Different contribution of interleukin-6 and cortisol activity to total plasma fibrin concentration and to acute mental stress-induced fibrin formation

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ABSTRACT

Acute mental stress may contribute to atherosclerosis by affecting inflammation and coagulation; however, the crosstalk between inflammation and coagulation during stress has not been studied. In the present study, we investigated the association of plasma fibrinogen, plasma IL-6 (interleukin-6) and free salivary cortisol with the procoagulant marker D-dimer reflecting fibrin formation both over a 2-h period and in response to acute mental stress. Twenty-one male volunteers (mean age, 47 ± 8 years) underwent the Trier Social Stress Test combining a 3-min preparation phase, a 5-min job interview and 5-min mental arithmetic test before an audience. IL-6, fibrinogen, D-dimer and cortisol were measured immediately before and after stress, and after 45 min and 105 min of recovery from stress. Two distinct areas under the curve were computed to obtain integrated measures of total protein activity over the entire 2-h period and of stress reactivity of proteins. IL-6 (P < 0.001), fibrinogen (P = 0.001), D-dimer (P = 0.021) and cortisol (P < 0.001) had all significantly changed across the four time points assessed, as determined by ANOVA. For the entire 2-h period, total fibrinogen activity (R² = 0.33, P = 0.007) and total cortisol activity (ΔR² = 0.17, P = 0.034) explained 50% of the variance in total D-dimer activity. Stress-induced changes in fibrinogen (R² = 0.47, P = 0.001) and IL-6 (ΔR² = 0.18, P = 0.008) together explained 65% of the variance in D-dimer reactivity to stress. Total fibrin formation was independently predicted by fibrinogen and hypothalamo–pituitary–adrenal activity. Pro-inflammatory and procoagulant changes with stress were associated. Aside from fibrinogen reactivity, IL-6 reactivity was an independent predictor of stress-induced fibrin formation.

INTRODUCTION

Atherosclerosis is an inflammatory disease [1] in which the pro-inflammatory cytokine IL (interleukin)-6 plays a key role [2]. IL-6 independently and strongly predicts coronary risk in healthy men [3], and the same has been shown for fibrinogen [4] and the coagulation activation marker D-dimer [5]. In fact, there is close cross-talk

Key words: cardiovascular disease, coagulation, cortisol, cytokine, inflammation, psychological stress.

Abbreviations: APR, acute-phase response; AUC, area under the curve; AUCG, AUC with respect to ground; AUCI, AUC with respect to increase; BP, blood pressure; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic BP; HPA, hypothalamo–pituitary–adrenal; HR, heart rate; IL, interleukin; PAI-1, plasminogen activator inhibitor-1; SBP, systolic BP; TNF-α, tumour-necrosis factor-α; TSST, Trier Social Stress Test.

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between inflammation and coagulation [6] both of which correlate with each other in plasma and show an additive association in terms of predicting CAD (coronary artery disease) risk [7,8]. This cross-talk also becomes apparent during the APR (acute-phase response) [9]. IL-6 is a strong inducer of the hepatic production of the acute phase reactants CRP (C-reactive protein) and fibrinogen [10] and of a series of other haemostasis factors [11]. For instance, infusion of IL-6 in humans and injection of IL-6 in primates promotes an increase in D-dimer [12].

Acute psychological stress induces an APR with increases in IL-6 [13], fibrinogen [14] and D-dimer [15], very comparable with those seen during sepsis and other inflammatory states [16]. In the present study, we aimed to test the hypothesis that the parallel increase in IL-6 and D-dimer with acute mental stress and during 105 min of recovery from stress would be associated with each other. Another aim of the present study was to investigate whether cortisol activity would modulate coagulant activity during stress and recovery. Previous studies found an inverse association between cortisol and IL-6 responses to acute mental stress [13,17]. We hypothesized that greater HPA (hypothalamo–pituitary–adrenal) axis activity during stress would similarly be associated with attenuated D-dimer reactivity. We have reported previously [14] that fibrinogen, D-dimer and cortisol were all responsive to acute mental stress in the sample investigated in the present study. The novel aspect of the present study was the investigation as to whether these measurements would be associated with each other and with that of IL-6 during acute mental stress and recovery from stress.

