

# Stress and Hemostasis: An Update

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Semin Thromb Hemost 2013;39:902–912.

## Abstract

Numerous naturalistic, experimental, and mechanistic studies strongly support the notion that—as part of fight-or-flight response—hemostatic responses to acute psychosocial stress result in net hypercoagulability, which would protect a healthy organism from bleeding in case of injury. Sociodemographic factors, mental states, and comorbidities are important modulators of the acute prothrombotic stress response. In patients with atherosclerosis, exaggerated and prolonged stress-hypercoagulability might accelerate coronary thrombus growth following plaque rupture. Against a background risk from acquired prothrombotic conditions and inherited thrombophilia, acute stress also might trigger venous thromboembolic events. Chronic stressors such as job strain, dementia caregiving, and posttraumatic stress disorder as well as psychological distress from depressive and anxiety symptoms elicit a chronic low-grade hypercoagulable state that is no longer viewed as physiological but might impair vascular health. Through activation of the sympathetic nervous system, higher order cognitive processes and corticolimbic brain areas shape the acute prothrombotic stress response. Hypothalamic–pituitary–adrenal axis and autonomic dysfunction, including vagal withdrawal, are important regulators of hemostatic activity with longer lasting stress. Randomized placebo-controlled trials suggest that several cardiovascular drugs attenuate the acute prothrombotic stress response. Behavioral interventions and psychotropic medications might mitigate chronic low-grade hypercoagulability in stressed individuals, but further studies are clearly needed. Restoring normal hemostatic function with biobehavioral interventions bears the potential to ultimately decrease the risk of thrombotic diseases.

## Keywords

- ▶ blood coagulation
- ▶ fibrinolysis
- ▶ platelets
- ▶ psychological stress
- ▶ risk factor

*Dr. Samuel Silverman, 62, is one psychoanalyst willing to declare that Richard Nixon's phlebitis is psychosomatic. The man has been under extraordinary pressure for more than a year, Dr. Silverman says. Mr. Nixon seems to keep his emotions under such control that we might have expected physical instead of emotional breakdown.*

Time Magazine, September 30, 1974, p. 65.

This introductory “case vignette” raises the question of whether intense emotional stress, such as experienced by the United States President Nixon in the wake of the Watergate scandal, is capable of causing thrombosis-associated diseases and, if so, by which mechanisms. Thus, the aim of this review is to provide an update on the sizeable literature on stress-related changes in the

published online  
October 10, 2013

**Issue Theme** Coagulation and the Brain;  
Guest Editors, Benjamin Brenner, MD,  
and Jean-Christophe Gris, MD, PhD.

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Publishers, Inc., 333 Seventh Avenue,  
New York, NY 10001, USA.  
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0033-1357487>.  
ISSN 0094-6176.

hemostatic system (i.e., coagulation, fibrinolysis, and platelets) and their potential role in thrombosis. As a prerequisite for the notion that stress-associated hypercoagulability contributes to thrombotic events,<sup>1</sup> abundant epidemiological and experimental data exist supporting the role of enhanced coagulation, impaired fibrinolysis, and hyperactive platelets in the development of atherogenesis, atherothrombosis, and acute coronary syndromes (ACSs).<sup>2</sup> Also, against a background risk from acquired prothrombotic conditions (e.g., varicosis, immobility) and inherited thrombophilia, even “trivial” triggers such as stress, might bring forward a prothrombotic state that results in onset of venous thromboembolism (VTE).<sup>3</sup>

After introducing the evolutionary meaning versus potential harm for the vasculature of a prothrombotic stress response, we present epidemiological and observational data on the role of stress in atherothrombotic diseases and VTE. We then depict the most salient mechanisms that may link psychosocial stress with hemostatic alterations, including the role of the brain and important health characteristics. Finally, we summarize findings from randomized, placebo-controlled drug trials, and behavioral interventions targeting stress-related hemostatic changes.

### Evolutionary Benefit versus Health Risk

First, we should highlight an important distinction between the vascular consequences of acute versus chronic stress effects on hemostasis. In the case of acute stress, a prothrombotic state is clearly viewed as an adaptive physiological response to prevent a healthy organism in fight-or-flight situations from potentially excessive bleeding in case of injury.<sup>4</sup> However, due to a dysfunctional endothelium having lost its anticoagulant properties (e.g., reduced release of nitric oxide and tissue-type plasminogen activator [t-PA]),<sup>5</sup> the prothrombotic stress response may be excessive in patients with cardiovascular disease (CVD), which may increase the risk of stress-triggered atherothrombotic events.<sup>1</sup> For instance, if tested 1 year after having survived an ACS, patients who reported emotional triggering showed significantly greater increases and longer recovery of platelet-leukocyte aggregates after acute psychosocial stress than the nontriggering group.<sup>6</sup> In the case of chronic stress, sustained low-grade hypercoagulability does not seem to be of evolutionary benefit in healthy individuals and might be harmful to the cardiovascular system in the long run, contributing to atherosclerosis progression.<sup>4,5,7</sup> Such harm might pose greater risk in those with comorbid conditions and thrombotic risk factors. Therefore, individuals with the largest prothrombotic responses to stress and the greatest stress exposure in everyday life would be predicted to be at greater risk for thrombotic diseases.<sup>8</sup>

