD) [1–3]. Vital exhaustion has been conceptualized as a state of undue fatigue, loss of energy, increased irritability, and demoralization reflecting a breakdown of the adaptation to chronic stress [4]. The concept of VE rose from the empirical observation that many patients perceived these feelings in the months preceding a cardiac event [4]. Subsequently conducted studies showed that VE predicted first-time myocardial infarction [5] and recurrent cardiac events after coronary angioplasty [6]. In terms of depression, the relationship with incident CAD was shown to lie along a continuum with, as yet, minimal symptoms of depression increasing CAD risk [3,7].

The psychophysiological mechanisms in the relationship between VE, depression, and CAD are not fully understood [1,2,4] but could partially relate to a hypercoagulable state that is characterized by activated coagulation and/or impaired fibrinolysis [8]. For instance, clotting factor VII,

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fibrinogen, and the main fibrinolysis inhibitor plasminogen activator inhibitor-1 were all elevated in VE [9–11] and depression [12–14]. Chronic low-grade hypercoagulability promotes atherosclerosis and its thrombotic complications [15,16]. Acute psychosocial stress physiologically enhances coagulation activity [8] which, if exaggerated, might increase the risk of atherothrombotic events in susceptible individuals, such as in those with negative affect, including depression [17,18].

As opposed to individual clotting and fibrinolysis factors, the hypercoagulability marker fibrin D-dimer indicates overall activation of coagulation and fibrinolysis. D-dimer is generated when the fibrinolytic enzyme plasmin dissolves fibrin—the end product of the coagulation cascade and main component of a blood clot [19]. A meta-analysis established the role of D-dimer as a predictor of CAD in healthy individuals and in patients with pre-existing vascular disease [20]. D-dimer showed reliable increases to acute psychosocial stress across different studies and populations [21–24].

We hypothesized an association of VE and depressive symptoms with changes in D-dimer in response to and during recovery from acute psychosocial stress in German teachers who are a population with compromised physical and mental health [25]. In a secondary analysis, we covaried for sex, age, and reactivity of stress hormones and blood pressure (BP) because these variables might affect the hypothesized relationships. Specifically, resting D-dimer is higher in women than in men [26] and it increases with age [24]. Norepinephrine (NE) and BP reactivity directly correlated with immediate increase in D-dimer and changes in other procoagulant molecules to acute psychosocial stress [23,27]. Depressive symptoms were associated with enhanced NE and cardiovascular stress reactivity [28]. Vital exhaustion was associated with dampened cortisol stress reactivity [29,30] which, in turn, might elicit enhanced coagulation reactivity [31]. Finally, a mediational analysis was performed to explore whether depression would mediate the effect of exhaustion on D-dimer change or vice versa given that the two constructs share conceptual similarity [4].

Materials and methods

Study design and participants

The present study is part of the Trier Teacher Stress Study investigating mental and physical health in school teachers from Germany and Luxembourg as previously described [32,33]. Specific exclusion criteria for enrollment were diabetes, a positive history of cancer, artery disease, heart failure, medication with corticosteroids, psychotropics, antidepressants, and pregnancy. We also excluded participants with any psychiatric disorder, including clinical forms of depressive disorders, and those who had previously undergone treatment for any depressive disorder. For the present study, 42 employed teachers consented to undergo twice an acute psychosocial stressor (cf. below). On the first test day, sex and age were recorded and all subjects completed psychological questionnaires (cf. below). We excluded two subjects who were smokers and one woman with oral contraceptive use, as these conditions may affect D-dimer levels [34,35]. We further excluded one subject with incomplete D-dimer measures, leaving a final sample of 38 teachers for the analysis. The ethic committees of the State Medical Association of Rheinland Pfalz and the University of Trier approved the study protocol. All participants provided written informed consent and were paid €70 on completion of the stress protocol.

Assessment of psychological measures

Vital exhaustion

We measured VE using a German version of the nine-item short form [11] of the original 21-item Maastricht VE Questionnaire [36]. Scores of the short version correlate well (r=.94) with those from the original 21-item questionnaire [37]. Items ask about undue fatigue, disturbed sleep, general malaise, irritability, loss of mental and physical energy, and feelings of demoralization. Typical items are “Do you often feel tired?,” “Do you feel weak all over?,” and “Do you sometimes feel that your body is like a battery that is losing its power?” [37]. Possible answers to each item are ‘‘no’’ (score=0), “uncertain” (score=1), and ‘‘yes’’ (score=2), giving rise to a total VE score between 0 and 18. Scores from 0 to 3 indicate “no VE,” scores from 4 to 10 are equivalent to “mild to moderate VE,” scores from 11 to 14 reflect “substantial VE,” and scores >14 indicate “severe VE”.

Depression

We applied the validated German version [38] of the depression subscale of the original Hospital Anxiety and Depression Scale (HADS-D) designed to rate symptom levels of depression in non-psychiatric populations [39]. Each of its seven items is rated on a four-point Likert scale (0=not at all, 3=mostly) giving rise to a total depressive symptom score between 0 and 21. Total scores are clinically interpreted with the following cut-off points: 0–7: no depression; 8–10: mild depression; 11–14: moderate depression; 15–21: severe depression. The HADS-D has excellent psychometric properties showing a test–retest reliability of 0.92 in healthy respondents [40]. Cronbach’s alpha for the English and German versions of the HADS-D range between 0.81 and 0.90 [41].

Stress experiment

Subjects were assessed between 3 and 4 p.m. on two separate days with a maximum interval of four days (i.e., no weekend in between assessments) and instructed to refrain from exercise, a heavy lunch and alcoholic drinks on the test day. Premenopausal women were tested during the luteal phase of the menstrual cycle to avoid confounding of the