WORK STRESS AND CARDIOVASCULAR DISEASE RISK

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SUMMARY AND DISCUSSION

The main research question of this thesis was whether chronic work stress is associated with increased risk for cardiovascular disease (CVD). Chronic work stress was measured by means of a questionnaire based on the Effort Reward Imbalance (ERI) model of Siegrist. This model defines chronically stressful experience at work by two components: 1) *imbalance*, the mismatch between high extrinsic effort spend and low reward received in occupational life and 2) *overcommitment*, a work related exhaustive coping style. Effort-reward imbalance at work has been found to predict new manifestations of coronary heart disease in Germany, Finland and England (Siegrist, Peter, Junge, Cremer & Seidel, 1990; Siegrist, 1996; Siegrist & Peter, 1994; Bosma, Peter, Siegrist & Marmot, 1998; Lynch, Krause, Kaplan, Tuomilehto & Salonen, 1997). The strongest associations with CVD mortality and morbidity are found for the interaction components, suggesting that high overcommitment, high extrinsic effort and low reward can be regarded as synergistically damaging.

Because overt cardiovascular disease is preceded by atherosclerosis, thrombosis and hypertension, high work stress should be associated with risk factors reflecting the development of these disease processes. The cross-sectional study described in this thesis focussed on two main groups of CVD risk factors: variables of the metabolic syndrome X cluster and ambulatory measured blood pressure, heart rate and cardiac autonomic reactivity to work related stressors. The main innovative approach in this thesis was the use of repeated assessments across a workweek of both metabolic syndrome X parameters and cardiovascular parameters, i.e. the measurement of the physiological responses to work-related stressors in "the real life work setting". Virtually all previous studies on the ERI model have 1) either used the standard epidemiological approach to look at the resting levels of the risk variables obtained during a single measurement in the laboratory or clinic (e.g. Peter et al., 1998), or 2) used short-term laboratory stressors to compare stress-evoked autonomic nervous activity between the various groups in the model (Siegrist & Klein, 1990).

Our choice for an ambulatory approach was doubly motivated. First, ambulatory monitoring may be the only alternative to study work stress in an ecologically valid way, because it is difficult or even impossible to envisage a laboratory test battery that could simulate the complex psychological factors involved in the work environment. Secondly, we hypothesised that work stress, in addition to repeated "hyperreactivity" to stressors at work, might be characterised by incomplete recovery in leisure time. Measuring repeatedly during an entire workweek allowed us to characterise various recovery processes in detail. For the

metabolic parameters, impaired recovery was expected to take the shape of a gradual increase of the risk factors in the course of the workweek, i.e. from the Monday morning via Wednesday morning to Friday morning samples. For blood pressure (BP), the difference between leisure time after work and leisure time during a non-workday was used as an index of recovery. The same measure was also obtained for heart rate (HR), root mean square of successive differences of inter beat intervals (RMSSD) and pre-ejection period (PEP), where the complete 24-hours data allowed further assessment of impaired recovery during sleep after work by contrasting it to the non-workday sleep. Implicit in our modelling of recovery was that the sleep levels during the weekend day could be regarded as an absolute baseline. If work stress would increase sleep levels during the weekend night (perhaps as a form of incomplete long-term recovery) such an effect would not be discriminable from an increase in the basal level of the variable.

The remainder of this chapter will first focus on the reliability and validity of this "real life" approach to work stress. Secondly, main outcomes with regard to the ERI model will be summarized and integrated with previous epidemiological findings. Finally, the limitations of this study are discussed and meaningful recommendations for future research will be attempted.

