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Review

# Fibrin D-Dimer: A Marker of Psychosocial Distress and Its Implications for Research in Stress-Related Coronary Artery Disease

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**Summary:** Psychosocial factors might mediate their adverse impact on coronary arteries by eliciting a hypercoagulable state via changes in sympathetic nervous system activity. A recent meta-analysis of prospective studies reported an association of the hypercoagulability marker D-dimer with an increased risk for coronary events. This review provides evidence that an elevated plasma D-dimer level is a suitable marker for acute and chronic psychosocial distress. Prospective studies need to show whether stress-related changes in D-dimer may help explain the increased coronary risk with psychosocial distress.

**Key words:** autonomic nervous system, coronary disease, hemostasis, D-dimer, psychological stress, thrombosis/embolism

## Introduction

Plasma fibrin D-dimer levels originate from the degradation of cross-linked fibrin by the fibrinolytic serine protease plasmin.[1] As a molecular marker of hemostatic activation,[2] D-dimer indicates fibrin turnover [u1]both from intravascular fibrin formation and from subsequent lysis of a fibrin clot.[3] In clinical application, a cut-off level of < 0.5 µg D-dimer/ml plasma is predictive for ruling out deep venous thrombosis and pulmonary embolism.[4] Conversely, numerous vascular diseases have been associated with increased D-dimer.[3] The predictive value of D-dimer for arterial thrombotic events may reflect the contribution of intravascular fibrin to both atherogenesis and thrombogenesis.[5]

A hypercoagulable state occurs when there is an imbalance between procoagulant and anticoagulant activities of hemostasis molecules.[6] Such a diffuse thrombotic diathesis might give rise to thrombotic lesions at distinct sites of the vascular tree, and the coronary arteries in particular.[6] To obtain direct information on particular dynamics of hemostatic activation processes and a hypercoagulable state, hemostatic activation products such as D-dimer rather than individual molecules of the coagulation and fibrinolysis cascades ought to be measured.[6]

Of the many hemostatic factors that have been associated with coronary artery disease (CAD), plasma fibrinogen and D-dimer have emerged as the strongest risk markers.[7] A recent meta-analysis of prospective studies found that subjects in the highest tertile compared with those in the lowest tertile of D-dimer values had an odds ratio for a CAD event of 1.7 (95% confidence interval [CI] 1.3–2.2) after an average follow-up of 5 years.[8] Accounting for established cardiovascular risk factors, which are well known to correlate with D-dimer, and for socioeconomic status provided essentially the same result.[8] Even within the normal range, D-dimer may predict coronary events in apparently healthy individuals[9] and in patients with atherosclerotic disease,[10] suggesting that increased fibrin turnover occurs along a continuum of severity, spanning health, a hypercoagulable state, and overt thrombosis.[3]

Acute and chronic mental stress have been associated with CAD.[11–13] Moreover, conventional cardiovascular risk factors are manifestly inadequate in predicting the coronary risk in many patients.[14] The relationship between psychosocial stress and CAD thus may be considered one of the most important pathophysiologic issues of the day in the field of cardiovascular medicine.[12] From a critical review of the literature, we have concluded that increased activities of clotting factors and

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platelets or a decreased fibrinolytic capacity, or both, might be one mechanism mediating the adverse impact of psychosocial distress on coronary arteries.[15, 16] Such a notion is in line with the concept of vascular bed-specific hemostasis and hypercoagulable states, which holds that thrombosis occurs in an organ-specific fashion through the critical interplay of genetic, endothelial, and environmental factors.[6, 17]

Given the evidence for an association of both D-dimer and psychosocial factors with CAD, we undertook a series of investigations on a possible link between acute and chronic mental stress and D-dimer in subjects with and without atherosclerotic diseases. This article integrates our work and work from other authors that suggests that D-dimer is a suitable marker of psychosocial distress. We discuss the particular meaning of D-dimer for atherosclerosis development under conditions of acute and chronic mental stress and the clinical implications for stress-related CAD. We further delineate the current understanding of how mental stress is thought to influence plasma D-dimer levels by discussing the role of the sympathetic nervous system (SNS) in the regulation of hemostatic function.