### Stress and Thrombotic Disorders

Meta-analyses from the past decade strongly suggest that psychosocial stress contributes to morbidity and mortality from atherothrombotic CVD with a 1.5- to 2.5-fold excess risk.<sup>8,9</sup>

In the worldwide INTERHEART case-control study, one-third of the population attributable risk of myocardial infarction (MI) could be assigned to psychosocial factors, including major life events, lack of control, depression, work stress, family stress, and financial stress.<sup>10</sup> The effect size of MI risk explained by psychosocial stress in INTERHEART was similar to that explained by traditional CVD risk factors.

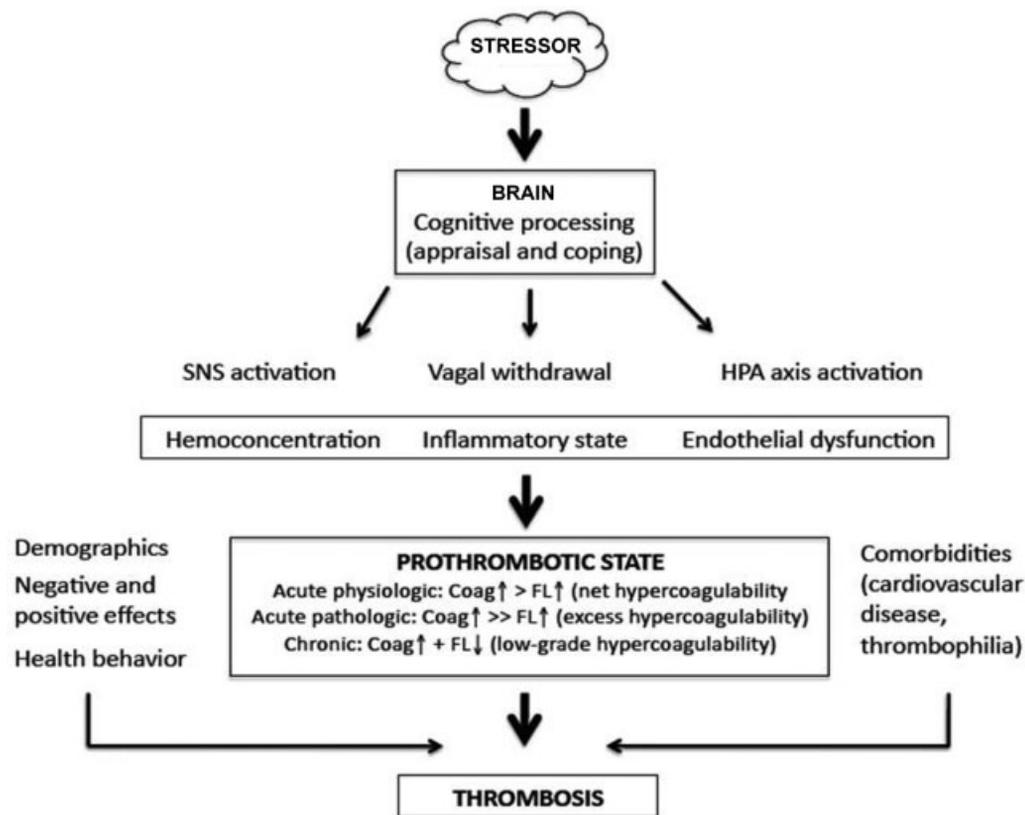
Similarly, evidence from prospective studies suggests that psychosocial factors are predictive of VTE. Persistently perceived stress and low socioeconomic status (SES) increase the risk of VTE independent of demographics, lifestyle, and CVD risk factors.<sup>11,12</sup> Depressed subjects from a population-based study had a 1.6-fold higher risk of incident VTE over a median follow-up of 12 years compared with those not depressed, controlling for other risk factors.<sup>13</sup> Conversely, those who often felt happy or optimistic had a reduced risk of VTE.<sup>13</sup> Acute traumatic stress arising after natural disasters has been implicated as a potential triggering factor of pulmonary embolism.<sup>14</sup> Moreover, the mental stress from fear of flying with the accompanying coagulation activation may contribute to VTE during long-haul air travel.<sup>15</sup>

Several mechanisms are suggested to link stress to increased risk of atherothrombotic events<sup>6,7</sup> and similar factors may play a role in VTE.<sup>16</sup> Stress particularly promotes adverse health behaviors and initiates autonomic and neuroendocrine changes, all bringing forth physiological perturbations (e.g., hypercoagulability) which are potentially harmful to the vasculature.<sup>1,4,5,7,17-19</sup> We will now discuss mechanisms possibly contributing to acute and chronic hemostatic changes as part of the human stress response, including brain processing of stressful stimuli and autonomic and neuroendocrine functioning.

