Relationship between overnight neuroendocrine activity and morning haemostasis in working men

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ABSTRACT

Sustained effects of SNS (sympathetic nervous system) and HPAA (hypothalamic–pituitary–adrenal axis) hyperactivity on haemostasis have not been investigated. In the present study, we tested for an association of overnight urinary catecholamine and cortisol excretion with morning plasma levels of fibrinogen, PAI-1 (plasminogen activator inhibitor-1) and D-dimer. Participants (639 male industrial employees) with a complete dataset were studied (age; 41 ± 11 years; mean ± S.D.). Subjects collected overnight urinary samples and had a fasting morning blood sample drawn. Measurement of urinary adrenaline (epinephrine), noradrenaline (norepinephrine) and cortisol were dichotomized to perform multivariate analyses of (co)variance. Haemostatic parameters were measured by ELISA. Fibrinogen was higher in men with high adrenaline (F_{7,631} = 5.68, P = 0.018; where the subscripted value represents the degrees of freedom) and high noradrenaline (F_{7,631} = 4.19, P = 0.041) compared with men with low excretion of the respective hormones. PAI-1 was higher in men with high cortisol than in men with low cortisol (F_{7,631} = 4.77, P = 0.029). Interaction revealed that subjects with high cortisol/low noradrenaline had higher PAI-1 than subjects with low cortisol/high noradrenaline (P = 0.038). Subjects with high adrenaline/high noradrenaline had higher D-dimer than subjects with high adrenaline/low noradrenaline (P = 0.029), low adrenaline/high noradrenaline (P = 0.022) and low adrenaline/low noradrenaline (not significant). When covariance for several confounders of haemostatic function was determined, the main effect of adrenaline on fibrinogen and the interaction between adrenaline and noradrenaline for D-dimer maintained significance. Although overnight SNS hyperactivity was associated independently with morning hypercoagulability, the relationship between the activity of HPAA and haemostasis was mediated by traditional cardiovascular risk factors.

INTRODUCTION

Although numerous studies have shown that short-term activation of SNS (sympathetic nervous system) regulates haemostasis, the effects of HPAA (hypothalamic–pituitary–adrenal axis) on haemostatic function have not been investigated. Physical exercise [1], acute mental stress [2] and catecholamine infusions [3] activate both the coagulation and fibrinolysis pathways, so that the balance between clot formation and dissolution is theoretically maintained. However, increased markers of a hypercoagulable state (e.g. thrombin–antithrombin III complexes and D-dimer) following SNS activation in healthy subjects indicate that procoagulant processes may outweigh anticoagulant forces as part of normal physiology [4,5]. Indeed, in a ‘fight-or-flight’ situation,
short-term hypercoagulability appeared to endow our ancestors with an evolutionary benefit limiting blood loss when wounded [6].

In contrast, sustained SNS and HPAA drive may subject humans to exaggerated acute procoagulant stress responses. For instance, in chronically distressed spousal Alzheimer caregivers, procoagulant changes following an acute speech stress were positively related to the number of negative-life events caregivers experienced in the 4 weeks preceding the stress test [7].

In the present study, we investigated the association between overnight urinary cortisol and catecholamine excretion on blood coagulation and fibrinolysis in 639 industrial male employees. We hypothesized that hyperactivity of SNS and HPAA would be associated with a procoagulant profile in the morning. Of the many haemostatic parameters, we chose to assess fibrinogen, the antifibrinolytic enzyme PAI-1 (plasminogen activator inhibitor-1) and D-dimer, which is a widely used hypercoagulability marker. All three measurements have been shown to predict CAD (coronary artery disease) events across different healthy and cardiovascular disease populations [8–10]. To a varying extent, haemostasis is influenced by demographic variables, socioeconomic status, classic cardiovascular risk factors and sleep [2,8–12]. There is also a crosstalk between haemostasis and inflammation [13]. Our ample sample size allowed us to account for these potential mediators of SNS and HPAA activity on haemostatic function.

