Sick and tired: psychological and physiological aspects of work-related stress

de Vente, W.

Publication date
2011

Citation for published version (APA):
de Vente, W. (2011). *Sick and tired: psychological and physiological aspects of work-related stress*. [Thesis, fully internal, Universiteit van Amsterdam].

8 A longitudinal study on the haemodynamic profile associated with work-related stress: Evidence for phase-specific physiological markers*

Abstract

Background: Stress-theories recognise different phases in the process of physiological adaptation to chronic stress. This study investigated both cross-sectionally and longitudinally whether these phases could be distinguished on the basis of haemodynamic profiles associated with work-related stress. *Method***:** Sixty patients with work-related stress complaints were exposed twice to an acute psychosocial stressor consisting of mental arithmetic and public speech. Time between the first (T_0) and second (T_1) exposure was four months. Duration of complaints, dichotomised in 'non-chronic' (i.e., < 6 months) versus 'chronic' (i.e., > 6 months), was used as an indicator variable for the phase of the stress-adaptation process. Pre-stressor levels of physiological variables, indicative of basal activity, and physiological reactivity and recovery during the psychosocial stressor were compared between groups. Physiological adaptation was assessed via measurement of blood pressure, heart rate, cardiac output, vascular resistance, and heart rate variability. *Results*: At T_0, non-chronic patients demonstrated a higher cardiac output and tended to have a higher heart rate than chronic patients. At T_1, non-recovered, initially non-chronic, patients showed a reduction of cardiac output and an increase of vascular resistance in comparison to T_0. *Conclusion*: Non-chronic work-related stress complaints were associated with a higher sympathetic tone than chronic work-related stress complaints. In addition, within 5 to 10 months, a more progressed stage of haemodynamic adaptation, characterised by an elevation of the vascular tone, became apparent in the patients who developed chronic work-related stress complaints during the study.

Work-related stress results from prolonged exposure to work-related stressors and is associated with psychosomatic complaints, burnout complaints, and distress complaints (Bauer et al., 2006; Lindblom, Linton, Fedeli, & Bryngelsson, 2006; Schaufeli & Buunk, 2003). In addition, changes in the sympathetic and parasympathetic functions have been observed in association with work-related stress (e.g., Steptoe, Siegrist, Kirschbaum & Marmot, 2004; de Vente, Olff, van Amsterdam, Kamphuis & Emmelkamp, 2003; Vrijkotte, van Doornen & de Geus, 2000). Adaptation of physiological activity in response to stressful conditions is a dynamic process. Various stress process theories, including the general adaptation syndrome (Selye, 1975) and the model of allostasis (McEwen & Wingfield, 2003), recognise different phases in the adaptation process: i.e., a) physiological balance, when adaptive responses are characterised by rapid and complete recovery (i.e., allostasis), b) sustained activation, or an allostatic state, consisting of enduring physiological imbalance, and c) exhaustion, or a state resulting in allostatic overload, characterised by physiological change that may be irreversible and/or may have adverse health effects. In this study, it was investigated whether different cardiovascular profiles could be distinguished between different phases of this adaptation process among patients with chronic and non-chronic work-related stress.

Cardiovascular changes associated with stress are commonly studied in the context of the development of hypertension. In humans, the development of hypertension generally starts with the development of an enhanced sympathetic tone (Grassi, Quarti-Trevano, Dell'Oro & Mancia, 2008; Palatini & Julius, 2009). Palatini and Julius (2009) have recently reviewed the evidence supporting the haemodynamic changes in the process of developing hypertension. During the initial phase of developing hypertension, sympathetic hyperactivity is expressed as tachycardia, enhanced cardiac output, and reduced cardiac vagal activation. Subsequently, heart rate and cardiac output reduce and vascular resistance increases. The reduction of heart rate and cardiac output are ascribed to cardiac adaptations such as reduced affinity and number of β–adrenergic receptors in the heart and reduced stroke volume. The increased vascular resistance is attributed to vascular hypertrophy and sensitisation to vasocontrictive agents. According to the 'reactivity hypothesis' (e.g., Manuck, 1994), enhanced cardiovascular responsiveness to stressors is a marker of developing hypertension. Evidence for this hypothesis has indeed been reported (see for reviews: Gasperin, Netuveli, Diasda-Costa & Patussi, 2009; Treiber et al., 2003). In addition, delayed *recovery* is also hypothesised to be a risk factor for hypertension (e.g., Schwartz et al., 2003), and initial support for this hypothesis has been obtained (Moseley & Linden, 2006).

Substantial evidence indicates that, over time, an enhanced sympathetic tone (Grassi, Arenare, Quarti-Trevano, Seravalle & Mancia, 2009; Palatini & Julius, 2009; Seals & Dinneno, 2004) and/or enhanced cardiovascular *reactivity* (Manuck, 1994; Treiber et al., 2003) results into other adaptational processes that predispose to cardiovascular disease, including atherosclerosis and left ventricular hypertrophy. In terms of the model of McEwen and Wingfield (2003), the initial phase of sympathetic hyperactivity may be interpreted as an allostatic state, while the secondary adaptations caused by the sympathetic hyperactivity may be viewed as allostatic overload.

Longitudinal studies have shown that in the development of hypertension, within about 10-

20 years the tachycardia and enhanced cardiac output change into enhanced vascular resistance, whereas actual hypertension develops within about 20-30 years (Lund-Johansen, 1989; Palatini & Julius, 2009). In addition, studies investigating reactivity to and recovery from psychosocial stressors showed that increased reactivity and delayed recovery predicted hypertension in initially normotensive individuals over similar periods of time (Treiber et al., 2003).

Studies about stress and hypertension suggest that exposure to stressors accelerates the physiological adaptational processes. Thus far, human studies have provided limited insight in the exact temporal association between stressor exposure and haemodynamic changes. Landsbergis et al. (2003) concluded that induction of hypertension would occur after at least 3 to 5 years of exposure to work-related stressors. Hence, the transition from a state characterised by tachycardia and enhanced cardiac output to a state characterised by enhanced vascular resistance that precedes development of actual hypertension expectedly occurs within this timeframe. Animal studies demonstrated that exposure to an enduring stressor results in elevated basal levels of catecholamines and blood pressure within 1 to 4 months (Forsyth, 1969; Henry, Meehan & Stephens, 1967; McCarthy, Horwatt & Konarska, 1988). Such elevations are typical for the initial stage of developing hypertension. In monkeys, between 4 to 8 months of stressor exposure, basal blood pressure increased, while heart rate gradually decreased (Forsyth, 1969), suggesting that the transition from tachycardia to enhanced vascular resistance takes 4 to 8 months. Animal studies further indicate a sustained hypertension of several months in absence of stressors after previous exposure for 6 to 12 months (Forsyth, 1969; Henry et al., 1967). This finding suggests that another haemodynamic balance has been established after stressor exposure of 6 to 12 months, which apparently reverses poorly and signifies a state of allostatic overload.

The results of studies investigating reactivity patterns in reaction to stressor exposure are consistent with the above findings; they illustrate that enhanced sympathetic reactivity develops within twelve months of exposure duration. In humans, stressor duration of more than eight months results in increased cardiovascular reactivity (Lepore et al., 1997), whereas in rodents increased catecholamine reactivity to novel stressors develops within two months of daily stressor exposure (McCarthy et al., 1988).

In this study, patients absent from work because of work-related stress were exposed to a psychosocial stressor twice, i.e., at baseline and four months later. It was evaluated whether a) different cardiovascular patterns were observed between patients with a chronic (> 6 months) and non-chronic (< 6 months) complaint-history; b) physiological changes were observed when comparing non-recovered and recovered chronic and non-chronic patients. Since no systematic information about the exposure duration of the work-related stressor was available, we chose for a proximate variable, i.e., the duration of work-related stress complaints, as an indicator of 'phase in the stress-adaptation process'. The categorisation of more of less than six months of complaints duration was based on the indications from animal studies described above (Forsyth, 1969; Henry et al., 1967). Furthermore, this criterion is also applied in clinical practise to discriminate adjustment disorder from undifferentiated somatoform disorder (American Psychiatric Association, 1994). To assess

the haemodynamic profile, indices of sympathetic and parasympathetic activity were measured. Resting values as well as dynamics during a psychosocial stressor were examined.