### Psychosocial Stress, the Brain, and the Prothrombotic State

“Stress” is an ambiguous term embedding different processes, namely, a stimulus (i.e., the “stressor” in the form of environmental challenges), perceptual processing of this input (i.e., perceived “distress” with the accompanying negative effects), and behavioral and physiological output (i.e., the “stress response”).<sup>20</sup> This cascade of events helps explain why not only demanding life circumstances (e.g., providing care to a spouse with dementia, working overtime), but also perceived distress (e.g., depressive symptoms) arising from such life circumstances have emerged as risk factors of CVD.<sup>7</sup> **►Fig. 1** shows a conceptual model of how stress may be linked to prothrombotic states and thrombosis.

Importantly, the stress response (e.g., the magnitude of an increase in clotting factor activity) is not a direct indicator of stress exposure, but needs to consider higher level of cortical information processing, such as cognitive appraisal.<sup>20</sup> The amount of threat and challenge a person appraises depends upon the predictability of the stressor and perceived coping resources (e.g., controllability of the situation), which will ultimately influence the intensity and duration of the stress response.<sup>21</sup> For example, healthy men who reported greater



**Fig. 1** Processes in the relationship between stress, hemostasis, and thrombosis. Depending on cortical information processing and appraised coping resources, environmental challenges initiate autonomic- and neuroendocrine-driven changes in the hemostatic system. Several demographic and health-related factors modulate and acquired prothrombotic conditions enhance the prothrombotic stress response, which may become pathological if excessive or chronic, thereby increasing thrombosis risk. Coag, coagulation activation; FL, fibrinolysis activation; HPA, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system ( $\uparrow$  = increased,  $\downarrow$  = decreased).

stress appraisal had greater increase and longer recovery of D-dimer levels over a 1-hour period following the Trier Social Stress Test (TSST), which combines a mock job interview with mental arithmetic in front of an audience for a total of 15 minutes.<sup>22</sup>

A role of the brain in shaping the procoagulant stress response is further evidenced by imaging studies showing corticolimbic brain areas to be jointly involved in processing stressors and regulating hemodynamic stress responses pertinent to CVD risk.<sup>23</sup> Congruent with these neuroimaging studies, early studies demonstrated that electrical stimulation of the lateral hypothalamus in dogs resulted in elevated clotting factor VIII activity (FVIII:C), whereas decreased FVIII:C was observed if the hippocampus was stimulated, with effects lasting approximately 1 hour.<sup>24</sup> Moreover, brain serotonergic neurotransmission dysfunction is evident in stress-related mental disorders such as depression and anxiety. Platelets of depressed and anxious individuals show heightened responses to serotonin.<sup>25,26</sup> Moreover, the 5-HT<sub>2A</sub> receptors in platelets and brain neurons share similarities with the same gene encoding for the platelet and brain serotonin transporter.<sup>27</sup> A brain-platelet-coronary artery interface was proposed, whereby serotonergic dysfunction related to stress might increase the risk of coronary thrombosis through platelet activation.<sup>28</sup>

## Acute Stress and Hemostasis

### Studies in Healthy Individuals

Numerous studies have investigated changes in hemostasis factors in response to acute psychosocial stressors applied in naturalistic and laboratory settings (→ **Table 1**), the latter using standardized speech tasks, mental arithmetic, mirror star tracing task, and the Stroop color-word conflict test. In healthy individuals, there is an increase in procoagulant markers, namely, FVII:C, FVIII:C, FXII:C, fibrinogen, platelets, and von Willebrand factor antigen (VWF:Ag), and of profibrinolytic t-PA indicating, on the whole, concomitant activation of coagulation and fibrinolysis pathways with acute psychosocial stress.<sup>1,4,5,7,18,19</sup> Levels of the coagulation activation markers thrombin-antithrombin complex (TAT) and D-dimer increase as well.<sup>22,29</sup> Thus, both coagulation and fibrinolysis increase during acute stress, but coagulation increases more than fibrinolysis, resulting in net hypercoagulability. Activity of several clotting factors (FVII:C, FVIII:C, FXII:C) as well as fibrinogen and VWF:Ag levels increased between 5 and 10% in response to acute stress in healthy subjects; this change was reproducible across three testings with 1-week intervals.<sup>30</sup> Accordingly, percent prothrombin time (PT%) significantly increased (i.e., indicating activation of the extrinsic coagulation pathway) and activated partial

**Table 1** Reliable changes in hemostasis factors with stress observed in several studies

Measure	Acute stress	Chronic stress
Fibrinogen	↑	↑
Factor XII:C	↑	?
Factor VII:C	↑	↑
Factor VIII:C	↑	↑
von Willebrand factor antigen	↑	↑
Platelet activity	↑	↑
Thrombin–antithrombin complex	↑	?
Fibrin D-dimer	↑	↑
Percent prothrombin time	↑	?
Activated partial thromboplastin time	↓	—
Tissue-type plasminogen activator activity	↑	↓
Tissue-type plasminogen activator antigen	?	↑
Plasminogen activator inhibitor-1 (antigen and activity)	—	↑