**METHODS**

**Setting and participants**

In the present study, we report the data obtained at entry to a longitudinally designed study on ‘Health and Work’. The research has been carried out in accordance with the Declaration of Helsinki of the World Medical Association. The Ethics Committee of the Swiss Federal Institute of Technology, Zurich, Switzerland has formally approved the study protocol. Study participants were recruited from an airplane manufacturing plant in Southern Germany. The recruitment procedure followed a stratified random sampling strategy such that approximately half of the 2000 employees were invited and 822 men and women volunteered to participate. Of these 822 subjects, we excluded all women \((n = 78)\) from our analyses to prevent confounding of haemostasis by the menstrual cycle. We also excluded 105 men due to incomplete datasets in terms of haemostatic and hormone measurements, leaving a final study sample of 639 volunteers. Because of the epidemiological nature of our study putting the focus on physiology in a general working population, we did not exclude subjects based on their medical history and medication use. All volunteers gave informed consent to participate in the study.

Occasional data were missing for BMI (body mass index; \(n = 3\)), SBP (systolic blood pressure; \(n = 3\)), DBP (diastolic blood pressure; \(n = 3\)), total cholesterol \((n = 1)\), LDL (low-density lipoprotein)-cholesterol \((n = 1)\), HDL (high-density lipoprotein)-cholesterol \((n = 1)\), smoking \((n = 19)\), alcohol \((n = 9)\), exercise \((n = 6)\), sleep \((n = 4)\) and CRP (C-reactive protein; \(n = 37\)). Marital status and level of education were not disclosed by 11 and 14 subjects respectively.

The study protocol comprised a comprehensive assessment of the medical history, health behaviour and anthropomorphic and biological measurements. Beyond paid working time spent to participate in the study and the possibility to request personal health counselling by two study physicians, no other incentives were offered.

Following a standardized oral introduction, assessment of questionnaire data took place in groups of 10–25 subjects in a quiet room separate from the working place. Subjects were rescheduled on the subsequent morning between 06:30 and 08:45 hours to have a fasting blood sample drawn and to provide urine samples of the preceding night ending with the first void in the morning. Collection of questionnaire and biological data was achieved within 14 days. Maintaining normal events during the work day was essential to gain the company’s co-operation in conducting the study, which is why we were unable to recruit subjects equally distributed in terms of demographic factors and health variables during the morning hours. However, to minimize effects of posture change on haemostasis, we required that subjects had to present for blood drawing 2 h after awakening at the latest.

**Medical data and health behaviour**

Questions for the medical assessment were derived from the Nurses Health Study [14] and MONICA study [15]. The questionnaire asked for subject’s age, marital status and level of education. It also asked for the numbers of cigarettes currently smoked per day, physical activity (computed as calories burnt exerting light and heavy exercise within an average week) and alcohol consumption (average number of days/week subjects drank alcohol in the previous year). Sleep quality was assessed using the Jenkins Sleep Questionnaire rendering a score between 0 and 20, with higher scores indicating relatively poorer sleep quality [16].

Immediately after having completed the medical questionnaire while sitting (which took most subjects 60 min), SBP and DBP were measured twice within 3 min by sphygmomanometry, and the average of the two readings was computed. Thereafter, subjects had their height and weight measured to compute BMI.

**Biochemical measurements**

All biological data were determined by a commercial laboratory (Synlab, Augsburg, Germany). Venous blood
for haemostasis variables was collected into citrate tubes by skilled lab technicians using a ‘butterfly’ needle system and immediately centrifuged at room temperature for 10 min at 1500 g in a room adjacent to the blood collection room. Plasma samples where post-collection issues are critical (e.g. blood for haemostatic measurements) were frozen immediately at −20 °C, whereas samples for routine clinical chemistry (e.g. differential white blood cell count and lipids) were kept at room temperature. All plasma samples were transported within 90 min to the core lab (Synlab, Augsburg, Germany) and either processed immediately or stored at −70 °C.

Measurements of PAI-1 antigen (Chromogenics, Sweden) and D-dimer (Dade Behring, Germany) were by ELISA. Fibrinogen was determined by a routine clotting assay following the Clauss method [17]. High-sensitive CRP was measured in plasma by immunonephelometry (Dade Behring, Germany). Blood samples for total serum cholesterol, LDL-cholesterol, HDL-cholesterol and HbA1c (glycosylated haemoglobin) were processed within 4 h of blood collection using standard laboratory procedures.