For the cross-sectional comparison on the first measurement, elevated systolic and diastolic blood pressure as compared to normal values were predicted for non-chronic and chronic patients. While no group-differences were expected for blood pressure, differences were predicted on underlying haemodynamic indicators. In line with characteristics of the allostatic phase and the review of Palatini and Julius (2009), non-chronic patients were expected to exhibit an increased sympathetic drive, characterised by higher heart rate, higher cardiac output, and lower cardiac vagal activation in comparison to chronic patients. In line with a transition to the phase resulting in allostatic overload, chronic patients were expected to have higher vascular resistance than non-chronic patients. Increased *reactivity* and delayed *recovery* were expected for the predicted elevated measures.

For the longitudinal analysis, different results were expected between the chronic and initially non-chronic patients with respect to change between the first (T0) and second (T1) measurement. In addition, the direction of change was expected to be dependent on the health status at the second measurement (i.e., recovered or not). With regard to basal activity, it was predicted that initially non-chronic patients that did not recover, and thus became chronic patients at T1, would develop a new haemodynamic profile characteristic of progressed physiological adaptation to stress. More specifically, initially non-chronic patients that did not recover were expected to demonstrate sustained levels of elevated blood pressure, decreases of heart rate and cardiac output, and increases of heart rate variability and vascular resistance. Recovered non-chronic patients were expected to show normalisation of the haemodynamic profile, indicated by decreases of blood pressure, heart rate, and cardiac output, an increase of heart rate variability, and stable vascular resistance. For chronic patients (recovered or non-recovered), in accordance with having developed a new haemodynamic balance, we predicted that the elevated vascular resistance would not be reversed. Consequently, sustained elevated blood pressure and vascular resistance were expected for recovered and non-recovered chronic patients. For non-recovered chronic patients, vascular resistance may even increase, reflecting further progression of the shift towards more vascular resistance. For both recovered and non-recovered chronic patients, it was expected that heart rate, cardiac output, and heart rate variability would remain stable, reflecting a new allostatic balance. Alternatively, in non-recovered chronic patients these measures could further reduce (heart rate, cardiac output) or increase (heart rate variability), reflecting progression of physiological adaptation.

Changes in *reactivity* to the psychosocial stressor were expected in the same direction as changes in basal activity and adequate recovery was expected for measures demonstrating normalisation. Thus, for example, a reduction in reactivity and adequate recovery from the stressor was predicted for cardiac output in recovered non-chronic patients. Further, equal reactivity and recovery were predicted for sustained elevated measures, such as blood pressure and vascular resistance in chronic patients.

Method

Participants

Eighty-one patients with occupational stress, recruited through occupational health services (n = 61), general practitioners (n = 7), and by self-referral in reaction to advertisements (n = 13), entered the study. Sixty patients took part in the second measurement (T1).

The intake procedure consisted of a screening interview by telephone examining the presence of work-related stress complaints and a follow-up semi-structured diagnostic interview. The screening interview and semi-structured diagnostic were conducted by a clinical psychologist. During the semi-structured diagnostic interview, the psychologist assessed the complaint history, and administered a short version of the Composite International Diagnostic Interview (CIDI; World Health Organisation (WHO), 1997). In addition, the patient filled out the Beck Depression Inventory (BDI; Beck & Steer, 1967). Inclusion criteria were: 1) fulfilment of the symptoms of neurasthenia, i.e., continuous mental and/or physical fatigue and increased fatigability, and at least two other stress complaints out of the following: dizziness, dyspepsia, muscular aches or pains, tension headaches, inability to relax, irritability, and sleep disturbance; 2) a major role of (a) work-related stressor(s) in the development of complaints as judged by the occupational physician, the clinical psychologist, and the patient; and 3) presence of impaired daily functioning as indicated by (partial) sickness absence which had lasted at least two weeks but less than six months. Exclusion criteria were: 1) a primary diagnosis of major depression, social phobia, panic disorder, somatoform disorder other than undifferentiated, posttraumatic stress disorder, obsessive-compulsive disorder, hypomania, or psychotic disorders, assessed with the short version of the CIDI; 2) severe depressive complaints (i.e., conservatively defined as $\geq$ 25 on the BDI (Beck & Steer, 1987); 3) a traumatic event in the past six months; and 4) presence of an illness that is generally associated with fatigue (e.g., diabetes); 5) excessive alcohol and/or drug use; and 6) pregnancy. Patients received refund of their travel expenses and a printed report of their blood pressure and heart rate.

Procedure

The ethics committee of the Department of Psychology of the University of Amsterdam approved the research protocol and all patients gave written informed consent. The current physiological study was a part of a comprehensive project, in which effects of individual and group-Stress-Management Training (SMT) on mental health complaints, sickness leave, and physiological measures was evaluated. Data were collected at the start of the study (T0) and four months later (T1). Between measurements, patients received psychomedical care for their complaints; patients were randomly assigned to individual SMT (n = 27), group SMT (n = 28), or Care as usual (n = 26). Support for differential treatment effects on complaints was only found in the subgroup with lower depressive complaints (de Vente, Kamphuis, Emmelkamp & Blonk, 2008). Evidence for differential treatment effects on physiological measures was found for cortisol (Chapter 7). This study reports

about the cardiovascular outcomes at both measurements in association with complaints duration. The measurements at T0 and T1 consisted of filling out questionnaires about biographical characteristics, background variables, and work-related stress, and attending the laboratory for the psychosocial stress session.

Materials and Measures

Acute psychosocial stressor
The psychosocial stressor consisted of a speech task preparation (5 min.), a mental arithmetic task (5 min.), and a speech task (5 min.; see also Figure 1). Psychosocial stressor procedures have shown to induce subjective stress as well as changes in cardiovascular and endocrine parameters (e.g., Childs & de Wit, 2009; Izawa et al., 2008; Kirschbaum, Pirke & Hellhammer, 1993; Nicholson & van Diest, 2000; Olff, Mulder, The, de Leij & Emmelkamp, 1999; de Vente et al., 2003).

Psychosocial stress sessions took place between 13.30 and 16.30 hrs. Participants were asked to refrain from smoking, and coffee and tea consumption for at least one hour before the start of the session. During the psychosocial stress session, saliva was collected several times to determine neuroendocrine variables; these results are not presented in this study. The blood pressure cuff was attached to the non-dominant arm, and the arm remained at approximately heart level throughout the session. During the whole psychosocial stress session, participants remained seated. To prevent a pulse dampening, the Finapres was switched off for three minutes during the first and fourth saliva collection (i.e., SC1 and SC4).