Notes: Qualitative changes (↑, increased level; ↓, decreased level; —, no change; ?, unclear). While there is coagulation and platelet activation in both acute and chronic stress conditions, fibrinolysis is activated with acute stress but attenuated with chronic stress.

thromboplastin time (aPTT) significantly decreased (i.e., indicating activation of the intrinsic coagulation pathway) during the TSST in healthy men between 20 and 50 years of age.<sup>31</sup> In agreement with the fight-or-flight response that protects organisms for a limited time, coagulation and platelet activity return to prestress levels within 20 to 45 minutes after termination of a laboratory stressor.<sup>30,32,33</sup>

### Modulating Factors of the Acute Prothrombotic Stress Response

Several sociodemographic, health-related, psychosocial, and behavioral factors are associated with excessive and prolonged hypercoagulability and thus might adversely impact vascular health (► Fig. 1). Age was positively associated with an increase in D-dimer levels during stress and 20 minutes poststress,<sup>33</sup> suggesting that the risk for stress-triggered thrombosis may be increased in elderly people. Men experienced greater net stress-hypercoagulability than women, indexed by a greater FVII:C increase to acute stress in men and greater t-PA activity in women.<sup>34,35</sup> Among those of low SES the stress-induced increase in FVIII:C remained elevated 45 minutes poststress, whereas FVIII:C returned to baseline levels among intermediate- and high-SES individuals.<sup>36</sup>

Compared with individuals free of CVD, those with coronary heart disease (CHD) and/or systemic hypertension showed greater platelet activation,<sup>32,37</sup> delayed recovery of platelet activity,<sup>32</sup> greater D-dimer increase,<sup>38</sup> delayed recov-

ery of declined (i.e., consumed) antithrombin III,<sup>39</sup> and reduced fibrinolysis activation,<sup>40</sup> all in response to acute stress.

Chronic stress and negative effects were also shown to exaggerate the acute prothrombotic stress response. For instance, men with higher job stress showed greater VWF:Ag response to acute stress.<sup>41</sup> In caregivers of a spouse with dementia, the number of negative life events during the last month correlated directly with changes in a prothrombotic score comprising procoagulant factors (i.e., TAT, D-dimer, VWF:Ag, t-PA:Ag) and antifibrinolytic plasminogen activator inhibitor (PAI)-1:Ag during speech stress.<sup>42</sup> In caregivers, but not in controls, depressive and anxiety symptoms were also related to increased expression and delayed recovery of platelet P-selectin with acute stress, controlling for age, sex, history of CHD, and use of aspirin and antidepressants.<sup>43</sup>

Factors associated with good cardiovascular health (e.g., positive effects and a diet rich in catechins) may favorably affect (i.e., mitigate) the prothrombotic stress response. Greater happiness over a working day was associated with lower fibrinogen responses to color-word interference and mirror tracing tasks after adjustment for sociodemographic and CVD risk factors.<sup>44</sup> Finally, platelet activation during acute stress was reduced after 6 weeks of black tea intake (i.e., increased catechin consumption) relative to placebo treatment.<sup>45</sup>

### Underlying Physiological Mechanisms with Acute Stress

The sympathetic nervous system (SNS) exerts major effects on hemostasis at times of acute stress.<sup>46</sup> A previous systematic review of human studies examined hemostatic changes after infusions of adrenergic compounds with and without administration of adrenergic blockers.<sup>47</sup> Catecholamines, particularly epinephrine, stimulate vascular endothelial  $\beta_2$ -adrenergic receptors within a few minutes and in a dose-dependent fashion, resulting in release of preformed FVIII, VWF, and t-PA from endothelial storage pools into the circulation.<sup>47</sup> Catecholamines also stimulate hepatic release of FVIII and affect hepatic clearance of t-PA and likely of D-dimer. Sympathetic nerves in densely innervated resistance arteries and arterioles are another important source of acute stress-induced release of t-PA into the circulation.<sup>48</sup> Moreover, greater sensitivity of the  $\beta_2$ -adrenergic receptor and norepinephrine increase were both associated with increased TAT levels during acute stress,<sup>29</sup> and there was a direct relationship between stress-induced increases in norepinephrine and D-dimer.<sup>22</sup> Stress-induced change in D-dimer was significantly associated with change in FVII:C, explaining 43% of the mutual variance, but not with change in fibrinogen, FVIII:C, FXII:C, VWF:Ag, or soluble tissue factor (sTF).<sup>49</sup> Consistent with SNS overactivity observed in hypertensive individuals, infusion of the nonselective  $\beta$ -receptor agonist isoproterenol resulted in greater increase of plasma VWF in hypertensives than in normotensives.<sup>50</sup>

Thrombin is a potent platelet agonist, and if formed during stress, might critically contribute to platelet activation in vivo.<sup>29</sup> During acute stress, platelets are activated by stimulation of their  $\alpha_2$ -adrenergic receptors, whereby stimulation

of their  $\beta_2$ -adrenergic receptors seems to exert platelet inhibition.<sup>47</sup> Compared with normotensives, patients with essential hypertension showed greater platelet activation (i.e., greater platelet size, increased plasma  $\beta$ -thromboglobulin [ $\beta$ TG] levels) to a physiological dose of infused epinephrine.<sup>51</sup>