To distinguish between the contribution of IL-6 and cortisol activity to fibrin formation during (i) the acute stressor and recovery time (total 2-h period) and (ii) in response to the acute stressor alone (13 min), we computed two different AUCs (areas under the curve), as described previously [18]. AUCG (AUC with respect to ground) incorporated measures obtained immediately before stress, immediately after stress, 45 min after stress and 105 min after stress in one single measure of total activity over the 2-h period (e.g. total concentration or ‘output’ of fibrin). AUCI (AUC with respect to increase) provides one single measure of stress reactivity of each molecule (e.g. stress-induced change in fibrin formation). In contrast with AUCG, AUCI ignores the distance from zero for all measurements, thereby emphasizing the changes over time in a particular parameter.

MATERIALS AND METHODS

Study participants
The Ethics Committee of the Federal Institute of Technology, Zurich, Switzerland formally approved the study protocol. All participants provided written consent. The recruitment procedure has been described in more detail elsewhere [14]. In brief, we included 28 men from a population of 1802 permanently employed non-faculty staff members (>35 years of age) of the Swiss Federal Institute of Technology. To ascertain that all participants were healthy, we performed an extensive medical history, physical examination and routine laboratory work-up (Synlab, Augsburg, Germany). Anthropomorphic data and screening BP (blood pressure) were also obtained. Specified exclusion criteria were any haematological, pulmonary, liver, renal, gastrointestinal, heart, cerebrovascular or psychiatric disease, any history of a thrombo-embolic event, any current major or minor infection, any trauma or surgery within the preceding 6 months, body mass index \(\geq 29 \text{ kg/m}^2\), and high-sensitive CRP levels \(\geq 1 \text{ ng/dl}\). Moreover, all subjects were not on any medication and refrained from any platelet-inhibiting drug for at least 10 days before testing.

Mental stress protocol
Subjects arrived at the laboratory between 07:30 and 08:30 hours and had an indwelling venous forearm 20-gauge catheter placed by intensive care unit personnel. Thereafter subjects received a light standardized breakfast without caffeine and remained seated for another 30 min until instruction on the stress protocol. We applied the TSST (Trier Social Stress Test) combining a 3-min preparation phase, followed by a 5-min free speech phase (job interview) and 5-min mental arithmetic test before an audience [19]. Due to its social evaluative threat and uncontrollability features, the TSST elicits a robust cortisol response [20]. After completion of the task, subjects remained seated for another 105 min in a quiet room. Blood samples for D-dimer, fibrinogen and IL-6, and saliva samples for cortisol were obtained (i) immediately before the preparation phase (‘rest’), (ii) immediately after stress (‘post-stress’), (iii) 45 min after stress (‘recovery 1’), and (iv) 105 min after stress (‘recovery 2’).

Haemodynamic reactivity measurements
HR (heart rate), SBP (systolic BP) and DBP (diastolic BP) were all measured at rest, during stress and 45 min after the end of the stressor. Average HR was computed from a digitally recorded ECG lead using a stable period of 30 s not showing any artefacts or extra periods of systole. Peak BP during stress was calculated as the highest mean value determined over 2 min from at least five valid readings at the left radial pulse (Vasotrac APM205A; Medwave, St. Paul, MN, U.S.A.). Measurements then were adjusted to readings obtained by sphygmomanometry at the other time points.