Cardiovascular assessment
Heart rate and blood pressure were measured performing continuous measurement of finger blood pressure using a Finapres (Ohmeda Finapres type 2300^E, Blood Pressure Monitor) and the software Vsrrp98 (Molenkamp, 1998, University of Amsterdam, The Netherlands). Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiac output (CO), and total peripheral resistance (TPR) were calculated using the software Beatscope (version 1.1; Finapres Medical
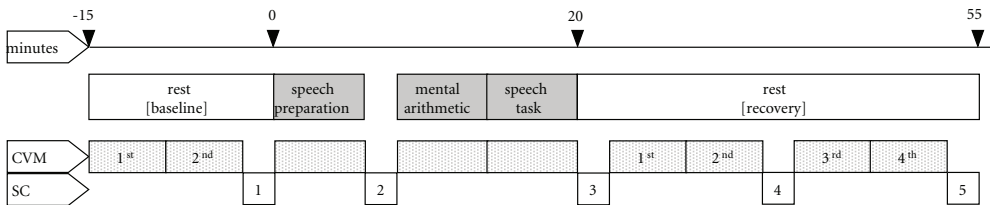

Figure 1: *Time diagram of the psychosocial stress session.*

Note: CVM: cardiovascular measurements; SC: saliva collection

Systems, 2002, The Netherlands). Cardiac vagal tone was determined by calculating beat-to-beat heart rate variability, using the root mean square of successive differences (RMSSD) of inter-beat intervals (IBI's): $\sqrt{(1/n \ \Sigma(IBI_i - IBI_{i-1})^2)}$. IBI's were defined as the number of milliseconds between peaks of subsequent systoles in the plethysmographic signal, analysed with Vsrrp98 (version 5.4b). The plethysmographic signal was inspected visually and artefacts and ectopic beats were removed. The obtained measure was called estimated heart rate variability (EHRV). Mean values of cardio-vascular measures were calculated per five minutes. Mean values during the second baseline phase of the psychosocial stress session were used as resting values. To investigate reactivity and recovery, the mean values of each of the stress-inducing tasks, and the first to the third recovery period, were related to the second baseline phase.

Work-related stress complaints, sickness absence, recovery, and control variables
Burnout complaints were measured with the Maslach Burnout Inventory-General Survey (MBI-GS; Schaufeli & van Dierendonck, 2000), which consists of 15 items regarding: Emotional exhaustion (5 items), Depersonalisation (4 items), and Professional competence (6 items). Items are scored on 7-point Likert scales (0 = never to 6 = always/daily) and average subscale scores are calculated. Higher scores reflect higher levels of work-related emotional exhaustion, depersonalisation/a cynical attitude towards work, and professional competence. Cronbach's alphas in the present sample were .82 for Emotional exhaustion, .81 for Depersonalisation, and .76 for Professional competence.

Distress complaints were measured with the Depression Anxiety and Stress Scales (DASS; de Beurs, van Dyck, Marquenie, Lange & Blonk, 2001) and with the subscale General fatigue of the Checklist Individual Strength (CIS; Beurskens, et al., 2000). The DASS comprise three subscales of 14 items each, referring to depressive, anxiety, and stress complaints. Severity of complaints during the past week is rated on 4-point Likert scales that range from 0 (not at all/never applicable) to 3 (very much/most of the time applicable). Higher scores represent higher levels of complaints. Internal consistency of the subscales in the present sample was high; Cronbach's alphas were .93 for Depression, .86 for Anxiety, and .93 for Stress. The subscale General fatigue of the CIS comprises eight items, which are scored on a 7-point Likert scale (1 = false to 7 = true). Lower scores indicate lower levels of fatigue. Internal consistency of the subscale is high (e.g. van der Ploeg, Kleber & van der Velden, 2000); Cronbach's alpha in the present sample was 0.91.

Duration of absenteeism at the start of the study was asked during the intake interview. Absenteeism during the study was assessed by self-reported hours of sickness absence per week. Recovery at T1 was based on the reported burnout and distress complaints. A recovered – non-recovered categorisation was defined on the basis of the median split of the sum of z-scores of all complaints measures (including the inversed score of Professional competence).

The control variables smoking, height, weight, and medication use were assessed by questionnaire.

Phase of stress-adaptation

Phase of the stress-adaptation process was operationalised by the duration of complaints. Complaints duration was measured using the following categories: a) < 3 months, b) > 3 and < 6 months, c) > 6 and < 12 months, d) > 12 months). For the present study, the variable was dichotomised into non-chronic (i.e., < 6 months) and chronic (i.e., > 6 months) duration.

Statistical analyses

Dropout analyses, group differences on demographic variables, control variables, complaints, and illness related variables at T0 were performed using Chi-square tests, Mann-Whitney U tests, and independent *t*-tests. Differences between measurements were analysed with McNemar tests for medication use, and with paired t-tests for complaint measures. Differences in complaints (T1), percentage work-resumption (T1), and change of complaints measures (i.e., T1 – T0) between recovered and non-recovered patients were analysed with independent t-tests.

Differences at T0 between chronic and non-chronic patients were investigated with ANOVA (resting values) and ANOVA for repeated measures (reactivity-recovery). As sex, age, Body Mass Index (BMI), and smoking are known to affect cardiovascular measures, these variables were added as covariates.

Longitudinal analyses to assess differences between recovered and non-recovered patients over measurements consisted of ANOVA's for repeated measures. First, in order to determine whether stratified analyses for chronic and non-chronic patients were justified, measurement (T0 versus T1) x group (chronic versus non-chronic) x health status at T1 (recovered versus non-recovered) interaction effects were examined. Second, when stratification was justified, ANOVA's for repeated measures investigating group differences between recovered and non-recovered patients were conducted for the chronic and non-chronic group separately. Within-group factors were 'measurement' (i.e., T0 and T1), and 'phase' (representing the phases of the psychosocial stress session). The between-group factor was health status at T1 (recovered versus non-recovered). Significant interactions were further analysed using simple contrasts, as implemented in the ANOVA for repeated measures. In this way, reactivity during the stress-inducing tasks and recovery after the stress-inducing tasks are related to baseline values. In addition to controlling for sex, age, BMI, and smoking, analyses were adjusted for treatment condition. For all ANOVA's for repeated measures, results were adjusted according to Greenhouse-Geisser's method when the assumption of sphericity was violated.

Outliers (i.e., values ± > 4 *SD*s of the mean for EHRV; ± >3 *SD*s of the mean for other variables) were excluded from the analyses (< 3.5%). Data of one patient was missing for CO, TPR, and EHRV due to equipment problems. Because of positively skewed data, EHRV was analysed using square-rooted values. Two-sided test were performed, applying a significance level of .10 for interactions and .05 for main effects. All analyses were conducted using SPSS 15.

Results

Drop-out analyses and baseline group-differences

Dropouts were 5.5 years younger than non-dropouts ($t(79)$ = -2.31, p = .023). No significant differences emerged between dropouts and non-dropouts for sex distribution, severity of any of the stress complaints, or any of the physiological measures, including values during rest and reactivity-recovery values (all p-values > .10).

Sample characteristics for the chronic and non-chronic group are presented in Table 1. The non-chronic group had a lower educational level, a lower score on Emotional exhaustion, and was absent during a shorter period than the chronic group. Educational level did not appear to be a confounding variable in the comparison of physiological characteristics between non-chronic and chronic patients; hence, the presented results are not adjusted for educational level. Use of medication use was modest at both measurements (beta-blockers T_0: n = 5, T_1: n = 4; antidepressants: T_0 and T_1: n = 3; anxiolytics: T_0 and T_1: n = 5). Medication use did not change significantly between T_0 and T_1 (p-values: 1.00). Furthermore, no between-group differences in medication use were found at either

Table 1: *Sample characteristics (N = 60); data are Ms / frequencies with SDs / % between parentheses and between-group test-results.*