## Acute Mental Stress and Changes in D-Dimer

We have examined acute stress and plasma D-dimer levels in two studies. One study investigated D-dimer during a public speaking task in elderly spousal caregivers of patients with Alzheimer's disease. The second study entailed reactivity testing in normotensive and hypertensive subjects.

Alzheimer caregiver distress is a widely acknowledged naturalistic model of human behavioral stress.[18] There is much reason for studying hemostatic function in distressed dementia caregivers, since a hypercoagulable state might ultimately relate to this population's increased risk for CAD[19] and overall increased mortality.[20] In the caregivers, a 15-min speech stressor provoked significant increases in D-dimer and in an additional hypercoagulability marker—thrombin/antithrombin III (TAT) complexes—indicating thrombin generation.[21] This finding implies that acute stress generated thrombin that ultimately converted fibrinogen to fibrin.[22] While we know of no prior study that had reported an increase in D-dimer with acute mental stress, enhanced thrombin formation (i.e., TAT) has been shown in pilots following stress of combat training.[23] In post hoc analyses, increase in D-dimer was found only in caregivers with a positive history of coronary or cerebrovascular disease[22] (Fig. 1). This observation is in line with previous studies on stress-related changes in hemostatic activity.[15] In essence, even though apparently healthy subjects may show hypercoagulable stress responses as evidenced by elevated D-dimer[24] and TAT,[23, 24] subjects with cardiovascular diseases might experience additional thrombotic threat with acute stress.[15] One explanation may be disturbances of the delicate balance between endothelial anticoagulant and procoagulant function in atherosclerosis,[25] such as impaired stress-related endothelial release of the fibrinolytic enzyme tissue-type plasminogen activator (t-PA).[15]

In our study of middle-aged and unmedicated men and women who either were normotensive or had mild hypertension, we confirmed significant increases in D-dimer and in TAT following a combined 12-min speech and mirror-star tracing task.[24]

There is evidence that the SNS affects hemostatic function with acute stress in a number of ways. We found that a 15- to 40-min infusion of stress hormones (i.e., adrenergic agonists) modulates in vivo activities of molecules of the clotting and fibrinolysis pathways, potentially resulting in a hypercoagulable state.[26] While to our knowledge no study has investigated the effect of an infused adrenergic agent on D-dimer, a 20-min epinephrine infusion led to increased TAT in healthy subjects.[27] This led us to speculate that the natural stress hormone surge with an acute behavioral stressor would also influence hemostatic function in terms of increases in TAT and D-dimer. We found some evidence for this notion and showed that changes in norepinephrine and in epinephrine from baseline to stress both were positively associated with the extent of thrombin formation (i.e., TAT) elicited by the 12-min mental stressor, although D-dimer did not correlate with catecholamine surge.[24]

Aside from the catecholamines, adrenergic receptor functioning may relate to acute hypercoagulable stress responses.[24, 26] Via stimulation of endothelial β2-adrenergic receptors, stress hormones acutely release clotting factor VIII, von Willebrand factor, and t-PA from their endothelial storage pools into the circulation. In addition, catecholamines activate platelets stimulating their α2-adrenoreceptors, while platelet β2-adrenergic receptors appear to have a modulating effect on the platelet activation state.[26] In agreement with these influences of adrenergic receptors on plasma levels of individual coagulation and fibrinolysis molecules, we found that β2-adrenergic receptor sensitivity was positively associated with stress-evoked changes in TAT and observed a similar trend for changes in D-dimer.[24] Of note, plasma norepinephrine surge and β2-adrenoreceptor sensitivity together accounted for almost 60% of the variance in stress-induced thrombin formation (Table I). It follows from our investigations that one mech-

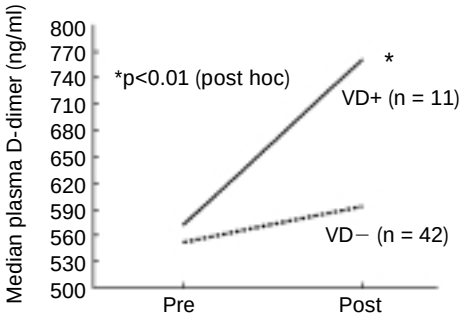


FIG. 1 While the acute mental stressor elicited a significant increase across all 53 Alzheimer caregivers, post hoc analyses revealed that increase in D-dimer was limited to the 11 caregivers who had clinical atherosclerosis. VD = vascular disease: coronary artery or cerebrovascular disease.[22]