Coagulation, IL-6 and cortisol assays
After discarding the first 2 ml, whole blood was drawn into 5 ml polypropylene tubes containing 3.8% sodium
citrate (Vacutainer; Becton Dickinson Biosciences, Allschwil, Switzerland). Immediately thereafter, samples were centrifuged at room temperature for 10 min at 3000 g, and aliquots of platelet-free plasma were stored in polypropylene Eppendorf tubes and frozen at −80 °C until analysed. Determination of plasma D-dimer levels was by a turbidimetric method (Dade Behring) [21]. Plasma fibrinogen was determined following a modified Clauss method (Multiﬁbrin U; Dade Behring) [22]. Plasma IL-6 was measured by means of an ultra-sensitive ELISA (range 0.16–10.0 pg/ml; hIL-6; Biosource International, Camarillo, CA, U.S.A). Saliva samples were obtained in polypropylene tubes specifically designed for saliva collection (IBL, Hamburg, Germany) and stored at −20 °C. Centrifugation of thawed samples was at 3000 g for 5 min to provide clear supernatant fractions. Determination of free salivary cortisol was by a luminescence immuno assay (LIA) kit (IBL Hamburg) [23]. All inter- and intra-assay coefficients of variation for IL-6, fibrinogen, D-dimer and cortisol were < 10 %.

**Statistical analyses**

Data analyses used the SPSS (Version 9.0) statistical software package (Chicago, IL, U.S.A.). The non-parametric tests applied were Wilcoxon signed ranks test for two related samples, Spearman’s rank correlation test to estimate bivariate correlation coefficients, and Friedman’s test for repeated measures ANOVA.

AUCs for IL-6, fibrinogen, D-dimer and cortisol across the four time points [rest (y1), post-stress (y2), 45 min after stress (y3), and 105 min after stress (y4)] were computed in accordance with the formulae proposed previously by Pruessner et al. [18].

The formula for AUCG considering the variable time between measurements is:

\[
AUC_G = \left[ \frac{(y_1 + y_2)}{2} \right] \times 13 + \left[ \frac{(y_2 + y_3)}{2} \right] \times 45 + \left[ \frac{(y_3 + y_4)}{2} \right] \times 60
\]

The equation reflects the total concentration, activity or ‘output’ of a particular measure over the 2-h period assessed.

The formula for AUC1 considering the variable time between measurements is:

\[
AUC_1 = \left[ \frac{(y_1 + y_2)}{2} \right] \times 13 + \left[ \frac{(y_2 + y_3)}{2} \right] \times 45 + \left[ \frac{(y_3 + y_4)}{2} \right] \times 60 - [y_1 \times (13 + 45 + 60)].
\]

The equation reflects the change in the concentration or reactivity of a variable in response to the acute mental stressor.

We performed all analyses on the 21 subjects who had complete data for IL-6, fibrinogen, D-dimer and salivary cortisol to compute AUCs and listwise regression analyses. Significance level was set at \( P \leq 0.05 \), and all tests were two-tailed. Data are given as means ± S.D.