RELIABILITY AND VALIDITY OF THE "REAL LIFE" APPROACH TO WORK STRESSORS

Metabolic syndrome X

Chapter 3 presented the results of the metabolic and hemostatic risk factors, also known as the metabolic syndrome X cluster. A key element of this syndrome is insulin resistance with compensatory hyperinsulinaemia, glucose intolerance, and hypertriglyceridemia. Even in premorbid subjects, significant correlations are often found between insulin, triglycerides, the ratio between high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol and hemostatic factors like type 1 plasminogen activator inhibitor (PAI-1) antigen (Daae, Kierulf, Landaas & Urdal, 1993; Juhan-Vague, Thompson & Jespersen, 1993; Juhan-Vague & Alessi, 1997), and, although less strong, with blood pressure (Grandi et al., 1996; Reaven, 1991). The clear clustering of these variables was replicated in this sample as well as in a companion study on work stress in women (Riese, Vrijkotte, Meijer, Kluft & De Geus, 2001).

A number of previous studies have examined responses of metabolic syndrome X parameters to acute (Brindley, McCann, Niaura, Stoney & Suarez, 1993; Halford, Cuddihy & Mortimer, 1990; Jern et al., 1989; Larsson, Wiman,

Olsson, Angelin & Hjemdahl 1990; Niaura, Stoney & Herbert, 1992,) and chronic stress (Bjorntorp, Holm, Rosmond & Folkow, 2000; Räikkönen, Keltikangas-Järvinen, Adlercreutz & Hautanen, 1996; Siegrist, Peter, Georg, Cremer & Seidel, 1991). This is the first study, to our knowledge, that addresses a possible change in these variables across a single workweek. In our study we obtained blood samples under strictly standardised conditions on three workday mornings within a same workweek (Monday, Wednesday, Friday). Samples were obtained at the same time (8:00-9:00) directly before starting work. No evidence was found for an accumulative effect of the work week on any of the variables. With the caveat in mind that eating patterns or alcohol consumption somehow masked intra-week changes, our results do not provide evidence for changes in metabolic and hemostatic risk factors as a function of day of the week.

Although this repeated sampling strategy did not reveal the hypothesized accumulation effects, it had an important advantage. Test-retest reliabilities were high for most of the metabolic variables, despite PAI-1, tissue type plasminogen activator (t-PA) activity and total cholesterol showing substantial within week variation (Riese et al., 2001). By averaging over three blood samples, this study obtained a reliable estimate of individual differences in the overall levels of the risk factors, increasing our confidence in the work stress results.

Blood pressure and heart rate

The results of this cross-sectional study convincingly demonstrate the feasibility of ambulatory recording in this naturalistic work setting. Twenty-four hour registration of HR and wake time registration of BP produced reliable and valid information about individual differences in physiological responses to work stress. It also allowed detailed examination of recovery during leisure. Again in contrast to our expectations, the evidence for impaired recovery was not very strong. Only blood pressure during leisure after work was significantly higher than during leisure on a non-workday. As there were no BP values during sleep available, the question remains whether this incomplete recovery continued during sleep.

As expected, posture and physical activity proved important potential confounding factors because they affect all ambulatory cardiovascular parameters. The use of a diary and accelerometer made it possible to control for these confounders by selecting only sitting periods or by comparing groups after stratification for their posture/activity patterns. We were fortunate that this cross-sectional study population consisted of subjects who were doing mainly sedentary work and the imbalance and overcommitment groups did not differ in their posture patterns during the ambulatory registrations. Therefore, any cardiovascular

differences between the groups cannot be attributed to differences in activity patterns.

The test-retest reliability of absolute HR and BP during various periods of the day was high, independently of correction for posture and activity (see for instance Table 4.2 and Table 6.2). In addition to overall levels, a number of reactivity and recovery measures were obtained. For reactivity we used the difference between work and leisure periods and between work and sleep periods on the two workdays. This may appear confusing at first sight because the baseline measurements (sleep, leisure) follow the stress measurement. One could argue that small reactivity in fact reflected incomplete recovery during the ensuing 'baseline' period. However, as outlined earlier, we dealt with this problem by using the non-workday sleep or leisure level as an absolute baseline. Impaired recovery, therefore, should be reflected in a difference between the non-workday and workday leisure and sleep levels. Evidence was found for such impaired recovery for BP, but not for HR.