In addition to SNS-related mechanisms governing acute hemostatic stress responses, plasma volume contraction (i.e., hemoconcentration) also influences hemostatic measures during acute stress. In healthy individuals, this stress-hemoconcentration is facilitated by an acute increase in blood pressure and net efflux of plasma into the interstitial spaces, thereby resulting in an elevated intravascular concentration of nondiffusible blood constituents (i.e., greater than 69 kDa), including fibrinogen, prothrombin, FV, FVIII, FXI, FXII, and the VWF.<sup>7</sup> The mechanisms underlying stress-hemoconcentration in patients with CHD are less clear.<sup>52</sup> Acute stress-induced changes in plasma volume only explain between 4 and 10% of the variance in changes of FVII:C, FVIII:C, and FXII:C.<sup>49</sup> The most accurate methods to investigate the relative contribution of stress-hemoconcentration to the acute prothrombotic stress response are of current debate.<sup>53–55</sup> Arithmetic adjustment for stress-hemoconcentration has differing effects on fibrinogen, FVII:C, FVIII:C, FXII:C, VWF:Ag, PT%, and aPTT.<sup>31,56</sup> Saline reconstitution of contracted plasma suggested that stress-induced elevations of most measures was due to hemoconcentration, with the notable exception of FVIII:C.<sup>31</sup> In fact, no correction technique removed the effects for FVIII:C, suggesting that the intrinsic pathway is genuinely activated during acute stress.<sup>31,56</sup>

Other psychobiological processes contributing to emotional triggering of ACS include stress-induced hemodynamic shear forces to a vulnerable plaque and inflammatory responses involving cytokines further destabilizing plaques.<sup>57</sup> Moreover, the hemostatic and inflammatory systems are associated during stress. After the TSST, D-dimer and interleukin (IL)-6 reactivity showed a significant and positive correlation over a 2-hour period.<sup>58</sup>

## Chronic Stress and Hemostasis

Different domains of chronic psychosocial stress and distress (e.g., SES, job stress, caregiver stress, posttraumatic stress disorder [PTSD]) have been associated with hemostatic alterations. Similar to acute stress, procoagulant markers, particularly fibrinogen, D-dimer, FVII:C, FVIII:C, and VWF:Ag, are increased by chronic stress (►Table 1).<sup>4,5,19</sup> Importantly, opposed to acute stress, chronic stress seems to impair fibrinolytic activity, reflected by increased PAI-1:Ag, PAI-1 activity, and t-PA:Ag, but decreased t-PA activity. Thus, chronic stress shifts the hemostatic balance between coagulation and fibrinolysis toward a chronic low-grade hypercoagulable state potentially increasing risk of thrombotic disease.<sup>4,5,19</sup>

### Low Socioeconomic Status

Low SES can be construed as a state of chronic stress.<sup>59</sup> Substantial evidence supports a relationship between low SES as measured by different constructs (e.g., education, occupational

class, and social class) and elevated levels of fibrinogen, FVII:C, and VWF:Ag.<sup>4</sup> A large meta-analysis revealed higher fibrinogen levels in unemployed persons than in employed workers, as well as in individuals with lower versus higher education, controlling for a range of CVD risk factors.<sup>60</sup>

### Job Stress

*Stress at work*—defined as a mismatch between job demands and decision latitude (i.e., high job strain)<sup>61</sup> or as an imbalance between effort spent and reward obtained<sup>62</sup>—has been associated with elevated fibrinogen and FVII:C and reduced fibrinolytic capacity (i.e., decreased t-PA activity and increased PAI-1:Ag), mainly in cross-sectional studies.<sup>4</sup> Accountants showed increased FVII:C, FVIII:C, and fibrinogen as well as exaggerated adenosine diphosphate (ADP)- and thrombin-induced platelet aggregation, but no difference in PT and aPTT, during a period of increased work load relative to a calmer period.<sup>63</sup> In male Korean workers with high job strain, FVIII:C, but not FVII:C, was increased after controlling for smoking, blood pressure, and lipids.<sup>64</sup> A recent review suggests that the relation between an adverse psychosocial working environment and elevated fibrinogen is a robust one.<sup>65</sup>

### Caregiver Stress

Providing in-home informal care to a demented spouse is a natural model of chronic human stress. We found higher resting D-dimer levels in Alzheimer caregivers than in age- and sex-matched noncaregiving controls, controlling for history of CHD, CVD risk factors, lifestyle, and medications.<sup>66</sup> Elevated D-dimer levels among caregivers were directly associated with norepinephrine and perturbed sleep measured by polysomnography.<sup>67,68</sup> Problem behaviors of the spouse with dementia were associated with a procoagulant index that included VWF:Ag, PAI-1:Ag, and D-dimer in the caregiver.<sup>69</sup> After the care recipient was deceased or placed in a long-term care facility, D-dimer levels in caregivers did not return to levels of noncaregiving controls until 6 to 30 months after the transition.<sup>70</sup>