**RESULTS**

**Health characteristics**

The health characteristics of the 21 men studied are given in Table 1. Despite their middle age (range 38–59 years), all men were in reasonably good health with regard to their cardiovascular risk profile. More precisely, the Wilson Framingham Index [24] predicted an average chance of 7.1 ± 5.5 % to develop CAD within the next 10 years (results not shown).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.4 ± 7.5</td>
</tr>
<tr>
<td>Level of education (n)</td>
<td>0/1/6/14</td>
</tr>
<tr>
<td>Marital status (n)</td>
<td>5/13/3/0</td>
</tr>
<tr>
<td>Smoking status (n)</td>
<td>3/2/4/12</td>
</tr>
<tr>
<td>Alcohol consumption (days/week)</td>
<td>2.57 ± 1.66</td>
</tr>
<tr>
<td>Physical exercise (n)</td>
<td>9/3/5/4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8 ± 2.4</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.88 ± 0.06</td>
</tr>
<tr>
<td>Screening SBP (mmHg)</td>
<td>125 ± 14</td>
</tr>
<tr>
<td>Screening DBP (mmHg)</td>
<td>82 ± 8 (1 &lt; 90)</td>
</tr>
<tr>
<td>Total serum cholesterol (mg/dl)</td>
<td>204 ± 33 (140–220)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>128 ± 29 (&lt; 160)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>51 ± 10 (&lt; 45)</td>
</tr>
<tr>
<td>Serum triacylglycerols (mg/dl)</td>
<td>123 ± 48 (40–200)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.91 ± 0.54 (4.3–6.1)</td>
</tr>
<tr>
<td>High-sensitive CRP (mg/dl)</td>
<td>0.13 ± 0.16 (&lt; 0.50)</td>
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<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Parameter</td>
<td>Value</td>
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<tr>
<td>TABLE 1 Health characteristics of 21 healthy men studied</td>
<td></td>
</tr>
</tbody>
</table>
Table 2  IL-6, coagulation and cortisol reactivity
Data are medians (range). Recovery 1, 45 min after stress; recovery 2, 105 min after stress. Friedman test for non-parametric repeated measures ANOVA was used to determine the significance across groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Stress</th>
<th>Recovery 1</th>
<th>Recovery 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/ml)</td>
<td>0.36 (0.14–1.3)</td>
<td>0.35 (0.13–1.0)</td>
<td>0.40 (0.15–1.2)</td>
<td>0.47 (0.23–1.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.50 (1.6–3.4)</td>
<td>2.50 (1.3–3.6)</td>
<td>2.50 (1.6–3.5)</td>
<td>2.40 (1.7–3.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>164 (68–369)</td>
<td>176 (58–384)</td>
<td>159 (67–345)</td>
<td>169 (57–364)</td>
<td>0.021</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>10.2 (4.0–24.1)</td>
<td>13.8 (5.2–28.4)</td>
<td>11.8 (3.6–32.3)</td>
<td>6.8 (2.3–12.2)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Inflammation, coagulation and cortisol reactivity
Levels of IL-6, fibrinogen and D-dimer in plasma and of free cortisol in saliva all changed significantly between rest, immediately post-stress and the two recovery times (Table 2). IL-6 levels were significantly higher ($P = 0.005$) 105 min after the end of the stressor than at rest and significantly increased ($P = 0.002$) from 45 min to 105 min of recovery. The absolute increases in fibrinogen ($P = 0.318$; increase $n = 12$, unchanged $n = 4$, and decrease $n = 5$) and D-dimer ($P = 0.122$; increase $n = 16$, and decrease $n = 5$) from rest to post-stress did not reach statistical significance. However, fibrinogen ($P = 0.044$) and D-dimer ($P = 0.035$) significantly decreased between post-stress and 45 min of recovery. Fibrinogen was lower 105 min after stress than at rest ($P = 0.049$). D-dimer was lower at 45 min of recovery than at rest ($P = 0.031$), and had returned to resting levels at 105 min of recovery. Cortisol significantly increased from rest to post-stress ($P = 0.019$) to reach resting levels again after 45 min of recovery. Cortisol levels at 105 min of recovery were lower than at rest ($P = 0.001$).

Association between total D-dimer concentration and inflammation and cortisol activity
D-dimer AUCG significantly correlated with fibrinogen AUCG ($P = 0.103$). According to the strength of the partial correlation coefficients with D-dimer AUCG, we entered the independent variables cortisol AUCG ($r = -0.58$), fibrinogen AUCG ($r = 0.51$) and IL-6 AUCG ($r = 0.37$) in this order and stepwise in the linear regression equation to test for their individual contribution to D-dimer AUCG (i.e. total concentration of fibrin formed during the entire 2-h testing interval). The first model rendered an independent association between D-dimer AUCG and cortisol AUCG ($R^2 = 0.258$, $P = 0.019$). The second model retained both fibrinogen AUCG ($R^2 = 0.327$, $P = 0.007$) and cortisol AUCG ($\Delta R^2 = 0.174$, $P = 0.022$), so that fibrinogen AUCG (33 %) and cortisol AUCG (17 %) together explained 50 % of the variance in D-dimer AUCG. In the final third model, IL-6 AUCG ($\beta = 0.239$, $P = 0.171$) was not revealed as a significant predictor of D-dimer AUCG. Table 3 shows the final linear regression model.
Table 3 Final multiple linear regression model for the total D-dimer concentration over 2 h