The test-retest reliability of ambulatory reactivity measures, like work minus sleep or awake time on a workday minus awake time on a non-workday, were much higher than reliability for reactivity indices found in the laboratory (Kamarck, Debski & Manuck, 2000; Manuck, 1994; Sherwood et al., 1997). The highest and most reliable reactivity scores were obtained by taking mean values during sleep on a workday as a "baseline" for the workday. The test-retest reliability of the recovery measures was slightly lower but still highly significant. Note, however, that the recovery values used the same baseline. For a more fair comparison to the test-retest reliability of the reactivity and the absolute values, the non-workday should have been measured twice.

The only less convincing results were obtained for HR values derived from the SpaceLabs ABP. Ambulatory HR is underestimated by an ABP device due to an effect of cuff inflation and changes in ongoing behaviour, the effect of which becomes more apparent during physical activity. Even in this sedentary population, mean daytime HR was underestimated by 4.0 beats/minute when obtained by HR-ABP (75.2 beats/minute) compared to HR-ECG (79.2 beats/minute). After stratification for physical activity, ABP-derived ambulatory HR can still be considered a reliable and valid measure in group comparisons. For the development and use of clinical criteria for ambulatory HR, however, we strongly recommend using HR derived from an ECG tracing rather than from a cuff based ABP device. HR results in this thesis were all based on the ECG (from the VU-AMS device).

Vagal tone and pre-ejection period

RMSSD, which can be obtained from a simple three lead ECG, appears to be an efficient index of vagal tone in large scale ambulatory studies. The comparison of RMSSD with heart rate variability in the respiratory range (RSA), either scored by peak-through or spectral methods, yielded satisfactory cross-method correlations. Likewise, ambulatory PEP appears to be a valid index of within subject changes in inotropic β-adrenergic cardiac tone that, because it is derived form non-invasive thorax impedance cardiography, is also feasible in epidemiology-scaled studies.

Average scores for both PEP and RMSSD over work, leisure, and sleep periods resulted in stable individual values with high test-retest correlations across days. In addition to overall levels, a number of reactivity and recovery measures were obtained similarly to those obtained for HR. No evidence was found for impaired recovery due to work stress for either PEP or RMSSD.

Test-retest correlations for the reactivity measures varied between .38 and .90 and were again higher than generally has been found for RSA or PEP using standardized laboratory stressors (Burns, Ferguson, Fernquist & Katkin, 1992; Fahrenberg, Schneider & Safian, 1987; Nelesen, Shaw, Ziegler & Dimsdale, 1999). This is in line with the idea that aggregating subjects' responses to repeated and different types of stressors (e.g. responses over several tasks and several sessions) increases reliability of the reactivity 'trait' (Kamarck, Debski, & Manuck, 2000; Manuck, 1994). The difference between the mean PEP and RMSSD levels during work and leisure with that of an 'ideal baseline' during sleep can be regarded as the aggregation of the responses to many different stressors during the day.

Table 7.1 summarizes the evidence for significant reactivity or recovery for the various variables of the metabolic syndrome and cardiovascular ambulatory monitoring. This table shows that, at group level, strong evidence is obtained for some form of reactivity to work for most variables, but that the evidence for impaired recovery, at least as defined in this thesis (see Figure 2.2), is much weaker. I now turn to the question to what extent do reactivity and recovery vary as a function of work stress.

Table 7.1 *Summary of the findings concerning intra week effects (across time of day/day of week). ++ indicates increase, — indicates decrease, 0/+ indicates a trend, 0 indicates no effect.*

	Accumulation during the workweek	
Syndrome X	Monday to Wednesday	Monday to Friday
Insulin	0	0
Glucose	0	0
TG	0	0
HDL/LDL ratio	0	0
TC	0	0
Fibrinogen	0	0
PAI-1	0	0
t-PA activity	0	0
t-PA antigen		0

	Reactivity			Incomplete recovery	
Ambulatory parameters	Δ work - leisure	Δ work - sleep	Δ workday - Non workday	Δ workday sleep - non-workday sleep	Δ workday leisure - non-workday leisure
SBP	++	n.a.	++	0	++
DBP	++	n.a.	++	0	++
HR	0/+	++	++	0	0
RMSSD	0/–	– –	0	0	0
PEP	0	– –	0	0	0

Note TG=triglycerides, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TC=total cholesterol, PAI-1=plasminogen activator inhibitor-1, t-PA=tissue plasminogen activator, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, RMSSD=root mean square of successive differences, PEP=pre-ejection period , n.a.=not applicable.