Catecholamines were protected from oxidation by adding HCl to urinary specimens. Overnight urine adrenaline (epinephrine), noradrenaline (norepinephrine) and cortisol excretion was measured by HPLC and expressed in relation to urine creatinine secretion (e.g. µg of cortisol/g of creatinine).

The intra- and inter-assay CV (coefficients of variation) for the various biochemical measurements were as follows: fibrinogen, 2.5 % and 4.0 %; PAI-1, not determined and 13.6 %; D-dimer, 4.6 % and 7.3 %; adrenaline, 1.7 % and 9.5 %; noradrenaline, 0.4 % and 10.8 %; cortisol, 5.1 % and 4.4 %; total serum cholesterol, 2.2 % and 2.2 %; LDL-cholesterol, 1.5 % and 2.1 %; HDL-cholesterol, 1.7 % and not determined; HbA1c, 1.2 % and 2.7 %; and CRP, 4.7 % and 5.9 %.

Statistical analyses

All calculations were performed using SPSS Inc. (version 9.0) statistical software package (Chicago, IL, U.S.A.). Results were considered statistically significant at the P ≤ 0.05 level; all tests were two-tailed. To approximate a normal distribution, values of fibrinogen, D-dimer, adrenaline, noradrenaline, cortisol, HbA1c, activity calories and CRP were log-transformed. For clarity, all transformed measurements are presented in original units and non-parametrically [medians (inter-quartile range)].

Bivariate correlation coefficients between variables of interest were computed using Pearson estimates. Differences between categorical variables were determined by the Pearson χ² test. In a first step, multivariate ANOVA was employed to test for an effect of stress hormone levels (independent variables) on fibrinogen, PAI-1 and D-dimer (dependent variables). All of the three stress hormones were entered together in the multivariate equation. For these analyses, urinary adrenaline, noradrenaline and cortisol measurements were dichotomized to categorize subjects in terms of high and low SNS and HPAA activity respectively. In a second step, all health factors as listed in Table 1 were considered to compute multivariate analysis of covariance. Post-hoc testing was performed by Fisher’s least significant difference. Fₐ values, where n is the degrees of freedom, are shown.

RESULTS

Health characteristics and stress hormones

The health characteristics of the subjects in relation to high and low levels of stress hormone excretion in overnight urine are shown in Table 1. Briefly, adrenaline excretion was higher in smokers, and had an inverse relationship with BMI. Aside from a relationship with age, noradrenaline and cortisol were related to abnormalities associated with the metabolic syndrome. More precisely, noradrenaline had a positive relationship with HbA1c and DBP, whereas cortisol was positively related to BMI, total serum cholesterol, LDL-cholesterol, SBP and DBP. These and other significant relationships between stress hormones and health characteristics justified adjustment for demographic and health factors in the subsequent multivariate analysis.

Bivariate correlation analyses

As expected, urinary stress hormone measurements had a significant correlation with each other: adrenaline–noradrenaline, r = 0.29, P < 0.001; adrenaline–cortisol, r = 0.18, P < 0.001; noradrenaline–cortisol, r = 0.20, P < 0.001. There was a positive relationship between fibrinogen and adrenaline (r = 0.11, P = 0.005), noradrenaline (r = 0.15, P < 0.001) and cortisol (r = 0.12, P = 0.002). While noradrenaline showed a trend for a positive correlation with D-dimer (r = 0.08, P = 0.060), none of the three stress hormones was significantly associated with PAI-1.

Multivariate general linear modelling

Fibrinogen

Consistent with the above correlation analyses, there were main effects of all stress hormones on fibrinogen. Compared with subjects with low urinary excretion of hormones, plasma fibrinogen levels were higher in subjects with high adrenaline, noradrenaline and cortisol excretion (Figure 1). When accounting for all covariates, the main effect of adrenaline excretion on fibrinogen maintained significance (F₁,₅₄⁴ = 5.41, P = 0.017). Of the covariates, LDL-cholesterol (F₁,₅₄⁴ = 4.17, P = 0.042), HbA1c (F₁,₅₄⁴ = 5.05, P = 0.025), smoking (F₁,₅₄⁴ = 4.85, P = 0.028), alcohol (F₁,₅₄⁴ = 3.90, P = 0.049) and CRP
Table 1  Health variables in 639 male subjects studied
Continuous variables are given as medians (inter-quartile range). Marital status, unmarried/married/divorced/widowed; level of education, did not finish regular school/primary school/secondary school/high school. 1 cal $\equiv$ 4.184 J.