TABLE I β2-adrenergic receptor sensitivity and changes in norepinephrine regressed on thrombin formation with acute stress

| | $R^2$ | $\Delta R^2$ | β coefficient | p Value |
|---|---|---|---|---|
| β2-adrenergic receptor sensitivity | 0.236 | 0.236 | 0.486 | <0.04 |
| Change in norepinephrine from baseline to stress | 0.593 | 0.357 | 0.656 | <0.01 |

In 19 normotensive and mildly hypertensive subjects, β2-adrenergic receptor sensitivity and norepinephrine surge together accounted for almost 60% of the variance in thrombin generation during the acute mental stress task.[24]

anism, by which catecholamine spillover following acute stress exerts its procoagulant effects, is via adrenergic stimulation of endothelial β2- and platelet α2-receptors.

## Chronic Mental Stress and Changes in D-Dimer

The effects of chronic stress on plasma D-dimer levels are similar to those found with acute stress. We found that D-dimer increased with superimposed negative life-event stress on top of distress of Alzheimer caregiving even when classical cardiovascular risk factors and demographic variables were accounted for. More precisely, the caregivers who had experienced at least four life-events over 4 weeks had higher D-dimer than those who reported less than four life-events (Fig. 2).[28]

In subjects with either systemic hypertension or sleep apnea, or both, we showed that psychological factors may contribute to increased fibrin turnover independent of the cardiovascular disease status.[29] In that study, perceived chronic distress and depressed and vigorous mood together accounted for 17% of the variance in D-dimer, while cardiovascular disease status and risk factors added another 12% (Fig. 3). It has been suggested that due to its relatively long half-life of several hours, D-dimer is more easily detected in the circulation than, for instance, TAT complexes, which have a half-life of only several minutes.[30] Indeed, while we found increased TAT in our studies on acute stressors, TAT was not significantly related to the number of negative life-events or to psychological factors in our chronic stress investigations on hypercoagulable states.[24, 29]

Elderly subjects with hypertension showed increased D-dimer 7 to 14 days after a major earthquake, with elevated D-dimer levels having decreased again 4 to 6 months after the catastrophic life-event.[31] To explain the increase in D-dimer in that study, the authors proposed that the disaster elicited increased secretion of catecholamines and aggravation of shear stress to the endothelium due to elevated hemodynamic activity.[31] However, SNS mechanisms regulating D-dimer with chronic stress are not fully understood. There is some evidence that elevated D-dimer might reflect a hypercoagulable state that derives from a combination of increased clotting activity with reduced fibrinolytic potential observed with sustained behavioral stress.[15] While acute stress releases t-PA from endothelial cells into the circulation via β2-adrenergic receptor stimulation,[15, 26] chronic stress appears to activate vascular β1-adrenoreceptors resulting in decreased endothelial t-PA release.[32, 33] A lack of circulating t-PA may underlie less inactivation of type I plasminogen activator inhibitor 1 (PAI-1) consistent with impaired fibrinolytic capacity.[32, 33] In mice, intraperitoneal injection of epinephrine and of the nonselective β-adrenergic agonist isoproterenol induced PAI-1 messenger ribonucleic acid (mRNA) expression in cardiovascular cells with a four-fold increased PAI-1 activity in cardiac homogenates for 6 h.[34] In rats, restraint stress between 2 and 20 h induced a three- to seven-fold increase in plasma PAI-1 antigen levels that was accompanied by induction of PAI-1 mRNA in different tissues.[35] Taken together, sustained arou-

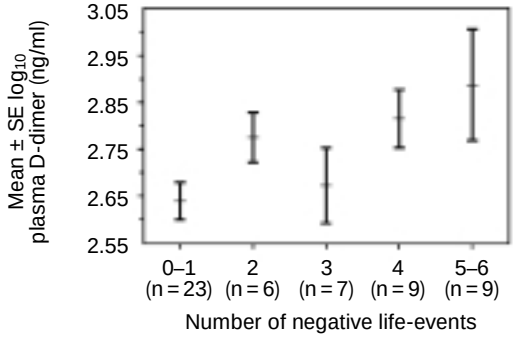


FIG. 2 The 18 Alzheimer caregivers who reported ≥ 4 negative life-events over a 4-week period had higher D-dimer than the 36 caregivers who had experienced < 4 life-events. After controlling for established cardiovascular risk factors and medication, the unique variance in D-dimer explained by the number of negative life-events was 9%. Of note, the amount of variance explained by life stress was similar to that explained by body mass index and higher than that explained by hypertension status.[28] SE = standard of error.