EFFECTS OF WORK STRESS ON CVD RISK

Selected subscales or proxy measures of imbalance or overcommitment, like forced job change in combination with frequent interruptions or low promotion prospects, have already been found to be associated with hypertension or high lipid levels (Siegrist, Matschinger, Cremer & Seidel, 1988; Siegrist et al., 1991; Siegrist 1996; Peter & Siegrist, 1997). In our study population, we made the a priori decision to use *only* the total imbalance component and the total overcommitment component to index work stress. No attempt was made to break down the full scales and examine any subscale of these two components. Thus, high imbalance was defined as an imbalance score > 1 (those subjects put more extrinsic effort in their job than reward received) and subjects scoring in the upper tertile of overcommitment were regarded as high overcommited persons. These

last criteria may look arbitrary, but the evidence in previous studies of adverse effects on cardiovascular health was based on comparison of controls to 'cases' whose scores exceeded precisely these thresholds (Peter et al., 1998; Matschinger, Siegrist, Siegrist & Dittmann, 1986)

Metabolic syndrome X

The question was whether subjects with high chronic work stress are at higher risk for CVD by having an unfavourable blood profile. Multivariate analysis showed that only overcommitment was significantly associated with the cluster of metabolic and hemostatic risk factors. The strongest association was found between overcommitment and an impaired fibrinolytic system, as reflected in decreased t-PA activity and increased PAI-1. Although not univariately significant, all other variables also showed more unfavourable levels in the overcommitted, reflected in a higher compound syndrome X index (*Chapter 3*).

Blood pressure

In the WOLF study (Peter et al., 1998) a combination of high effort (frequency of being distressed by time pressure, responsibility, overtime work, and increasing responsibility during the past 12 months) and low occupational reward (esteem and reciprocal support, occupational status control) was associated with hypertension. No associations were found between BP and overcommitment. These findings were supported and extended in the present study. Imbalance was associated with higher systolic blood pressure during work and leisure time on all three measurement days (*Chapter 4*), whereas overcommitment was not. Taken the solid prognostic value of ambulatory BP, which is now widely regarded to be higher than "classical" clinical resting BP (Clement, De Buyzere & Duprez, 1994; Khattar et al., 1999; Mancia & Parati, 2000), this suggests that increased BP may be an important pathway by which effort-reward imbalance influences the risk for myocardial disease.

Heart rate, vagal tone, pre-ejection period

Our results strongly suggest that imbalance may affect blood pressure by increasing heart rate reactivity to the work setting. Ambulatory registration of heart rate indicated that imbalance was related to increased heart rate during work, that even extended into leisure (*Chapters 4 and 5*). These results were very robust, and observed on both workdays. On Thursday, high HR even extended into the first hour of sleep. As the underlying causes for exaggerated stress-related HR reactivity, four possibilities should be distinguished: an exaggerated increase in cardiac sympathetic tone, an exaggerated decrease in vagal tone, a lower basal

vagal tone that amplifies a normal sympathetic response, and a higher overall sympathetic tone that amplifies the effect of vagal withdrawal. The latter two are based on the phenomenon of accentuated antagonism (Aprigliano, Rybin, Pak, Robinson & Steinberg, 1997). In this study we did not find support for deviant cardiac sympathetic nervous system tone or reactivity (indexed by absolute level and change in PEP respectively) in high imbalance subjects. Figure 4.2 in chapter 4 is suggestive of enhanced vagal reactivity to stress but, in view of the large standard deviations for RMSSD, a larger sample size may be needed to prove this. Strong evidence, however, was provided for lower basal vagal tone in subjects high in imbalance. Significant lower overall vagal tone (indexed by RMSSD) was obtained on all three days during all periods of the day. According to the principles of accentuated antagonism subjects with an imperfect 'vagal brake' may show exaggerated HR reactivity in response to increased cardiac sympathetic activity, even if their sympathetic response is not exaggerated itself.