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>df</th>
<th>F value</th>
<th>P value</th>
<th>Entered variables</th>
<th>$\beta$</th>
<th>$t$ value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.327</td>
<td>0.327</td>
<td>1,19</td>
<td>9.25</td>
<td>0.007</td>
<td>Fibrinogen AUC$_S$</td>
<td>0.501</td>
<td>2.969</td>
<td>0.008</td>
</tr>
<tr>
<td>0.502*</td>
<td>0.174</td>
<td>1,18</td>
<td>6.30</td>
<td>0.034</td>
<td>Cortisol AUC$_S$</td>
<td>-0.423</td>
<td>-2.509</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Table 4 Final multiple linear regression model for D-dimer change in response to stress

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>df</th>
<th>F value</th>
<th>P value</th>
<th>Entered variables</th>
<th>$\beta$</th>
<th>$t$ value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.469</td>
<td>0.469</td>
<td>1,19</td>
<td>16.79</td>
<td>0.001</td>
<td>Fibrinogen AUC$_I$</td>
<td>0.689</td>
<td>4.917</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0.646*</td>
<td>0.177</td>
<td>1,18</td>
<td>9.01</td>
<td>0.008</td>
<td>IL-6 AUC$_I$</td>
<td>0.421</td>
<td>3.002</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Figure 2** Correlation between D-dimer and fibrinogen responsiveness to stress

The univariate relationship with the fitted line is shown between D-dimer AUC$_I$ and fibrinogen AUC$_I$ ($r = 0.59$, $P = 0.005$). Spearman’s rank correlation was applied to estimate the correlation coefficient. Units are arbitrary units.

**Association between D-dimer response and inflammation and cortisol reactivity to stress**

D-dimer AUC$_I$ significantly correlated with fibrinogen AUC$_I$ (Figure 2), but not with IL-6 ($r = 0.200$, $P = 0.385$) or cortisol ($r = -0.018$, $P = 0.938$). The final linear regression model shown in Table 4 revealed that acute stress-induced changes in fibrinogen (47%) and IL-6 (18%) together explained 65% of the variance in D-dimer responsiveness to stress. IL-6 AUC$_I$ showed no significant correlation with fibrinogen AUC$_I$ and with cortisol AUC$_I$.

**DISCUSSION**

The first aim of the present study was to investigate whether the integrated D-dimer change in response to stress would show an association with accompanying changes in inflammatory and HPA axis activity. Increases in haemodynamic activity and free salivary cortisol verified that our stress protocol elicited a significant activation of the sympathetic nervous system and the HPA axis. All three coagulation and inflammation variables showed a stress effect from rest to post-stress and recovery. Corroborating two previous studies [25,26], IL-6 only increased with a delay of 105 min after stress. A power issue may underlie the observation that the increase in fibrinogen and D-dimer between rest and stress did not reach statistical significance. In fact, only a few subjects experienced an absolute decrease in fibrinogen and D-dimer.

The associated increase in D-dimer indicating overall systemic fibrin formation with the proinflammatory cytokine IL-6 highlights the notion that acute mental stress is accompanied by, or even induces, an APR [16]. Besides its effect on plasma IL-6, acute mental stress also elicits an increase in circulating levels of TNF-$\alpha$ (tumour-necrosis factor-$\alpha$) and IL-1 [27,28]. Notably, during the APR of early infection with the Dengue virus, TNF-$\alpha$ was significantly associated with D-dimer [29]. Unfortunately, we did not measure TNF-$\alpha$ and IL-1, which become activated in this order before IL-6 in the inflammation cascade [30]. Future studies are needed to investigate whether these or other cytokines are even more strongly related to stress-induced fibrin formation than IL-6. We are unable to prove whether the IL-6 increase eventually induced D-dimer increase or vice versa. We assume the former mechanism to be more reliable in the context of our acute stress setting, because synthesis and release of IL-6 by monocytes incubated with D-dimer took 24 h [31]. Accordingly, we modelled the regression equation with D-dimer as the dependent variable and with IL-6 as the independent variable. The independent association between fibrinogen and D-dimer was expected, because fibrinogen is converted into fibrin in the coagulation cascade [32].
Unlike previous studies [13,17], we did not find that IL-6 was negatively controlled by cortisol. However, the stressor used in those studies provoked relatively minor cortisol responses compared with the TSST used in our experiment [20]. The relatively higher cortisol activity with the TSST could suppress other pro-inflammatory cytokines (e.g. TNF-α and IL-1) even before IL-6 stimulation occurs in the inflammation cascade.