	Non-chronic (n = 28)	Chronic (n = 32)	χ^2 / t [b]	p
Sex (male / female)	14 / 14 (50 / 50)	20 / 12 (63 / 37)	0.95	.330
Age (years)	40.46 (8.63)	44.59 (9.80)	-1.72	.091
Education (1 – 6) [a]	3.21 (1.29)	4.03 (1.51)	-2.23	.029
Employment (hrs/wk)	35.46 (5.47)	37.16 (4.09)	-1.43	.157
Body mass index (kg/m^2)	25.56 (4.50)	24.34 (3.25)	1.18	.243
Smokers (yes / no)	6 / 22 (21 / 79)	6 / 26 (19 / 81)	0.07	.796
Emotional exhaustion (range: 0-6)	3.81 (1.27)	4.47 (1.07)	-2.16	.035
Depersonalisation (range: 0-6)	2.62 (1.32)	3.05 (1.52)	-1.17	.249
Professional competence (range: 0-6)	3.86 (1.06)	3.81 (1.08)	0.18	.855
General fatigue (range: 8-56)	41.89 (11.34)	41.91 (8.52)	-0.01	.996
Depression (range: 0-42)	13.09 (9.14)	11.69 (7.07)	0.67	.506
Anxiety (range: 0-42)	9.33 (8.33)	7.41 (4.96)	1.10	.275
Stress (range: 0-42)	18.55 (9.52)	18.12 (8.36)	0.19	.851
Absenteeism (duration: wks)	6.44 (4.91)	11.91 (9.53)	-2.69	.009
Absenteeism T_0 (% of working hours)	86.36 (23.64)	88.65 (20.39)	-0.34 [c]	.731
Absenteeism T_1 (% of working hours)	35.16 (38.24)	43.08 (40.72)	-0.79 [c]	.431

Note: [a] 1 = Primary school – 6 = University; [b] Df's for χ^2 were 1, df's for t were 57/58; [c] Z-statistic of the Mann-Whitney U test.

measurement (non-chronic group: beta-blockers: T0: $n = 1$, T1: $n = 1$, antidepressants: T0: $n = 0$, T1: $n = 1$; anxiolytics: T0: $n = 1$, T1: $n = 2$; chronic group beta-blockers: T0: $n = 4$, T1: $n = 3$, antidepressants: T0: $n = 3$, T1: $n = 2$; anxiolytics: T0: $n = 4$, T1: $n = 3$; p-values >.095).

Complaints, absenteeism, and recovery

All work-related stress complaints, except Professional competence ($p = .609$), reduced significantly between T0 and T1 (p-values <.05). Mean complaints-scores at T1 for recovered and non-recovered patients are presented in Table 2. Values in the recovered group were similar to values found in healthy samples, while the non-recovered group still scored in the clinically elevated range (Huibers et al., 2004; Nieuwenhuijsen, de Boer, Verbeek, Blonk & van Dijk, 2003; Schaufeli & van Dierendonk, 2000). At T1, the recovered group had lower scores on all complaints and higher Professional competence than the non-recovered group (p-values <.01). Absenteeism in the recovered group (26.8%) at T1 was also lower than in the non-recovered group (51.1%; $Z = -2.36$, $p = .018$). For all complaints, observed reductions between T0 and T1 (increase for Professional competence) in the recovered group were larger than in the non-recovered group. Group-differences were statistically significant for General fatigue ($F_{(1,58)} = 10.88$, $p = .002$), Emotional exhaustion ($F_{(1,53)} = 5.56$, $p = .022$), and Professional competence ($F_{(1,53)} = 4.54$, $p = .038$).

**Table 2:** *Descriptive information [i.e., M (SD)] of complaints at T1 for recovered and non-recovered patients.*

	recovered	non-recovered
Emotional exhaustion (range: 0-6)	1.96 (1.28)	3.56 (1.32)
Depersonalisation (range: 0-6)	1.75 (1.37)	2.92 (1.27)
Professional competence (range: 0-6)	4.39 (0.85)	3.52 (0.95)
General fatigue (range: 8-56)	21.93 (9.59)	37.10 (10.21)
Depression (range: 0-42)	1.79 (1.90)	9.81 (7.51)
Anxiety (range: 0-42)	0.76 (0.99)	6.95 (6.98)
Stress (range: 0-42)	3.41 (3.20)	14.70 (6.70)

Effects of the acute stressor on physiological variables

At both measurements, all physiological measures increased during the stress-inducing tasks and decreased during the recovery-phase. *P*-values of the factor 'phase' in the ANOVA's for repeated measures were all ≤ .01. These outcomes provide support for stress-induction by the psychosocial stressor.

Chronic versus non-chronic patients at T0

Descriptive results of SBP, DBP, HR, CO, TPR, and EHRV of patients with chronic and non-chronic complaints at T0 are presented in Figures 2a-f. Table 3 demonstrates the test-results re-
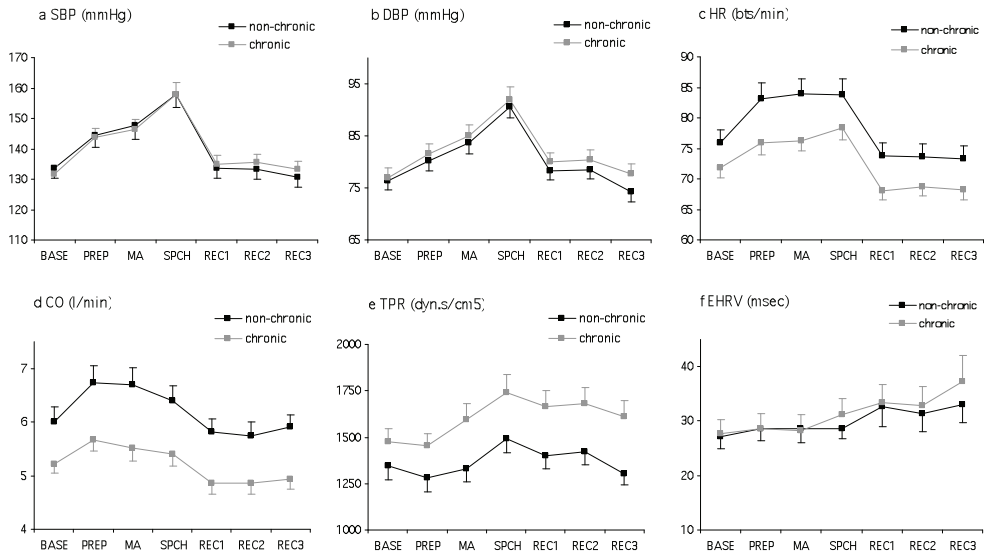
Figures 2a-f: *Means and standard errors of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), and estimated heart rate variability (EHRV; untransformed values) for chronic and non-chronic patients at T0.*

Note: BASE: baseline; PREP: speech-task preparation; MA: mental arithmetic; SPCH: speech-task; REC: recovery phase.

Table 3: *Test-results* comparing pres-stressor resting values (ANOVA), mean levels during the psycho-social stress session (ANOVA for repeated measures), and reactivity-recovery (ANOVA for repeated measures) of cardiovascular measures between chronic and non-chronic patients at T0.*

| | resting | | | mean level psycho-social stress session | | | reactivity-recovery | | |
| | group | | | group | | | group*phase | | |
	df's	F	p	df's	F	p	df's	F	p
SBP	1,54	0.41	.524	1,54	0.11	.746	2.8,153.5	0.59	.613
DBP	1,54	<0.00	.979	1,54	0.09	.766	3.2,174.1	0.43	.744
HR	1,53	0.98	.326	1,53	3.27	.076	2.7,142.6	2.06	.114
CO	1,53	2.34	.132	1,53	4.86	.032	3.2,167.7	1.10	.354
TPR	1,52	0.52	.619	1,52	5.07	.155	3.4,177.2	1.61	.183
EHRV	1,52	0.52	.476	1,52	2.66	.109	3.0,158.6	0.52	.671

Note: Group: mean difference between the chronic and non-chronic group; group*phase: interaction effect; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CO: cardiac output; TPR: total peripheral resistance; EHRV: estimated heart rate variability.
* Outcomes are adjusted for sex, age, BMI, and smoking.

garding group differences in cardiovascular measures at T0. Group-differences in resting values, mean values during the psychosocial stress session, and reactivity-recovery were investigated. Similar to resting values, mean values during the psychosocial stress session give, in absence of differences in reactivity-recovery, an indication of basal levels.