Various studies have shown that low vagal tone is associated with high blood pressure (Huikuri et al., 1996; Julius, 1991; Tsuji et al, 1996), including the present thesis, and predictive evidence now exists to support a causal role for vagal tone (Sing et al., 1998). Apart from being instrumental for hypertensive risk, both high HR and low vagal tone have been shown to be risk factors for myocardial disease in their own right (Liao et al., 1997) through their effects on electrical stability (Fetsch, Reinhardt, Wichter, Borggrefe & Breithardt, 1998) and coronary flow (Beere, Glagov & Zarins, 1984). In addition to blood pressure, the underlying deficit of low vagal tone may be instrumental for effort-reward imbalance to influence the risk for myocardial disease.

In contrast to these results for imbalance, overcommitment did not effect BP, HR or RMSSD. Moreover, a shorter PEP and an unexpected *smaller* PEP decrease from sleep to awake periods with a *lower* overall PEP lability, indexed by standard deviation in PEP, were found in the overcommitted. Overcommitment has evolved from a critical analysis of the global pattern of type A behaviour and reflects the individual's way of coping with work demands. Individuals who score high on overcommitment are competitive, impatient, have a high need for approval and are unable to 'let go'. In line with this conceptualization we found subjective sleep quality to be lower in the high overcommitment group. Overcommitment strongly resembles the behaviour style that precedes vital exhaustion (Falger & Schouten, 1992), a mood state that is characterized by excess fatigue, a decrease in energy and feelings of helplessness or the sense of a loss of control (Appels & Mulder, 1989). Vital exhaustion is a powerful predictor of first myocardial infarction (Appels & Mulder, 1988; Falger & Schouten, 1992). It is tempting to interpret the ambulatory PEP profile of overcommitted subjects as

indicative of a chronic increase in cardiac β-adrenergic tone coupled to a loss of ionotropic responsiveness to acute stress-induced (nor) epinephrinergic reactivity. This decrease in the dynamic regulation of cardiac contractility would be in line with the concept of 'allostatic load' (McEwen, 1998; McEwen, 2000) and was explained in terms of down-regulation of cardiac β-adrenergic receptors.

IMBALANCE AND OVERCOMMITMENT INTERACTION: THE SYNERGY IS ACROSS VARIABLES NOT WITHIN

The various results of the work stress analyses reported in this thesis are summarized in Table 7.2. Taken together, the table clearly shows that "real life" work stress has "real life" physiological consequences. At first glance, however, the results do not give a consistent pattern of the relation between perceived chronic work stress and the studied risk factors.

***Table 7.2**: Summary of the findings with imbalance and overcommtiment. ++ indicates increase, — indicates decrease, 0/+ indicates a trend, 0 indicates no effect.*

Blood Parameters	**Overcommitment**			**Imbalance**		
Insulin	++			0		
Glucose	++			0		
TG	0			0		
HDL/LDL ratio	0			0		
TC	0			0		
Fibrinogen	0			0		
PAI-1 antigen	++			0		
t-PA activity	—			0		
t-PA antigen	0			0		
Ambulatory parameters	Level	Reactivity	Incomplete recovery	Level	Reactivity	Incomplete recovery
SBP	0	0	0	++	0	0
DBP	0	0	0	0	0	0
HR	0	0	0	0	++	0/+
RMSSD	0	0	0	—	0/–	0
PEP	—	—	0	0	0	0

Note: TG=triglycerides, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TC=total cholesterol, PAI-1=plasminogen activator inhibitor-1, t-PA=tissue plasminogen activator, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, RMSSD=root mean square of successive differences, PEP=pre-ejection period.