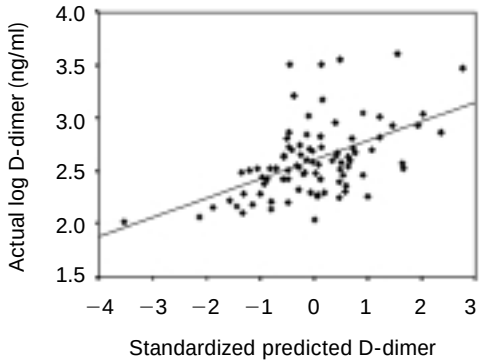


FIG. 3 The scatterplot depicts the association for the significant regression model between the actual $\log_{10}$ normalized D-dimer levels (ng/ml) and the standardized D-dimer values as predicted by perceived stress (Cook-Medley Hostility Scale), depressed mood (Center for Epidemiological Studies, Depression Scale), and vigorous mood (Profile of Mood States) in 88 subjects after controlling for cardiovascular disease status and risk factors.[29]

sal might elicit PAI-1 activity via catecholamine effects that might underlie elevated D-dimer observed with chronic mental stress.

## Discussion

We have reviewed studies suggesting that the plasma D-dimer level is a marker of both acute and chronic mental stress. D-dimer is perhaps most relevant in stressed subjects with preexistent atherosclerotic disease who have impaired endothelial anticoagulant function. D-dimer's relatively long half-life of up to 48 h, and its value in directly indicating a hypercoagulable state, make it a very useful hemostatic marker for purposes of behavioral stress studies related to CAD.[3, 6, 30] Our investigations further provide evidence that the SNS plays a major role in the regulation of fibrin turnover under circumstances of stress.

Given the strong predictive value of D-dimer for future coronary events,[8] it appears fruitful to test prospectively whether mental stress adds to coronary risk predicted by D-dimer. Such a study design might help elucidate the clinical meaning of increased clotting diathesis with mental stress. For instance, a patient with CAD who had high D-dimer before an earthquake, experienced unstable angina 3 to 7 weeks following the catastrophic stressor.[31] Large epidemiological studies have been mounted to test for a prospective relationship between hemostatic factors and atherothrombotic events.[36–38] In many of these study populations, investigators have also assessed data on different domains of psychosocial distress.[39–41] Reanalyzing these data sets in terms of a hypothesized prospective interaction of fibrin turnover with measures of perceived mental stress could advance our knowledge on the psychophysiology of CAD tremendously.

Increased hemodynamic reactivity during a stressful task may predict atherosclerosis development of carotid arteries.[42] In analogy to this observation, the question arises whether subjects who show relatively increased fibrin turnover in response to acute mental stress would be those with accelerated atherosclerosis progression and higher rates of acute coronary events at follow-up. If increased procoagulant stress responses indeed are associated with CAD, studies should test whether anticoagulant, platelet antiaggregatory, and adrenergic receptor blocking drugs may diminish this coronary risk from stress effects on a hypercoagulable state.

Endothelial β2- and platelet α2-adrenergic receptors play an apparent role in the regulation of hemostatic function.[24, 26] Subjects with the Arg16/Gly β2-adrenergic receptor gene polymorphism show relatively greater blood pressure increase during mental arithmetic.[43] Accordingly, taking into account adrenergic receptor polymorphisms when measuring the extent of fibrin turnover following stress might further refine our understanding of hemostatic regulation by the SNS. For instance, one might speculate that distinct adrenergic receptor polymorphisms might subject a particular individual to elevated thrombotic risk by virtue of eliciting greater acute stress procoagulant activity.

## Conclusions

While plasma D-dimer is an attractive surrogate marker for future CAD events and for psychosocial distress, further studies are needed to show whether D-dimer may similarly predict coronary risk in mentally stressed subjects with and without atherosclerotic disease.

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