<table>
<thead>
<tr>
<th></th>
<th>Adrenaline ($\mu$g/g of creatinine)</th>
<th>Noradrenaline ($\mu$g/g of creatinine)</th>
<th>Cortisol ($\mu$g/g of creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low ($\leq 2.466$) High ($\geq 2.467$)</td>
<td>P</td>
<td>Low ($\leq 23.72$) High ($\geq 23.84$) P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 (33–49) 42 (33–50)</td>
<td>0.652</td>
<td>40 (32–49) 44 (35–51)</td>
</tr>
<tr>
<td>Marital status (n)</td>
<td>84/216/12/0 86/211/17/2</td>
<td>0.404</td>
<td>82/215/13/2 88/212/16/0</td>
</tr>
<tr>
<td>Level of education (n)</td>
<td>8/199/5/45 1/208/60/45</td>
<td>0.131</td>
<td>3/205/6/54 6/202/63/42</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>27 (24–29) 26 (24–28)</td>
<td>0.027</td>
<td>26 (24–28) 26 (24–29)</td>
</tr>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>5.2 (5.0–5.5) 5.2 (5.0–5.6)</td>
<td>0.230</td>
<td>5.1 (4.9–5.5) 5.3 (5.0–5.6)</td>
</tr>
<tr>
<td>Total serum cholesterol (mg/dl)</td>
<td>218 (183–264) 213 (185–243)</td>
<td>0.688</td>
<td>217 (186–264) 245 (216–274)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>145 (120–169) 142 (116–163)</td>
<td>0.369</td>
<td>168 (142–189) 147 (122–169)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>52 (44–60) 51 (45–60)</td>
<td>0.664</td>
<td>51 (45–60) 51 (45–60)</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
<td>0 (0–3) 0 (0–16)</td>
<td>0.008</td>
<td>0 (0–8) 0 (0–8)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128 (120–140) 130 (120–142)</td>
<td>0.890</td>
<td>128 (120–140) 130 (122–142)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82 (78–89) 82 (78–88)</td>
<td>0.745</td>
<td>83 (78–90) 83 (78–90)</td>
</tr>
<tr>
<td>Alcohol consumption (days/week)</td>
<td>2 (1–4) 3 (1–4)</td>
<td>0.910</td>
<td>2 (1–5) 2 (1–4)</td>
</tr>
<tr>
<td>Physical exercise (cal/week)</td>
<td>461 (221–812) 534 (266–1049)</td>
<td>0.532</td>
<td>440 (210–1005) 468 (210–884)</td>
</tr>
<tr>
<td>Sleep quality (Jenkins score)</td>
<td>4 (2–7) 4 (2–7)</td>
<td>0.715</td>
<td>4 (2–7) 4 (2–8)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0.10 (0.06–0.20) 0.10 (0.05–0.27)</td>
<td>0.204</td>
<td>0.09 (0.05–0.20) 0.10 (0.05–0.25)</td>
</tr>
</tbody>
</table>

$(F_{1,544} = 200.92, P < 0.001)$ were associated with fibrinogen levels.

**PAI-1**

Subjects with high urinary cortisol excretion showed higher PAI-1 than those with low cortisol excretion [1.56 (0.23–3.15) compared with 1.20 (0.06–2.75) ng/ml; $F_{1,631} = 4.77, P = 0.029$]. There was an interaction between noradrenaline and cortisol, suggesting that high cortisol excretion, independently of noradrenaline excretion, was associated with higher PAI-1 (Figure 2). When accounting for the entire set of covariates, the main effect of cortisol, as well as the interaction between cortisol and noradrenaline for PAI-1, disappeared. PAI-1 was associated with measures of insulin resistance and dyslipidaemia [BMI ($F_{1,544} = 60.48, P < 0.001$), total cholesterol ($F_{1,544} = 31.21, P < 0.001$), LDL ($F_{1,544} = 18.97, P < 0.001$) and HDL ($F_{1,544} = 13.15, P = 0.001$)].

