Prolonged cardiac activation, stressful events and worry in daily life.

Pieper, S.

Chapter 7: *General Discussion*

The main focus of the present thesis was to study prolonged cardiac effects of stressful events and worry in daily life. In two review papers a theoretical background as well as a review of studies was provided that served as a basis for the empirical study presented here. For the empirical papers we measured cardiac activity in the laboratory and in daily life in a group of high school teachers. Additionally, the participants reported on their experience of stressful events and worry. This resulted in three empirical papers investigating the effects of stressful events and worry on immediate and prolonged cardiac activity, as well as cardiac activity during sleep. This chapter starts with a summary of the main results reported, followed by an overview of the status quo of the prolonged activation hypothesis, in light of which we will discuss our findings. Additionally, this discussion is divided in various subsections focussing on immediate cardiac effects of worry, the possible role of content of worry, the lack of evidence for the suggestion that worry mediates the prolonged cardiac effects of stressors, the prolonged effects of worry, the absence of evidence for an association between worry and average levels during daytime or during sleep, as well as the importance of measuring trait worry in future studies. Furthermore, we discuss methodological considerations and conclude with recommendations for future research.

OVERVIEW OF FINDINGS

This thesis starts by describing a theoretical framework in which prolonged physiological activation before or after stressors is regarded as an important factor in the development of cardiovascular disease (CVD; see Chapters 2 and 3). This contadicts the more conventional reactivity hypothesis which emphasizes activation during stressors and overlooks cardiovascular (CV) activation that continues beyond the presence of a stressor. Hence, the reactivity hypothesis focuses on states of such short duration that, even if frequent and intense, they alone cannot explain the development of chronic pathogenic states leading to CV disease.

In contrast, prolonged activation is viewed as an important element in several disease theories, such as Selye's (sustained preparation causes exhaustion (1)), Ursin's (sustained activity (2)), McEwen's (allostatic load (3)). Indeed, recent studies have suggested that prolonged duration of physiological activity during recovery phases relates to several CVD outcomes (Chapters 2 and 3). However, we argue that most psychological processes postulated to mediate the process of stressors resulting in prolonged activation are insufficient and vague, with the exception of perseverative cognition (4, 5). As a result of this insufficiency, only a small amount of CV stress research has explicitly addressed the relation between stressors and prolonged activity, and not many studies have implicitly tested the issue of possible psychological mediators.

In Chapter 2, we review real life (ambulatory) studies testing the hypothesis that various stress sources can have prolonged CV effects. The review is focussed on real life studies for two reasons. Firstly, a summary and discussion of laboratory findings have been done elsewhere. Secondly, ambulatory field studies enable measurement over a larger time scope, which is crucial for the ecological validity of studying prolonged activity. We conclude that these studies indeed suggest that several stress sources, including discrete and chronic stressors, negative affective states and negative emotional dispositions, are related to prolonged CV activity, although the evidence is still very modest. Additionally, we conclude that potential

psychological mediators of stress-related prolonged activity such as perseverative cognitions were largely overlooked in the reviewed studies.

In Chapter 3 we focus on perseverative cognition as a potential psychological mediator, because it has the capacity to chronically activate the cognitive representation of stress-related content, thereby chronically inducing physical activation. Perseverative cognition is manifested in phenomena such as worry, rumination and anticipatory stress. However, still far from sufficient, evidence is emerging that links these phenomena to physiological activation, including cardiovascular, endocrinological and immunological parameters.

To further investigate the role of perseverative cognitions, we conducted an ambulatory study in which we measured subjects' HR and HRV in daily life during two periods of 48 hours (see Methods Chapters 4, 5 and 6). The participants also completed an hourly set of questions concerning, among others their stress experience and worry behavior during daytime, and each morning after waking up they reported on their stress experience and worry behavior during the night and the nocturnal sleep period. These measurements were preceded by a short laboratory session in which two neutral laboratory stressors were completed to assess the subject's cardiac recovery, as well as a hostility interview. Although the studies reported in Chapters 4, 5 and 6 were partly based on the same data, these reports used such different statistical approaches that the analyses could not be combined (see below).