Most surprisingly none of risk factors were highest in subjects scoring high on overcommitment and high on imbalance, i.e. the group with the most work stress. Put differently: no evidence was found for an interaction between high imbalance and overcommitment such that the possible synergistic effect of these two stressful experiences evoked the largest increases in metabolic syndrome X risk factors or ambulatory cardiovascular and autonomic reactivity measures.

The correlation between the two work stress components was low (r=0.29) indicating that they do indeed measure two different aspects of perceived work stress. Possibly, statistical power was too low to detect an overcommitment by imbalance interaction, because of the low number of subjects in the high-high group. But even trends in this direction were not observed in the results from the ambulatory or the metabolic syndrome X parameters. An alternative explanation is that imbalance and overcommitment truly do not interact on any single risk factor but that they exert their detrimental effects through different physiological pathways.

To explore this idea further, a factor analysis was used to combine the results from ambulatory registration and blood sampling. From the ambulatory data, the values during sleep (leisure for blood pressure) were used to represent basal levels, the difference between sleep and work (leisure and work for blood pressure) were used to represent reactivity. The metabolic syndrome X cluster was represented as Insulin, LDL/HDL-ratio and PAI-1. Only values > 0.50 are presented. Table 7.3 shows the 5 components that were distracted after varimax rotation. These data suggest that the syndrome X parameters load on a separate component and represent a different physiological pathway than the ambulatory parameters. Secondly, within the ambulatory set PEP and PEP reactivity constitute a separate component. That HR reactivity is mainly dependent on basal vagal tone and changes in vagal tone is again supported as these three parameters formed a single component. Blood pressure and blood pressure reactivity, however, loaded on different components. The position of imbalance and overcommitment was assessed by correlating the factor scores with imbalance and overcommitment scores. Subjects with high scores on effort-reward imbalance are characterized by higher HR reactivity to work. The main toxic component of imbalance appears to be lower overall vagal tone. High overcommitted subjects are characterized by higher metabolic and hemostatic risk in combination with a reduction in PEP variation that may reflect reduced capacity for dynamic regulation of cardiac inotropic function. Both phenomena, high hemostatic risk and reduced inotropic dynamics, could be explained by a chronic increase in sympathetic nervous system activity (Aarons, Nies & Gerber, 1983; Björntop, 1999; Eisenhofer, Lambie & Johnson, 1985; Teger-Nilsson,

Larsson, Hjemdahl & Olsson, 1991). Since the crucial aspect of vital exhaustion and overcommitment is loss of control associated with a submissive, defeat reaction, additional effects of a chronic increase in cortisol must not be discarded. In addition, a number of interactions exist at various levels of the hypothalamic-pituitary and sympathetic-adrenal medullary axes (Sapolski, Romero, & Munck, 2000; Kvetnansky et al., 1995).

Because overcommitment might cause incomplete unwinding after work, we expected this component, and in particular the overcommitment by imbalance interaction, to be associated with the largest effects in physiology, leading to an accumulation of work-related fatigue towards the end of the workweek. As noted above, however, no evidence was found for a gradual accumulation across the work week in the high overcommitment and/or high imbalance group. However, the increased basal levels could be the result of incomplete recovery on a larger time scale.

Table 7.3 *Overview of the integration of the results (factor analysis) and the relation with imbalance and overcommitment (correlations with factor-scores).*

	Component				
	1	2	3	4	5
HR_{sleep}	0.55				
$\Delta HR_{work\text{-}sleep}$			0.57		
$RMSSD_{sleep}$			0.77		
$\Delta RMSSD_{work\text{-}sleep}$			0.83		
PEP_{sleep}				0.90	
$\Delta PEP_{work\text{-}sleep}$				0.91	
$DBP_{leisure}$	0.88				
$\Delta DBP_{work\text{-}leisure}$		0.90			
$SBP_{leisure}$	0.86				
$\Delta SBP_{work\text{-}leisure}$		0.94			
Insulin					0.69
PAI-1					0.78
LDL/HDL-ratio					0.79
	Correlation coefficients				
Imbalance	0.11	0.10	**0.34**	0.04	0.02
Overcommitment	-0.10	0.11	0.13	**-0.27**	**0.23**

Note: HDL=high density lipoprotein cholseterol, LDL=low density lipoprotein cholseterol, PAI-1=type 1 plasminogen activator inhibitor-1, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, RMSSD=root mean square of successive differences, PEP=pre-ejection period.