SBP and DBP were highly similar in both groups. However, non-chronic patients tended to have a higher mean HR during the psychosocial stress session (78.2 bts/min.) than chronic patients (72.5 bts/min.). Furthermore, non-chronic patients demonstrated a higher mean CO during the psychosocial stress session (6.2 l/min.) than chronic patients (resting: 5.2 l/min.). Chronic patients also demonstrated higher levels of resting TPR and mean TPR during the psychosocial stress session, but group differences were not statistically significant.

Change in recovered and non-recovered chronic and non-chronic patients
Statistically significant interaction effects regarding group (chronic versus non-chronic at T0) x health status (recovered versus non-recovered at T1) indicating different change between measurements for chronic versus non-chronic recovered versus non-recovered patients were found for all measures (p-values < .10), except for EHRV. Therefore, stratified analyses were performed for chronic and non-chronic patients for all measures, except for EHRV.

In Figures 3a-j, descriptive results of SBP, DBP, HR, CO, and TPR of recovered and non-recovered chronic and non-chronic patients at T0 and T1 are presented. In Table 4, test-results are listed regarding change between T0 and T1 of recovered and non-recovered chronic and non-chronic patients. Results of change between measurements (M) of values during rest and change between measurements (M) of mean levels during the psychosocial stress session provide information about change of basal levels, independent of state of recovery at T1. Results of group-differences in change of values during rest (M * group), and mean values during the psychosocial stress session (M * group) reflect differences between recovered and non-recovered groups in change of basal values. Finally, results of group-differences in change of reactivity-recovery during the psychosocial stress session (M * group * phase) inform about differences between recovered and non-recovered groups in change of reactivity-recovery.

Figures 3a-j: *Means and standard errors of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), for recovered and non-recovered non-chronic and chronic patients at T0 and T1.*
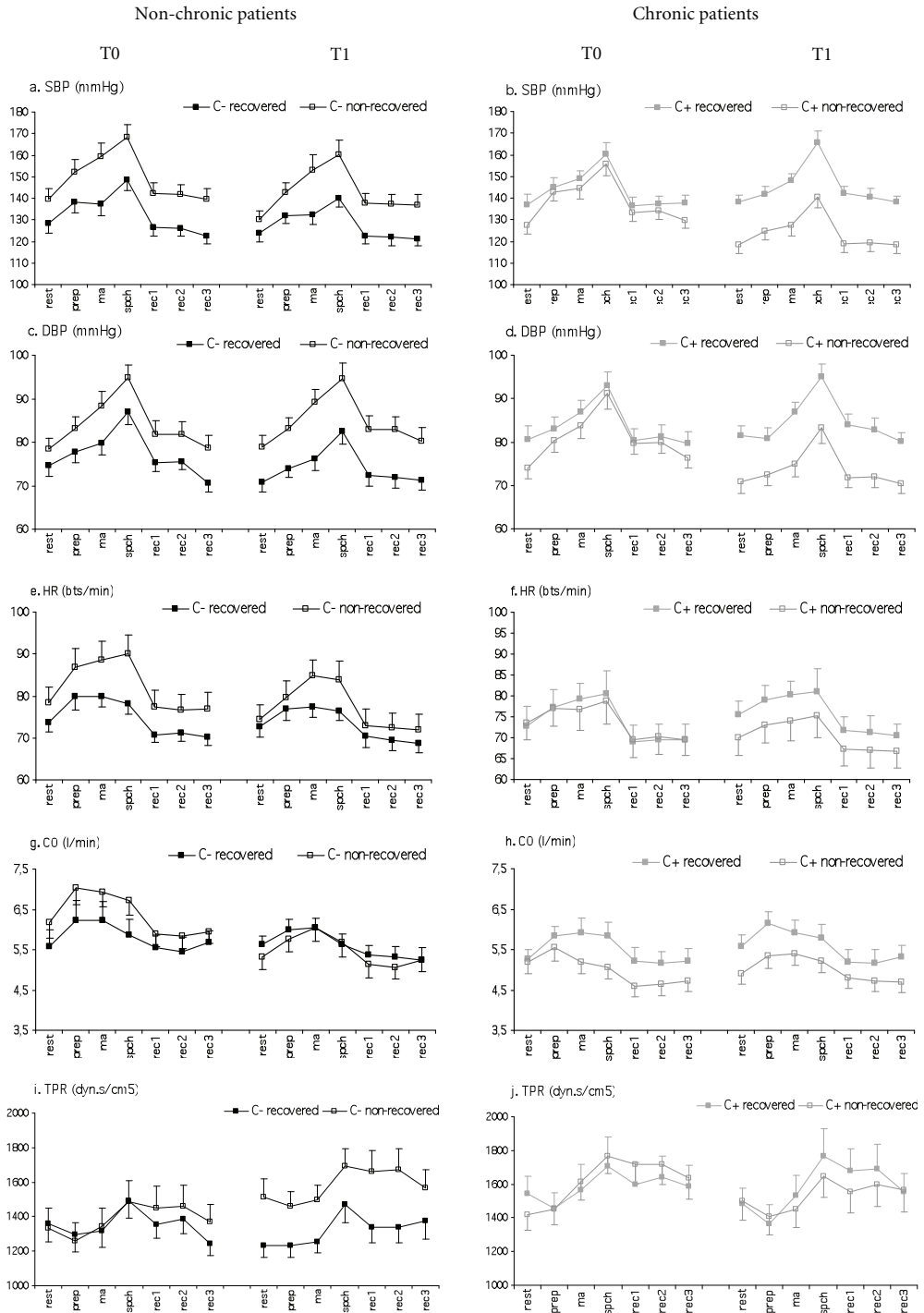
Non-chronic patients   Chronic patients

T0   T1   T0   T1

Note: BASE: baseline; PREP: speech-task preparation; MA: mental arithmetic; SPCH: speech-task; REC: recovery phase; C-: non-chronic group; C+: chronic group.

Table 4: *Test-results (ANOVA for repeated measures) of change between T0 and T1 of basal levels and reactivity-recovery between recovered and non-recovered chronic and non-chronic patients.*

	value during rest						mean level psychosocial stress session						reactivity – recovery		
	df's	M		M * group			df's	M		M * group			df's	M * group * phase	
		F	p	F	p			F	p	F	p			F	p
Non-chronic															
SBP	1,21	0.04	.852	1.36	.257		1,21	0.15	.700	0.15	.699		3.0,63.5	0.40	.754
DBP	1,21	0.22	.644	1.40	.250		1,21	<0.00	.995	1.35	.259		2.5,53.5	0.27	.818
HR	1,21	0.11	.742	0.33	.574		1,21	0.44	.513	0.67	.424		3.4,72.1	0.79	.517
CO	1,19	0.45	.513	3.74	.068		1,19	0.09	.774	4.50	.047		2.5,48.0	1.37	.266
TPR	1,20	0.05	.821	5.35	.031		1,20	0.03	.865	4.48	.047		2.3,45.1	1.12	.340
Chronic															
SBP	1,25	0.25	.625	2.68	.114		1,25	0.05	.825	8.75	.007		3.6,89.1	1.01	.400
DBP	1,25	0.57	.456	1.01	.324		1,25	<0.00	.964	4.13	.053		3.4,87.5	1.63	.182
HR	1,24	4.16	.053	7.10	.014		1,24	1.92	.179	4.76	.039		4.1,99.3	1.24	.298
CO	1,25	0.74	.398	7.65	.010		1,25	0.40	.535	0.65	.428		3.4,85.4	4.34	.005
TPR	1,24	<0.00	.947	2.24	.147		1,24	<0.00	.986	0.05	.819		3.3,80.3	2.62	.050

Note: Non-chronic: Non-chronic group; Chronic: Chronic group; M: factor measurement, i.e., T0 versus T1; group: factor group, i.e., recovered versus non-recovered; M*group, M*group*phase: interaction effects; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CO: cardiac output; TPR: total peripheral resistance.