**D-dimer**

There was an interaction between adrenaline and noradrenaline, suggesting that subjects with high adrenaline/noradrenaline excretion had higher D-dimer than all other groups (Figure 3). This observation maintained significance when all covariates were taken into account ($F_{22,544} = 5.56, P = 0.019$). Of the covariates, only HbA$_{1c}$ showed a significant association with D-dimer ($F_{1,544} = 14.86, P < 0.001$).

**DISCUSSION**

In the present study of 639 male industrial employees, we tested for the relationship between overnight SNS and HPAA activity, as well as their interaction with morning plasma levels of haemostatic parameters associated previously with CAD. We found that overnight SNS hyperactivity was positively associated with morning fibrinogen and D-dimer, indicative of relative hypercoagulability. More precisely, subjects with greater overnight adrenaline excretion had higher plasma levels of fibrinogen than subjects with low adrenaline excretion. Also, plasma D-dimer was highest in subjects who excreted exaggerated amounts of both adrenaline and noradrenaline. The association between adrenaline and fibrinogen and the interaction between adrenaline and
neuroendocrine activity and haemostasis

Figure 1  Stress hormones and plasma fibrinogen levels
Boxes depict the median values and inter-quartile ranges (i.e., the boxes reach from the 25th to the 75th percentile of the data) of fibrinogen for high compared with low levels of the three stress hormones. The whiskers extend from the 25th to the 5th percentile and from the 75th to the 95th percentile of the data. Plasma fibrinogen levels were higher in subjects with high overnight excretion (n = 320) of adrenaline (high E; \( F_{7,631} = 5.68, P = 0.018 \)), noradrenaline (high N; \( F_{7,631} = 4.19, P = 0.041 \)), and cortisol (high C; \( F_{7,631} = 3.36, P = 0.067 \)) than in subjects with low excretion (n = 319) of respective hormones.

Figure 2  Stress hormones and plasma PAI-1 levels
There was an interaction between noradrenaline and cortisol in terms of plasma PAI-1 (\( F_{7,631} = 4.38, P = 0.037 \)). Absolute PAI-1 values of subjects with high cortisol (high C)/high noradrenaline (high N; n = 180) and high cortisol/low noradrenaline (low N; n = 140) were higher than PAI-1 levels in subjects with low cortisol (low C)/high noradrenaline (n = 140) and low cortisol/low noradrenaline (n = 179). The difference between subjects with high cortisol/low noradrenaline and low cortisol/high noradrenaline reached statistical significance (\( P = 0.038 \)).

Figure 3  Stress hormones and plasma D-dimer levels
There was an interaction between adrenaline (E) and noradrenaline (N) in terms of plasma D-dimer (\( F_{7,631} = 6.94, P = 0.009 \)). Absolute values of D-dimer were higher in subjects with high adrenaline (high E)/high noradrenaline (high N; n = 190) than in subjects with high adrenaline/low noradrenaline (low N; n = 130; P = 0.029), low adrenaline (low E)/high noradrenaline (n = 130; P = 0.022) and low adrenaline/low noradrenaline (n = 189; not significant).

Of note, the results of the present study do not confirm a causal relationship between stress hormone levels and haemostatic activity. Nonetheless, our observations are compatible with the literature on short-term effects of sympathetic activation on haemostasis [1–3]. An acute catecholamine surge, via an effect mediated by \( \beta_2 \)-adrenergic receptors, results in an increase in plasma levels of clotting factor VIII, von Willebrand factor and t-PA (tissue-type plasminogen activator) within minutes [3]. Catecholamines also activate platelets in vivo via their \( \alpha_2 \)-adrenergic receptors [3]. Eventual fibrin formation requires both \( \alpha_2 \)- and \( \beta_2 \)-adrenergic stimulation [18], and \( \beta_2 \)-adrenergic receptor sensitivity accounts for some of the variance in thrombin formation with acute stress [5]. Sustained SNS activation appears to impair t-PA release from the endothelium by activating \( \beta_1 \)-adrenergic receptors. This may result in decreased inactivation of circulating PAI-1, compatible with impaired fibrinolysis [19]. Unfortunately, we did not assess any indices of adrenergic receptor function and, thus, we were unable to investigate their potential role in mediating haemostatic changes related to nocturnal SNS and HPAA activity.