Taken together, we conclude from the summary in Table 7.3 that the significant interaction of imbalance and overcommitment found at the level of the disease endpoints, like acute myocardial infarction, sudden cardiac death or stroke, is not reflected in the individual risk factors. Instead the interaction arises across these risk factors, not within. Imbalance and overcommitment each influence different risk factors, but together these risk factors exert a clear synergistic effect on CVD risk.

LIMITATIONS

The main limitation of this study is that the assessment of imbalance in our study was based on a single measurement. It did not take into account the duration of imbalance, effort/reward in previous jobs, or possible effects of periods of unemployment. These factors may complicate the interpretation of our self-reported imbalance measure (Johnson, Steward, Hall, Fredlund & Theorell, 1996). However, all our subjects were between 35 and 55 of age and the average number of years of service in our study was 21.2 years, meaning that most subjects developed their job career at the same computer company and had not been unemployed for several years. Item analyses showed very little variance in two of the three aspects of reward: subjective experience of low status control (including job instability) and low economic reward (income). These aspects, however, largely determine intensity of stressful experience and are the most important variables in predicting cardiovascular disease (Johnson et al., 1996; Kirschbaum et al., 1995; Lynch et al., 1997; Siegrist, 1996). So, in this homogenous white-collar population, effort-reward imbalance depended mainly on low esteem reward which may explain why it failed to associate more strongly with some of the CVD risk factors.

A second limitation is the large time interval between metabolic and ambulatory monitoring. The first subjects were monitored 6 months after blood collection but the last subjects were monitored after 21 months. Although long term test-retest reliability of the blood parameters may be high, the direct comparison of blood data with the ambulatory data should be viewed with this limitation in mind.

The third limitation was the restriction of ambulatory BP monitoring to the wake period. There are many advantages to night time blood pressure measurement, not the least of which is that they would have given more insight in recovery processes of BP. BP after all was the only variable to show evidence of impaired recovery. Because our subjects were already equipped with the ECG/ICG VU-AMS recorder we decided to not further increase the burden for the study

participants, who were measured on three whole days in a single week, by adding a second device to their nightstand.

For similar reasons we did not collect additionally urinary or salivary cortisol. This is a fourth limitation. There is growing evidence that the hypothalamic pituitary adrenal axis, associated with cortisol secretion, is a central component of chronic stress related states. The relation between overcommitment and the metabolic syndrome X clearly supports this idea. Salivary measurements of the diurnal variation in cortisol would have made a valuable asset to this data-set.

Finally, this thesis represent only a single study with a "mere" 120 subjects. I am fully aware that replication is the work horse of science. Only one comparable study has examined work stress according to the ERI model in an ambulatory setting (Hanson, Godaert, Maas & Meijman, 2001). This study measured ambulatory cardiac vagal tone during a normal workday in a group of 70 subjects, working as health professionals or as office clerks. They found a decreased vagal tone in the high overcommitment group, but not in the imbalance group. In this thesis a decrease in vagal tone was found in the imbalance group, but not in the overcommitted. There is no ready explanation for these differences, but they clearly signal caution in the interpretation of the results of any single study.