### Posttraumatic Stress Disorder

Typically, patients with PTSD reexperience aspects of a traumatic event, such as combat, accidents, and MI in thoughts or dreams, and avoid cues/activities reminding them of the event and develop hyperarousal symptoms, such as irritability and insomnia, all during at least 1 month. Following an accident, patients with PTSD had significantly higher levels of sTF than those who did not develop PTSD.<sup>71</sup> Reexperiencing and avoidance symptoms as well as total PTSD symptoms also showed direct associations with sTF,<sup>71</sup> while hyperarousal and total PTSD symptoms were directly associated with plasma fibrinogen levels.<sup>72</sup> Among civilians with war-related chronic PTSD, VWF:Ag levels were significantly higher than in non-PTSD controls; additionally, the most severe PTSD cases had higher VWF:Ag and FVIII:C than those with less severe PTSD symptoms and controls.<sup>73</sup> Conversely, PTSD symptomatology was unrelated to baseline levels of PT, aPTT, FVII:C, D-dimer, fibrinopeptide A, and prothrombin fragments 1 + 2 across several studies.<sup>72–74</sup> Baseline platelet activity and soluble

P-selectin did not differ between combat veterans with and without PTSD<sup>75</sup>; however, platelets from PTSD patients showed exaggerated reactivity to in vitro epinephrine/ADP stimulation mediated by the  $\alpha_2$ -adrenergic receptor.<sup>76</sup> Post-MI patients with PTSD caused by their MI showed a significant increase in soluble P-selectin during a trauma interview compared with non-PTSD controls<sup>77</sup> and increased fibrinogen and D-dimer reactivity if perceived stress before the interview was high.<sup>74</sup>

### Psychological Distress

Psychological distress can be conceptualized as a maladaptive behavioral response in the form of negative effects, such as depressive and anxiety symptoms both of which may reach a degree that qualifies for a clinical/psychiatric diagnosis (e.g., major depression, panic disorder).<sup>9</sup> Depression has been associated with an increased platelet activity<sup>78</sup> and elevated fibrinogen levels<sup>19</sup> in numerous studies. Patients with ACS and clinical depression showed higher plasma levels of platelet releasing factors (platelet factor 4,  $\beta$ TG) compared with ACS patients without clinical depression.<sup>79</sup> Two prospective studies showed direct correlations between depressive symptom scores and fibrinogen levels across five annual assessments in women<sup>80</sup> and across two annual assessments in teachers.<sup>81</sup> Higher self-rated distress was associated with greater fibrinogen levels in a large sample of healthy young adults, controlling for a range of important confounders.<sup>82</sup> Plasma levels of PAI-1 activity were also greater in depressed than nondepressed individuals, independent of traditional CVD risk factors and status of CHD.<sup>83</sup>

In patients with previous VTE referred for diagnostic thrombophilia work up, we showed a direct association of depressive symptoms with TAT levels and, in those with low perceived social support, also with D-dimer levels, after controlling for demographic and medical covariates.<sup>84</sup> In VTE patients, more symptoms of depression, anxiety, worrying, and anger were all associated with a reduced international normalized ratio, suggesting hastened clotting of the extrinsic coagulation pathway; worrying anger and hostility also showed a direct association with FVII:C levels.<sup>85</sup> Interestingly, relatively lower FX:C in relation to anxiety and worrying and relatively lower FVII:C in relation to anger and hostility were observed in patients with oral anticoagulant (OAC) therapy compared with those without.<sup>85</sup> This difference might be explained by a stress-related innate immune response<sup>86</sup> that attenuates the metabolism of OACs to increase inhibition of vitamin K-dependent clotting factors.<sup>87</sup>

Predominantly impaired fibrinolysis (i.e., increased PAI-1: Ag and  $\alpha_2$ -antiplasmin levels) has been found in patients with an anxiety disorder.<sup>88</sup> Moreover, similar to healthy controls, those anxiety patients medicated with a serotonergic antidepressant showed lower fibrinogen and PAI-1:Ag levels and higher plasmin- $\alpha_2$ -antiplasmin complex, relative to patients with no serotonergic antidepressant.<sup>89</sup> Anxiety symptoms were associated with increased platelet reactivity to serotonin using flow cytometry in CHD patients.<sup>25</sup> In factory workers, panic-like anxiety was associated with higher D-dimer and lower fibrinogen levels, but not PAI-1:Ag.<sup>90</sup> However, in a

population-based study, anxiety and fibrinogen levels showed a direct relation controlling for covariates.<sup>91</sup>

Additional negative affect states being associated with an increased CVD risk<sup>9</sup> have also been associated with a pro-thrombotic state. For instance, early bereavement has been associated with increased levels of platelet-granulocyte aggregates, VWF:Ag and FVIII:C, but not fibrinogen, PAI-1:Ag and t-PA:Ag levels,<sup>92</sup> whereas exhaustion has been related to increased levels of fibrinogen<sup>93</sup> and PAI-1 activity.<sup>94</sup>