Glucocorticoid therapy may enhance blood coagulability [20,21]; however, short-term and prolonged effects of increased HPAA activity on haemostasis have not been investigated. The same is true in terms of studying an interaction between SNS and HPAA on haemostasis. For PAI-1, we found an interaction between cortisol and noradrenaline excretion, suggesting...
an association between increased HPAA activity and decreased fibrinolysis. In contrast with D-dimer, health factors mediated the effect of the HPAA on PAI-1. In particular, there was an association of PAI-1 with BMI and an unfavourable lipid profile, both clustering with insulin resistance [22]. The association between PAI-1 and variables defining insulin resistance was expected given that PAI-1 itself has been recognized as a component of the insulin resistance syndrome [23]. Also, and in line with previous studies [24], several of the insulin-resistance variables were higher in participants with high compared with low excretion of stress hormones.

Our present study has several limitations. First, the inter-individual variability in catecholamine and cortisol excretion was considerably large (see Figures 1–3). This phenomenon has been shown in previous studies [25–27] and may relate to the fact that the sympatho-medullary and HPAA systems are readily activated and deactivated in response to a variety of different stimuli which are not fully preventable in an epidemiological study. One important consequence may be that a true relationship between the quantity of excreted stress hormones and haemostatic activity is underestimated. Secondly, although statistically significant, the bivariate correlation coefficients between stress hormone levels and haemostatic parameters, as well as the differences in haemostasis across high and low night-time SNS and HPAA activity, were rather small and thus of questionable clinical significance. Moreover, absolute plasma levels of haemostatic parameters were well within normal ranges in subjects with high and low nocturnal SNS and HPAA activity. Although fibrinogen, D-dimer and PAI-1 are all viewed as intermediate endpoint measures for CAD even in subjects initially free of atherosclerosis [8–10], there is a spirited debate as to whether procoagulant changes are predictive for or simply reflect underlying atherosclerosis [28]. Thirdly, although plasma PAI-1 antigen and PAI-1 activity levels are highly correlated [29] and are both predictors of coronary events [30], measurement of PAI-1 activity instead of PAI-1 antigen might be more informative in terms of subjects’ haemostatic status. Fourthly, because of logistical reasons, the time window during which we sampled blood was rather wide given that PAI-1 [31] and fibrinogen [32], but not D-dimer [33], show a diurnal course with a steep rise during the morning hours. The circadian variability in haemostatic and neurohormonal activities complicates the interpretation of a correlation between the basal (nocturnal) neuroendocrine stimulus and the activated (morning) values of PAI-1.

Bearing these limitations in mind, we offer three clinical implications of our findings. First, short-term compared with prolonged catecholamine effects on haemostasis may be of different importance in cardiovascular disease. Increased shear stress to the atherosclerotic vessel wall with intense emotions [34] or physical exercise [35] may initiate the rupture of a so-called vulnerable plaque. Concomitant hypercoagulability might help accelerate coronary thrombus growth following plaque rupture [36]. On the other hand, sustained procoagulability might contribute to fibrin deposition within the vessel wall, thereby promoting atherosclerosis development [37]. Secondly, as mentioned above, there is a physiological nadir of plasma fibrinolytic activity (i.e. decreased t-PA and increased PAI-1) contrasted by a zenith in platelet activity and fibrinogen levels during the morning hours [38]. Morning hypercoagulability is mediated by different factors, among them a circadian catecholamine increase and catecholamine surge when assuming an upright posture [39]. Elevated morning levels of fibrinogen, PAI-1 and D-dimer in relation to night-time SNS and HPAA hyperactivity might add to the procoagulant state in the morning hours. Morning procoagulability is thought to be one important contributor to the empirically observed peak in acute coronary events within the first couple of hours after awakening [40]. Thirdly, the concept of allostatic load refers to the cost of wear and tear to the body as a consequence of the organism’s inefficient adaptation to environmental stressors [41]. Following this concept, individuals whose stress systems fail to recuperate during the night might be those with exaggerated clotting in the morning and perhaps increased coronary risk.

Taken together, the present study shows that overnight hyperactivity of SNS and HPAA is associated with relative hypercoagulability in the morning. Although the effects of SNS on haemostasis were to some extent independent of other health variables, effects of HPAA on haemostasis were related to parameters clustering with insulin resistance. It remains to be seen whether procoagulability in relation to night-time SNS and HPAA activity may predict some of the variance in the clinical manifestation of CAD in men.

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