Change of basal activity

Non-chronic patients

As predicted, various indications for a transfer towards a chronic profile were found among non-recovered initially (i.e., at T_0) non-chronic patients. Resting CO and mean CO during the psychosocial stress session (T_0: 6.4, T_1: 5.5 l/min.) reduced, and resting TPR and mean TPR during the psychosocial stress session (T_0: 1387.1, T_1: 1581.0 dyn.s./cm^5) increased considerably. In addition, support was found for sustained elevated SBP and DBP in non-recovered non-chronic patients, as no statistically significant change was observed between T_0 and T_1. Resting SBP and mean SBP during the psychosocial stress session (T_0: 149.0, T_1: 142.6 mmHg) remained elevated, as well as resting DBP and mean DBP during the psychosocial stress session (T_0: 83.8, T_1: 84.6 mmHg). Reductions of resting HR and mean HR during the psychosocial stress session (T_0: 82.1, T_1: 77.1 bts/min) were in the expected direction, i.e., conform a transition towards a chronic profile, though not statistically significant.

For recovered non-chronic patients outcomes primarily illustrated that, already at T_0, this group had more favourable cardiovascular profiles. Some support for normalisation was also found. Resting TPR, mean TPR during the psychosocial stress session (T_0: 1350.8, T_1: 1320.6 dyn.s./cm^5), and mean CO during the psychosocial stress session (T_0: 5.8, T_1: 5.6 l/min.) reduced over time. Furthermore, reductions of resting SBP, mean SBP during the psychosocial stress session (T_0: 132.5, T_1: 127.6 mmHg), resting DBP, mean DBP during the psychosocial stress session (T_0: 77.2, T_1: 74.1 mmHg), resting HR, mean HR during the psychosocial stress session (T_0: 74.7, T_1: 73.1 bts/min.) were in the expected direction, though not statistically significant. The observed values at T_1 indicated that blood pressure levels and heart rate were in the normal healthy range. Not supporting normalisation, however, was the highly similar value of resting CO at both measurements.

Chronic patients

In the recovered, initially (i.e., at T_0) chronic group, the majority of outcomes were in support of sustained elevated physiological activation. Specifically, resting SBP, mean SBP during the psychosocial stress session (T_0: 143.3, T_1: 144.9 mmHg), resting DBP, mean DBP during the psychosocial stress session (T_0: 83.5, T_1: 84.4 mmHg), resting HR, mean HR during the psychosocial stress session (T_0: 74.0, T_1: 75.6 bts/min.), and resting CO remained elevated, and even increased to a small extent. Only the decrease of resting TPR was not in the expected direction; the change was, however, not statistically significant.

In contrast to prediction, certain findings in the non-recovered chronic group suggested normalisation at T_1. In particular, mean SBP during the psychosocial stress session (T_0: 138.3, T_1: 124.0 mmHg) and mean DBP during the psychosocial stress session (T_0: 80.7, T_1: 73.6 mmHg) reduced over time. In addition, resting SBP and resting DBP reflected normal, healthy values at T_1. In accordance with progression of physiological adaptation to stress were the decreases of resting HR, mean HR during the psychosocial stress session (T_0: 73.6, T_1: 70.6 bts/min.), and resting CO. The

increase of resting TPR was also in the expected direction; the change was, however, not statistically significant.

Change of reactivity-recovery

In non-chronic patients, contrary to prediction, no differences in reactivity-recovery to the psychosocial stressor were found between the recovered and non-recovered group. In chronic patients, consistent with the predictions, reactivity-recovery of SBP, DBP, and HR were stable between measurements. For CO, differences between recovered and non-recovered chronic patients were found in reactivity to the mental arithmetic task (p = .013) and the speech task (p = .015), and in recovery during the first (p = .012) and second episode (p = .028). For TPR, differences between recovered and non-recovered chronic patients were found in reactivity to the mental arithmetic task (p = .026) and the speech task (p = .038), and in recovery during the first episode (p = .016).

As predicted, recovered chronic patients showed a reduction of CO-reactivity (baseline-mental arithmetic: T_0: 5.3-5.9 l/min., T_1: 5.6-5.9 l/min; baseline-speech task: T_0: 5.3-5.8 l/min., T_1: 5.6-5.8 l/min.). Additionally, recovered chronic patients demonstrated signs of improved CO-recovery at T_1 (recovery 1-baseline: T_0: 5.2-5.3 l/min., T_1: 5.2-5.6 l/min., recovery 2-baseline: T_0: 5.2-5.3 l/min., T_1: 5.2-5.6 l/min). Conform the predicted sustained physiological activation, recovered chronic patients showed an increase of TPR-reactivity (baseline-mental arithmetic: T_0: 1544.8-1564.9, T_1: 1485.3-1532.7 dyn.s./cm^5; baseline-speech task: T_0: 1544.8-1706.5, T_1: 1485.3-1767.8 dyn.s./cm^5). In addition, recovered chronic patients demonstrated less adequate TPR-recovery at T_1 (T_0 recovery 1-baseline: 1600.0-1544.8, T_1: 1678.7-1485.3 dyn.s./cm^5).

For non-recovered chronic patients, an increase in CO-reactivity was observed (baseline-mental arithmetic: T_0: 5.2-5.2 l/min., T_1: 4.9-5.3 l/min; baseline-speech task: T_0: 5.2-5.1 l/min., T_1: 4.9-5.2 l/min.), which is in accordance with sustained physiological activation, but does not reflect continuing progression of the transition to less sympathetic cardiac activation and more vascular resistance. Non-recovered chronic patients also demonstrated less adequate CO-recovery at T_1 (recovery 1-baseline: T_0: 4.6-5.2 l/min., T_1: 4.8-4.9 l/min., recovery 2-baseline: T_0: 4.6-5.2 l/min., T_1: 4.7-4.9 l/min). Contrary to predictions was the finding that non-recovered chronic patients showed a reduction of TPR-reactivity (baseline-mental arithmetic: T_0: 1419.9-1616.5, T_1: 1502.1-1449.2 dyn.s./cm^5; baseline-speech task: T_0: 1419.9-1768.5, T_1: 1502.1-1648.5 dyn.s./cm^5). In addition, a sign of more adequate TPR-recovery was found (T_0 recovery 1-baseline: 1718.8-1419.9, T_1: 1554.8-1502.1 dyn.s./cm^5).

Discussion

The aim of this study was to investigate whether patients that presumably had reached different phases in the physiological stress-adaptation process demonstrated different patterns in cardiovascular measures. The hypothesis that in presence of similarly elevated systolic and diastolic blood pressure, patients with non-chronic work-related stress complaints (i.e., non-chronic patients)

would demonstrate an increased sympathetic tone and patients with chronic work-related stress complaints (i.e., chronic patients) would demonstrate elevated vascular resistance was partially supported. At the first measurement, non-chronic patients demonstrated higher cardiac output and tended to have higher heart rate in comparison to chronic patients. Furthermore, between the first and second measurement, patients with initially non-chronic complaints that developed chronic complaints during the study indeed developed various haemodynamic characteristics of a more progressed phase of physiological adaptation to stress. More specifically, these patients demonstrated a decrease of cardiac output and an increase of vascular resistance, while blood pressure remained elevated. Because complaints of non-chronic patients were present for 1 to 6 months at the first measurement already, our results suggest that in humans under stress, a shift from an enhanced sympathetic tone towards an enhanced vascular tone occurs when the complaints are present for at least 5 to 10 months. It is interesting to note that this period of time is similar to the time span during which primates and mice that are exposed to stressors develop cardiovascular changes (Forsyth, 1969; Henry et al., 1967).

For the recovered non-chronic patients only few indications for normalisation were found, that is, reductions of both cardiac output and vascular resistance. This limited evidence for normalisation of physiological allostasis may be partly explained by the fact that the physiological values were already very close to, or within the normal range at the first measurement. Without impaired physiological balances, change is less likely to occur, because there is no necessity to improve homeostatic and allostatic balances.