### Positive Effects and Related Constructs

Positive psychological states might attenuate hypercoagulability so to buffer harmful hemostatic effects of negative effect states. However, studies on associations of positive effects and related constructs with hemostatic measures are still sparse. Dispositional optimism was associated with lowered fibrinogen levels in a multiethnic population-based study.<sup>95</sup> Similarly, in healthy subjects, increases in uplift intensity over the past month predicted lower levels of PAI-1:Ag levels, whereas increase in distress related to hassle severity predicted elevated levels of D-Dimer.<sup>96</sup> In women, but not in men, aged 50 years and older, greater enjoyment of life was associated with lower fibrinogen levels after controlling for a range of health characteristics, including depressed mood.<sup>97</sup>

### Underlying Physiological Mechanisms with Chronic Stress

Activation of the hypothalamic-pituitary-adrenal axis and decreased parasympathetic activity (i.e., vagal withdrawal) might be more important processes underlying hypercoagulability associated with chronic stress compared with acute stress.<sup>5,19</sup> Factory workers showed associations of overnight urinary excretion of cortisol and catecholamines with morning plasma levels of PAI-1 antigen, fibrinogen, and D-dimer.<sup>98</sup> Plasma cortisol levels were also directly correlated with fibrinogen and VWF:Ag levels in women with stable CHD<sup>99</sup> and with fibrinogen in middle-aged men and women.<sup>100</sup> Lower high frequency heart rate variability (HF-HRV; indicating reduced vagal function) was associated with increased levels of PAI-1: Ag in healthy individuals<sup>101</sup> and with fibrinogen and activated FVII in women with stable CHD,<sup>102</sup> controlling for a range of covariates. The association of increased circulating PAI-1 levels with autonomic dysfunction in humans is supported by studies in rodents showing increased gene expression of PAI-1 after several weeks of unpredictable chronic mild stress,<sup>103</sup> following restraint stress,<sup>104</sup> and after epinephrine and isoprenaline injection.<sup>105</sup> In factory workers, night-time HF-HRV was inversely related to plasma fibrinogen levels, with a stronger relationship for women than men.<sup>106</sup> Vagal withdrawal in chronic stress might mediate hypercoagulability in part via systemic low-grade inflammation. Cross-talk between inflammation and hemostasis plays a key role in atherosclerosis progression,<sup>2</sup> and low-grade inflammation (e.g., increased circulating levels of IL-6 and C-reactive protein) is an important mechanism linking chronic psychosocial stress to atherosclerosis.<sup>107</sup> In healthy men and women, there was a direct relation between plasma levels of IL-6 and sTF if HF-HRV was low, but not if HF-HRV was high.<sup>108</sup>

**Table 2** Intervention studies examining the relationship between stress and hemostasis

Study population	Intervention	Outcome	
		Significant	Nonsignificant
56 healthy men and women undergoing the TSST <sup>107</sup>	5-d RCT: aspirin 100 mg and/or 80 mg propranolol daily versus placebo	Stress response of VWF:Ag ↓ with aspirin, propranolol, or aspirin + propranolol	Stress response of fibrinogen, FVII:C, FXII:C, D-dimer
54 healthy men and women undergoing the TSST <sup>108</sup>	5-d RCT: aspirin 100 mg and/or 80 mg propranolol daily versus placebo	Stress response of FVIII:C ↓ with aspirin + propranolol	Stress response of FVIII:C with aspirin
9 men and women with essential hypertension undergoing mental arithmetic <sup>109</sup>	12-wk RCT: benidipine 2–4 mg daily versus placebo	Stress-induced platelet activation ↓ (ADP-induced aggregation, βTG)	Serotonin-induced platelet aggregation
13 men and women with essential hypertension undergoing mental arithmetic and Stroop <sup>110</sup>	4-wk RCT: verapamil 240–480 mg daily versus placebo	Stress response of ADP-induced platelet aggregation ↓	Stress response of VWF:Ag, t-PA:Ag, PAI-1:Ag
45 healthy men undergoing the TSST <sup>111</sup>	RCT: single dose of 3 mg melatonin versus placebo	Stress response of D-dimer ↓	Stress responses of fibrinogen, FVII:C, FVIII:C
16 men and women with essential hypertension undergoing the Stroop <sup>112</sup>	6-wk RCT: ramipril 5 mg daily versus placebo		Stress responses of TAT, fibrinogen, activated FVII
21 men with hypercholesteremia undergoing the Stroop <sup>113</sup>	10–12-wk RCT: simvastatin 20 mg daily versus placebo		Stress responses of platelet aggregation, βTG
21 men with hypercholesteremia undergoing the Stroop <sup>114</sup>	10–12-wk RCT: gemfibrozil 600 mg twice daily versus placebo	Stress response of platelet aggregation ↑	Stress response of βTG
64 postacute coronary syndrome patients <sup>115</sup>	24-wk RCT: sertraline 50–200 mg daily versus placebo	βTG ↓, sP-sel ↓	Platelet factor 4
57 patients with stable CHD and current major depression <sup>116</sup>	12-wk RCT: citalopram 20–40 mg daily versus placebo		βTG, sP-sel
108 depressed men and women, 45 controls <sup>117</sup>	6-mo outpatient psychotherapy and/or antidepressants	CD62p and CD63 positive platelets ↓, CD63 exposure on platelets after ADP activation ↓, large platelet microparticles ↓	CD62p exposure to ADP-stimulation, platelet-leukocyte aggregates
12 men and women with a severe anxiety disorder and depression <sup>118</sup>	8-wk inpatient psychotherapy with or without psychotropic medication	FVII:C ↓ PAI-1:Ag ↓	VWF:Ag
159 women with stable CHD <sup>119</sup>	1-y cognitive behavioral stress management (20 2-h sessions) versus usual care		Fibrinogen, VWF:Ag, PAI-1:Act, t-PA:Act, t-PA:Ag, t-PA/PAI-1 complex
18 healthy individuals <sup>120</sup>	30-min comedy movie provoking laughter	sP-sel ↓	Fibrinogen VWF:Ag