FUTURE RESEARCH

Causality

In our subjects, the mood questionnaire showed that subjects scoring high on imbalance also scored high on negative mood (depression, anxiety and anger). It is unclear to what extent an unfavourable psychological profile precedes work stress or is a consequence of it. Thus, the causality of the association between self-reported work stress and the unfavourable risk profile found in our subjects remains to be established. Two future strategies could resolve this issue. In genetic epidemiology, the measurement of work stress and CVD risk factors in genetically related subjects is used to test directional causality versus models that allow an underlying factor (same genes) to influence both work stress and CVD risk (Duffy & Martin, 1994). This approach may be very valuable here. Secondly, or perhaps in combination, longitudinal follow-up of changes in work stress paired to changes in the pace of increased risk with ageing may help resolve the problem of causality.

Gene environment interaction

A stress-diathesis model of disease susceptibility emphasizes the interaction of dispositional characteristics of the individual (e.g. genetic predisposition) and the

exposure to contextual determinants of disease (environment) in disease progression. Altered gene function or hormone-induced gene expression as a consequence of exposure to certain environmental factors, like chronic stress, could speed up the progression of atherosclerosis, hypertension or other risk factors for CVD. Support for this idea that the "wrong" genes combined with the "wrong" environment is deleterious in the development of stress-related cardiovascular disease is found in animal studies (Ely, Caplea, Dunphy, Smith, 1997; Harshfiled & Grim, 1997; Kaplan, Petterson, Manuck & Olsson, 1991) as well as in humans. (Light et al., 1999; Everson et al., 1997). At this moment it is possible to genotype individuals for quantitative trait loci (QTLs) influencing risk factors for CVD, like blood pressure, fibrinogen, PAI-1 and t-PA. Associations have been found, for instance, between the 4G/5G polymorphism of the PAI1 gene, certain polymorphisms of the t-PA gene and myocardial infarction (Eriksson, Kallin, Van 't Hooft, Bävenholm & Hamsten, 1995; Van der Bom et al., 1997). An intriguing question is whether these genotypes show interaction with work stress as defined under the ERI model. Understanding the genetic and environmental contributions and their possible interactions to cardiovascular risk clearly should help focus intervention and prevention programmes on that part of the population most clearly at risk.

Women

So far, most studies relating work stress to CVD have been conducted in men. Unfortunate little attention has been paid to the association between work stress and the risk for CVD in women. In this study the analyses were also restricted to men, because the number of women was too small for gender-specific statistical analyses. There are a number of reasons to expect significant gender specific associations. There may be different effects of stress in general on the male and female physiological system (e.g. see the different clustering of the syndrome X between men and women in Riese et al., 2001). Furthermore, women may have different expectations regarding work and career than men, which could be reflected in lower sensitivity for effort reward imbalance. In contrast, impaired recovery may be a larger problem for women as a consequence of the fact that women more often have the double load by combining work and children. Intriguingly, the WOLF study (Peter et al., 1998) included 2656 males and 2088 women and showed lower imbalance scores for women paired to higher overcommitment scores. Only by including women in work stress studies will the physiological consequences of such gender differences be revealed.

MAIN FINDINGS

1. Ambulatory monitoring in 'real life' work settings is feasible and gives reliable estimates of the cardiovascular level, reactivity and recovery of HR, BP and autonomic cardiac tone.
2. Effort-reward imbalance, characterized by putting more extrinsic effort in the job than occupational rewards received, is associated with higher heart rate reactivity during work and directly after work, with higher systolic blood pressure during work as well as during leisure time and with an overall reduced cardiac vagal tone.
3. Overcommitment, a way of coping with work demands which is characterized by competitiveness, impatience, to have a high need for approval and being unable to 'let go', is associated with an unfavourable metabolic syndrome X blood profile. The strongest associations were found in the fibrinolytic system, as reflected in decreased tissue-type plasminogen activator (t-PA) activity and increased type 1 plasminogen activator inhibitor (PAI-1) antigen.
4. Overcommitment is further associated with decreased 24-hour levels of ambulatory pre-ejection period (PEP), a decreased reactivity in PEP from sleep to wake and decreased variability in PEP. This pattern points to a decreased range for cardiac inotropic regulation, possibly due to β-receptor down-regulation.
5. The interaction of imbalance and overcommitment is not within but across physiological systems.