The second aim of the present study was to investigate whether the total output of fibrin formation during the 2-h period would correlate with pro-inflammatory and HPA axis activity. In regression analyses, not surprisingly, total D-dimer output was predicted by the total concentration of fibrinogen, which is the main substrate for thrombin that converts fibrinogen into fibrin [32]. The total free salivary cortisol concentration was the second independent predictor of total D-dimer output, suggesting that the less active the HPA axis the higher the concentration of D-dimer, a strong and independent predictor of CAD [5]. We offer one possible clinical consequence of this finding. The concept of allostatic postulates that physiological (stress) systems adapt to environmental challenges through change [33]. Allostatic load accumulates in individuals who fail to mount functional responses of the HPA axis providing an explanation why some individuals develop cardiovascular disease prematurely [33]. We propose that coronary arteries of subjects showing a relatively weaker cortisol activity throughout the day become exposed to exaggerated fibrin concentration (i.e., allostatic load), perhaps resulting in accelerated atherosclerosis progression.

How exactly cortisol down-regulates total fibrin formation is to further studies. Given the 2-h observation phase of our present study, gene transcription should be considered, although we know of no previous studies testing whether cortisol has the potential to suppress expression of genes coding for haemostasis molecules. In these terms, relatively more is known about the effect of catecholamines. Enhanced transcription of PAI-1 (plasminogen activator inhibitor-1) mRNA was shown 3 h after injection of adrenaline in mouse cardiovascular cells [34]. PAI-1 inhibits the fibrinolytic enzyme tissue-type plasminogen activator thereby decreasing D-dimer production. Plasma D-dimer levels do not show a diurnal change [35]. In contrast, cortisol and catecholamine levels gradually decrease during the morning hours. Although speculation, relatively higher catecholamine levels (accompanying similarly high cortisol levels) via enhancing PAI-1 gene expression might be one cause for the relatively greater D-dimer decrease. Unfortunately, we did not measure catecholamines. Investigating whether cortisol and catecholamine activity interact in determining fibrin formation throughout the day seems warranted.

Again, a power issue is likely to underlie the finding that the expected positive correlation between total D-dimer and IL-6 output did not reach statistical significance. Therefore this observation is in line with epidemiological studies measuring coagulation and inflammatory variables at one single point in time and showing significant associations between, for example, D-dimer and IL-6 [7] and between D-dimer and CRP [8].

Besides the rather small sample size, we discuss two limitations of our study. First, we investigated men in reasonably good health. Therefore our findings may not generalize to women and subjects with cardiovascular diseases. Secondly, our subjects were middle-aged. IL-6, fibrinogen and D-dimer all increase with greater age [7,36,37], and IL-6 and D-dimer both are indices of frailty related to a functional decline and mortality in older people [38]. Hence our findings might be of even greater importance in elderly individuals of whom a substantial proportion also suffer from clinically overt or inapparent atherosclerosis.

In summary, total fibrin output was predicted by total fibrinogen concentration and cortisol activity, and the amount of fibrin formed in response to acute mental stress was predicted by fibrinogen and IL-6 reactivity. The first observation may broaden our understanding of why some individuals may develop atherosclerosis over decades (e.g. subjects with attenuated HPA axis activity), whereas others show greater resilience to stress. The second observation is the first to show that pro-inflammatory and procoagulant activity are intertwined during acute mental stress, similar to that observed during APR with infectious diseases.

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**REFERENCES**


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Stress, inflammation and coagulation