Unexpectedly, signs of normalisation were found in chronic patients that were not recovered at the second measurment. Significant reductions over time were observed for levels of basal blood pressure and heart rate and for reactivity of cardiac output and vascular resistance. These findings imply that the physiological state of chronic patients is still reversible to some extent. Alternatively, reductions of basal heart rate and reactivity of cardiac output could indicate that physiological adaptation to stress was still progressing.

Initially chronic patients that were recovered at the second measurement, by contrast, demonstrated various signs of sustained elevated physiological activation. Basal levels of blood pressure, heart rate, and cardiac output remained elevated and vascular reactivity increased. Alternatively, the physiological activation observed at the second measurement may actually be reactivation, rather than sustained activation. A cause of physiological reactivation may be work-resumption during the study. Assuming the physiological activation as reactivation due to work-resumption would also explain the contrast in physiological activation between recovered and non-recovered chronic patients, because the extent of work-resumption was larger in recovered than in non-recovered chronic patients. An increase in workload may cause the elevated physiological activity through a higher activity level and/or through an increase of stress by more direct exposure to the stressor again.

Limited evidence was obtained for changed reactivity-recovery to an acute psychosocial stressor in association with different phases of physiological adaptation to stress. Based on the descriptive outcomes at the first measurement, elevated basal values generally went along with increased

reactivity, which is consistent with the reactivity hypothesis and with findings from animal re-search (e.g., McCarthy et al., 1988). Between measurements, only reactivity and recovery of cardiac output and vascular resistance changed in chronic patients. The association between the change between measurements of basal cardiac output and cardiac output reactivity was not in line with the predicted consistency between basal levels and reactivity-recovery, or with the findings at the first measurement. More specifically, recovered chronic patients demonstrated an increase of basal cardiac output between measurements and a reduction of cardiac output reactivity, while non-recovered chronic patients showed a reduction of basal cardiac output between measurements and an increase of cardiac output reactivity. Repeated exposure to the same psychosocial stress session may be suggested as an explanation for the lack of obtaining more evidence for enhanced reactivity at the second measurement, as familiarity with a stressor generally results in lower reactivity. However, this suggestion was not supported by the data. In fact, for most measures similar reactivity rather than lower reactivity was observed at the second measurement in comparison to the first (statistical outcomes not shown). A lack of finding differences in reactivity and recovery between the two measurements may be a consequence of two opposite effects in non-recovered, non-chronic and chronic patients: a decrease of physiological reactivity due to repeated exposure and an increase of reactivity due to sustained physiological activation.

Various observed physiological changes are consistent with the animal and human models of the development of hypertension (Forsyth, 1969; Henry, et al., 1967; Palatini & Julius, 2009). However, elevated vascular resistance was not clearly present in the group with a chronic duration of complaints at the first measurement. This may indicate that the categorisation of non-chronic and chronic patients based on duration of self-reported complaints was not optimal to distinguish the physiological features of different phases of the stress-adaptation process. A categorisation based on self-reported complaints may be less optimal when for example physiological change lags behind change of self-reported complaints, or the other way around. Discrepancy between reported complaints and physiological characteristics is not unusual (e.g., Mendez-Luck, Yu, Meng, Jhawar & Wallace, 2004; Sonnenschein et al., 2007). In future research about this topic actual exposure duration may rather be used to distinguish different phases in the physiological stress adaptation process than an indicator based on self-reported complaints.

The level of the sustained elevated blood pressure among recovered chronic patients is a reason for clinical concern, since it can be labelled as borderline hypertensive or pre-hypertensive (systolic: 138 mmHg, diastolic: 82 mmHg; American Heart Association, 2004). This observation suggests that chronic patients require more time than non-chronic patients to normalise their allostatic balances. A need for extended time to recover in chronic patients has consequences for the pace of reintegration. Alternatively, if the elevated physiological activation is actually a reactivation as a consequence of more direct exposure to the stressor (work) again, rather than sustained activation, it may be sensible during the process of reintegration to pay special attention to changing the work-environment, by for example changing of tasks and responsibilities, changing department, or even changing employment.

This study has a few limitations. First, physiological change between measurements was likely to be influenced by the degree of work-resumption at the second measurement. Although no indications for effect-modification of physiological change by the degree of work-resumption were found (results not shown), future research may strive to standardise factors like this to a larger extent. Second, instead of using heart rate variability based on the electrical heart signal as a measure of parasympathetic activity, variability of time between the peaks in the plethysmographic blood pressure signal was calculated. This is an indirect, and potentially confounded, measure of actual high frequency heart rate variability. However, the estimated variability outcomes demonstrated the expected pattern over time (i.e., reduction under stress-conditions, increase under recovery), with comparable differences between stress and recovery periods as reported by other groups (e.g., Bosch, de Geus, Veerman, Hoogstraten & Nieuw Amerongen, 2003; Kunz-Ebrecht, Mohamed-Ali, Feldman, Kirschbaum & Steptoe, 2003; Vrijkotte et al., 2000). Despite this support, interpretation of the estimated variability as a measure of parasympathetic activity should be done with caution.

In summary, the haemodynamic profile associated with non-chronic work-related stress complaints bears signs of a stronger cardiac sympathetic activation than the haemodynamic profile associated with chronic work-related stress. In addition, within 5 to 10 months the haemodynamic profile associated with non-chronic work-related stress demonstrates changes towards a progressed state of physiological stress adaptation, consisting of a reduction of cardiac output and an increase of vascular resistance. Our data suggest that careful attention is needed for the reintegration conditions of patients with chronic complaints, as they demonstrated close to clinically elevated values of blood pressure.

References

American Heart Association. (2004). 2004 *Heart and Stroke Statistical Update*. Dallas, Texas: American Heart Association.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders: 4th ed. (DSM-IV)*, Washington: American Psychiatric Association.

Bauer, J., Stamm, A., Virnich, K., Wissing, K., Müller, U., Wirsching, M. & Schaarschmidt, U. (2006). Correlation between burnout syndrome and psychological and psychosomatic symptoms among teachers. *International Archives of Occupational and Environmental Health*, *79*, 199-204.

Beck, A.T. & Steer, R.A. (1987). *Beck Depression Inventory*, Manual, New York: Harcourt Brace.

Beurskens, A., Bültmann, U., Kant, IJ., Vercoulen, J.H.M., Bleijenberg, G. & Swaen, G.M.H. (2000). Fatigue among working people: validity of a questionnaire measure. *Occupational and Environmental Medicine*, *57*, 353-357.

Bosch, J.A., de Geus, E.J.C., Veerman, E.C.I., Hoogstraten, J. & Nieuw Amerongen, A.V. (2003). Innate secretory immunity in response to laboratory stressors that evoke distinct patterns of cardiac autonomic activity. *Psychosomatic Medicine*, *65*, 245-258.

Childs, E. & de Wit, H. (2009). Hormonal, cardiovascular, and subjective responses to acute stress in smokers. *Psychopharmacology*, *203*, 1-12.

Dahlgren, A., Kecklund, G., Theorell, T. & Akerstedt, T. (2009). Day-to-day variation in saliva cortisol-relation with sleep, stress and self-rated health. *Biological Psychology*, *82*, 149-155.

de Beurs, E., van Dyck, R., Marquenie, L.A., Lange, A. & Blonk, R.W.B. (2001). De DASS: Een vragenlijst voor het meten van depressie, angst en stress [The DASS: a questionnaire for the measurement of Depression, Anxiety and Stress]. *Gedragstherapie*, *34*, 35-53.

de Vente, W., Kamphuis, J.H., Emmelkamp, P.M.G. & Blonk, R.W.B. (2008). Individual and group cognitive-behavioral treatment for work-related stress complaints and sickness absence: A randomized controlled trial. *Journal of Occupational Health Psychology*, *13*, 214-231.

de Vente, W., Olff, M., van Amsterdam, J.G.C., Kamphuis, J.H. & Emmelkamp, P.M.G. (2003). Physiological differences between burnout patients and healthy controls: blood pressure, heart rate and cortisol responses. *Occupational and Environmental Medicine*, *60*, 54i- 61i.