Following our theoretical framework, we hypothesized that in daily life increased HR and decreased HRV occur not only during stressors, but also during periods of worry in absence of a stressor (Chapter 4). Indeed, our findings indicate that worry has substantial independent effects on HR and HRV in addition to the effects of stressful events. These effects were independent of the effects of biobehavioral variables and psychological traits. The findings of this study extend the findings of laboratory studies of worry by showing that worry during daily life also leads to cardiac effects. Furthermore, we found that these cardiac effects were most pronounced for work-related worry and worry about anticipated future stress. Conventional stress measurements are restricted to the past and neglect anticipation of future stressors. Also, studies measuring anticipatory stress are rare. As such, in the current scientific discourse on including duration of the stress response, the latter finding underscores the importance of studying anticipated stress as source of cardiac effects.

In Chapter 5, we elaborate on these findings by hypothesizing that increased HR and decreased HRV are not only due to concurrent stressful events, but are also effected by stressors occurring before and by stressors that are anticipated. Additionally, we expected that worry would mediate at least part of these effects. The results indicate that stressors have prolonged cardiac effects up to one hour. We did not find evidence for the mediating role of worry, although worry alone displayed even longer lasting prolonged effects, i.e. up to two hours. Since biobehavioral factors, psychological traits and laboratory recovery after neutral stressors cannot explain this association, we reason that unconscious perseverative processes might have mediated the prolonged effects of both stressors and worry.

In Chapter 6 we attempt to extend these findings by showing that accumulated stressful events and worry influence mean levels of daytime and sleep HR and HRV. We argued that the possibility of stressful events or worry inducing

nocturnal physiological arousal is significant for health. Sleep is a typical period to recover from daily life physiological activation. If physiological arousal generated by stress does not stop during sleep it leads to a situation not unlike being exposed to a virtually permanent stressor and this might eventually cause serious health problems. An earlier study by our group (6) showed that worry mediated the prolonged effects of stressors on daily and nocturnal HR and HRV. Furthermore, worry displayed an additional effect on daily and nocturnal HR and HRV independent of those of stressors. The study described in Chapter 6 was designed to replicate these findings, but failed to do so. We did find, though, that a tendency to worry and a more incomplete HR recovery to neutral laboratory stressors were associated with increased daytime and sleep HR, stressing the importance of measuring both variables in future studies.

The results presented in this thesis are discussed below.

STATUS OF THE PROLONGED ACTIVATION HYPOTHESIS

By addressing various elements of the prolonged activation model Chapters 2 and 3 contribute valuably to the field of stress-research. Firstly, we summarized studies that tested the predictive effect of prolonged activation on CVD. Secondly, we were the first to summarize ambulatory studies that tested the prolonged effects of various stress sources. Lastly, possible psychological mechanisms were summarized that might be responsible for the relation between stressors and prolonged activation and focussed specifically on the possible role of perseverative cognitions.

An increasing number of studies have found that the duration of stress response even after simple laboratory stress tasks is predictive of physiological changes. Attenuated blood pressure (BP) recovery after psychological tasks predicted increased BP values in the clinic 3 years afterwards, while reactivity values did not (7). Faster HR recovery after a mental arithmetic and a speech task predicted less thickness of the carotid artery intima-media complex (an index of preclinical atherosclerosis) 2 years later (8). Surprisingly, HR and pre-ejection period (PEP) during these stressors (i.e. reactivity) were not related to carotid thickness, which suggests that elevated reactivity is not necessarily related to negative outcome with regards to atherosclerosis. Furthermore, increased (>195 mm Hg) systolic BP 2 minutes after a laboratory exercise test leads to an increased risk for acute myocardial infarct 13.1 years later, even after correction for cardiac reactivity values. Delayed cardiac recovery is seen as a measure of impaired autonomic nervous system functioning, more specifically impaired vagal tone (9), which seems to suggest that this imbalance is a crucial mediating factor causing these disease states. Thus, in contrast to the reactivity model, which received critical comments on its limited predictive value (10, 11), slow recovery indeed has predictive value with regard to CVD (see above and Chapter 2).