Abbreviations: Act, activity; ADP, adenosine diphosphate; Ag, antigen level; βTG, β-thromboglobulin; CHD, coronary heart disease; d, day; FVII:C, clotting factor VII activity; h, hour; PAI, plasminogen activator inhibitor; RCT, randomized controlled trial; sP-sel, soluble P-selectin; t-PA, tissue-type plasminogen activator; TAT, thrombin–antithrombin complex; TSST, Trier Social Stress Test; VWF, von Willebrand factor; wk, week(s); y, year(s).  
Note: Quantitative changes (↓, decreased level; ↑, increased level).

## Results from Intervention Studies

The few randomized placebo-controlled trials testing whether cardiovascular medications and antidepressants reduce the

prothrombotic state associated with acute and chronic stress are shown in ► **Table 2**. Even fewer in number are behavioral intervention studies targeting prothrombotic measures. Compared with placebo, the stress response of some prothrombotic

measures was mitigated by aspirin,<sup>109,110</sup> propranolol,<sup>109,110</sup> calcium antagonists,<sup>111,112</sup> and melatonin.<sup>113</sup> Conversely, angiotensin converting enzyme inhibitor<sup>114</sup> and statin<sup>115</sup> administration were both ineffective and fibrinolytic therapy even increased platelet activation during acute stress.<sup>116</sup> However, these findings are limited by small sample sizes and heterogeneity of study populations. Selective serotonin reuptake inhibitors significantly reduced platelet activation in CHD patients in two studies,<sup>117,118</sup> but the decrease in  $\beta$ TG levels was similar to that achieved by placebo in one of these studies.<sup>118</sup>

In- and outpatient psychiatric treatment (psychotherapy and/or psychotropic medication) for patients with anxiety and/or depressive disorders resulted in a decrease of some platelet activation markers<sup>119</sup> and of VWF:Ag and FVII:C.<sup>120</sup> Moreover, reductions in depressive symptoms and platelet activation were significantly correlated with each other after 6 months of outpatient psychiatric therapy for depression.<sup>119</sup> In contrast, cognitive behavioral stress management had no effect on several hemostasis measures in CHD patients when compared with usual care after 1 year.<sup>121</sup> The systematic provocation of laughter might also benefit low-grade hypercoagulability.<sup>122</sup>

## Conclusions

A truly physiological prothrombotic stress response is part of fight-or-flight response, but can be excessive in vulnerable individuals under acute stress and become chronic in persons unable to cope with ongoing life demands. Plausible neurobiological, neuroendocrine, and autonomic processes have been identified to partially explain how stress affects hemostasis. This knowledge underscores the notion that stress should be considered an important preanalytical confound of coagulation tests<sup>123</sup> and a reason for fluctuations in the international normalized ratio in patients under OAC therapy.<sup>85</sup> However, clinical implications likely reach much further. Given that hemostasis is important in atherothrombotic disease and VTE, a prothrombotic state seems a conceivable mechanism linking stress to thrombotic manifestations. To support this assumption, prospective studies are needed to demonstrate the predictive value of acute and chronic prothrombotic stress responses for incident and recurrent thrombotic events in healthy individuals and patients with CHD and VTE. Some small studies suggest that medications and perhaps behavioral interventions have the potential to attenuate the prothrombotic stress response.<sup>109–113,117–120</sup> To potentially prevent emotional triggering of atherothrombotic events, stress management, relaxation, emotion regulation, and even medication in an effort to sever the link between stress and pathophysiological consequences have been proposed.<sup>124</sup> More controlled studies are warranted to investigate whether behavioral and/or medication interventions reduce stress-related hypercoagulability and subsequent thrombotic risk.

## Acknowledgments

The authors are grateful to Annette Kocher for the editorial support. Roland von Känel dedicates this article to his

former doctoral thesis supervisor and director of the Department of Hematology, Bern University Hospital, Switzerland, Prof. Dr. Bernhard Lämmle, on the occasion of his retirement.

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