Finapres Medical Systems BV (2002). *Beatscope* 1.1. *User's guide*, Arnhem, The Netherlands.

Forsyth, R.P. (1969). Blood pressure responses to long-term avoidance schedules in the restrained rhesus monkey. *Psychosomatic Medicine, XXXI*, 300-309.

Grassi, G., Arenare, F., Quarti-Trevano, F., Seravalle, G. & Mancia, G. (2009). Heart rate, sympathetic cardiovascular influences, and the metabolic syndrome. *Progress in Cardiovascular Diseases*, *52*, 31-37.

Grassi, G., Quarti-Trevano, F., Dell'Oro, R. & Mancia, G. (2008). Essential hypertension and the sympathetic nervous system. *Neurological Sciences*, *29*, S33-S36.

Henry, J.P., Meehan, J.P. & Stephens, P.M. (1967). The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. *Psychosomatic Medicine, XXIX*, 408-432.

Huibers, M.J.H., Beurskens, A.J.H., van Schayck, C.P., Bazelmans, E., Metsemakers, J.F.M. & Knottnerus, J.A.

(2004). Efficacy of cognitive-behavioural therapy by general practitioners for unexplained fatigue among employees: A randomised controlled trial. *British Journal of Psychiatry*, *184*, 240-246.

Izawa, S., Sugaya, N., Shirotsuki, K., Yamada, K.C., Ogawa, N., Ouchi, Y., Nagano, Y., Suzuki, K. & Nomura, S. (2008). Salivary dehydroepiandrosterone secretion in response to acute psychosocial stress and its correlations with biological and psychological changes. *Biological Psychology*, *79*, 294-298.

Kirschbaum, C., Pirke, K.M. & Hellhammer, D.H. (1993). The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*, 76-81.

Kunz-Ebrecht, S.R., Mohamed-Ali, V., Feldman, P.J., Kirschbaum, C. & Steptoe, A. (2003). Cortisol responses to mild psychological stress are inversely associated with pro-inflammatory cytokines. *Brain, Behavior, and Immunity*, *17*, 373-383.

Landsbergis, P.A., Schnall, P.L., Pickering, T.G., Warren, K. & Schwartz, J.E. (2003). Life course exposure to job strain and ambulatory blood pressure in men. *American Journal of Epidemiology*, *157*, 988-1006.

Lepore, S.J., Miles, H.J. & Levy, J.S. (1997). Relation of chronic and episodic stressors to psychological distress, reactivity, and health problems. *International Journal of Behavioral Medicine*, *4*, 39-59.

Lindblom, K. M., Linton, S. J., Fedeli, C., & Bryngelsson, I. L. (2006). Burnout in the working population: relations to psychosocial work-factors. *International Journal of Behavioral Medicine*, *13*, 51-59.

Lund-Johansen, P. (1989). Central haemodynamics in essential hypertension at rest and during exercise: A 20 year follow-up study. *Journal of Hypertension*, *7*, S52-S55.

Manuck, S.B. (1994). Cardiovascular reactivity in cardiovascular disease: "Once more unto the breach". *International Journal of Behavioural Medicine*, *1*, 4-31.

McCarthy, R., Horwatt, K. & Konarska, M. (1988). Chronic stress and sympathetic-adrenal medullary responsiveness. *Social Science and Medicine*, *26*, 333-341.

McEwen, B.S. & Wingfield, J.C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*, 2-15.

Mendez-Luck C.A., Yu, H., Meng Y.Y., Jhawar, M. & Wallace, S.P. (2004). Over four million California adults age 45 and older have high blood pressure. Policy Brief, UCLA, Center for Health Policy Research. PB 2004-7, 1-8.

Molenkamp, E. VRSSP98, http://www2.fmg.uva.nl/ozi_psychologie/Software.htm (11th May 2005)

Moseley, J.V. & Linden, W. (2006). Predicting blood pressure and heart rate change with cardiovascular reactivity and recovery: Results from 3-year and 10-year follow-up. *Psychosomatic Medicine*, *68*, 833-843.

Nicholson, N.A. & van Diest, R. (2000). Salivary cortisol pattern in vital exhaustion. *Journal of Psychosomatic Research*, *49*, 335-342.

Nieuwenhuijsen, K., de Boer, A.G.E., Verbeek, J.H.A., Blonk, R.W.B. & van Dijk, F.J.H. (2003). The Depression Anxiety Stress Scales (DASS): detecting anxiety disorder and depression in employees absent from work because of mental health problems. *Occupational and Environmental Medicine,* 60S1, i77-i82.

Olff, M., Mulder, L.J.M., The, T.H., de Leij, L. & Emmelkamp, P.M.G. (1999). The psychobiological stress response in depressed patients compared to healthy controls. *Proceedings of the 29th Annual Congress of the EABCT*, p. 345, Dresden.

Palatini, P. & Julius, S. (2009). The role of cardiac autonomic function in hypertension and cardiovascular disease. *Current Hypertension Reports*, *11*, 199-205.

Penttilä, J., Helminen, A., Jarrti, T., Kuusela, T., Huikuri, H.V., Tulppo, M.P., Coffeng, R. & Scheinn, H. (2001). Time domain, geometrical and frequency domain analysis of cardiac vagal outflow, effects of various respiratory patterns. *Clinical Physiology*, *21*, 365-376.

Schaufeli, W.B. & Buunk, B.P. (2003). Burnout: An overview of 25 years of research and theorizing. In: M.J. Schabracq, J.A.M. Winnubst, C.C. Cooper (Eds.), *The handbook of work and health psychology* (2nd ed., pp. 383–429). Wiley, West Sussex, England.

Schaufeli, W. & van Dierendonck, D. (2000). *UBOS, Utrechtse Burnout Schaal. Handleiding.* [MBI-GS, Maslach Burnout Inventory – General Survey. Manual]. Swets & Zeitlinger B.V., Lisse, The Netherlands.

Seals, D.R. & Dinneno, F.A. (2004). Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. *American Journal of Physiology: Heart and Circulatory Physiology*, *287*, 1895-1905.

Selye, H. (1975). Implications of stress concept. *New-York State Journal of Medicine*, *75*, 2139-2145.

Sonnenschein, M., Mommersteeg, P.M., Houtveen, J.H., Sorbi, M.J., Schaufeli, W.B. & van Doornen, L.J. (2007). Exhaustion and endocrine functioning in clinical burnout: an in depth-study using the experience sampling method. *Biological Psychology*, *75*, 176-184.

Steptoe, A., Siegrist, J., Kirschbaum, C. & Marmot, M. (2004). Effort reward imbalance, overcommitment and blood pressure over the working day. *Psychosomatic Medicine*, *66*, 323-329.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*, *93*, 1043-1065.

Ursin, H. & Eriksen, H.R. (2004). The cognitive activation theory of stress. *Psychoneuroendocrinology*, *29*, 567-592.

van der Ploeg, E., Kleber, R.J. & van der Velden, P.G. (2000). Acute en chronische werkstress. Implicaties voor psychische gezondheid [Acute and chronic stress at work: Implications for psychological health]. *Gedrag & Gezondheid*, *28*, 172-184.

Vrijkotte, T.G.M., van Doornen, L.J. & de Geus, E.J.C. (2000). Effects of work stress on ambulatory blood pressure, heart rate and heart rate variability. *Hypertension*, *61*, 880-886.

World Health Organisation (1997). *Composite International Diagnostic Interview (CIDI). Manual* (ed. 2.1). Geneva, World Health Organisation.