Additionally, in contrast to the limited laboratory-to-life generalizability (12, 13) of cardiovascular reactivity measurements, there is evidence that even small recovery periods in the laboratory are reproducible in daily life. One study suggests that attenuated laboratory BP recovery predicts ambulatory BP levels during daytime and sleep (14). Additionally, another study (15) shows that BP, cardiac output and total peripheral resistance during recovery were related to ambulatory BP independent of resting BP and reactivity values. Our findings presented in Chapters 4 and 5 are in line with these results and contribute to them by showing that

attenuated laboratory HR recovery is predictive of HR levels during 15 minute periods, as well as mean levels during daytime and during sleep. However, not all studies consistently show that recovery is dominant over reactivity in predicting CVD outcomes. For instance, Moseley and Linden (16) found that BP and HR recovery to psychological laboratory tasks in normotensives predicted ambulatory BP and HR 3 years later, but not 10 years. On the other hand, reactivity to these tasks predicted ambulatory HR and BP 3 years later, as well as systolic BP 10 years later. In light of this, and in comparison with the excess amount of reactivity studies, the stability of the recovery effect needs to be replicated in future research.

Apart from the predictive value of delayed recovery, several studies have found psychophysiological factors which lead to physical CVD risk factors that may be mediated by delayed recovery. There is cross-sectional evidence that increased obesity (17, 18), a family history of cardiovascular disease risk (19), social isolation and poor mental health (20) are related to poor diastolic BP recovery in the laboratory. Delayed HR recovery after a treadmill test was observed in rehabilitated cardiac patients who reported an increased level of depressive symptoms (21), which is also a CVD risk factor (22). On the other hand, in line with findings that increased positive affect is associated with reduced risk of mortality (23, 24) reduced mortality (25) and reduced risk of physical disease (26), one study showed that high reporting of positive affect was related to faster BP recovery (27).

Steptoe and colleagues have published a number of papers indicating that the important CVD risk factor of low social economic status (SES) seems to be mediated by delayed recovery and CVD. After behavioral laboratory tasks, subjects with low SES (versus those with high SES) showed less complete cardiovascular recovery of BP and HRV (28), total peripheral resistance (29), HR and pro-inflammatory cytokine interleukin-6 (30), systolic BP (20). Moreover, one study found that delayed HR, BP, PEP and SV recovery values were typical for older subjects and even more pronounced in older subjects with low SES, indicating that high SES can be protective against the effects of increasing age on cardiovascular condition (31). Additionally, delayed BP recovery predicted increased carotid intima-media thickness 3 years later, but only in subjects with low SES (32). Although these studies provide some insight into the possible physiological route from these factors to CVD, we believe that our main comment that the possible psychological route from these factors to delayed recovery is still unclear (formulated in Chapter 2 (5)) remains valid. This is discussed below.

Apart from the above, the psychological concept of need for recovery has received increasing attention. It generally refers to the need for a stress-free period to recuperate from experienced stressors or mental load for example during a work day and to refill ones resources. This "psychological unwinding" is considered to be essential for well-being, work satisfaction and work engagement (33). A more demanding or longer lasting stressful situation will consume more resources and will lead to increased need for recovery. A situation where resources are continuously reduced, will lead to more effort to compensate for lack of resources while trying to adequately work. This accumulative situation is thought to lead to symptoms such as fatigue, disturbances of mood, physiological changes and eventually, burnout, exhaustion, sleep problems and disease (34). Concepts similar to this psychological recovery have been prospectively linked to CVD. Need for recovery was related to more self-reported CVD after 32 months (35). Lack of recovery during free

weekends was related to elevated risk of CVD death after 25.6 years (36). Recently, Geurts and Sonnentag (34) have explicitly formulated processes that can hinder the recovery from load, such as prolonged exposure to work demands and cognitive processes, including perseverative cognitions. However, their research mainly focuses on the psychological effects, but not the direct prolonged physiological effects of related concepts such as ability to psychologically detach from work (37), mental relaxation (38) and non-work experiences that are accompanied by positive feelings such as competence (39). It seems fruitful for future research to study prolonged physiological effects. Moreover, in our view (Chapters 2 and 3) the concept of perseverative cognition is theoretically better suited for a psychological process that can explain prolonged effects of stressors, since it explicates a direct trigger of physiological activation in the form of a mental representation of a stressor, as well as the repeated activation of this representation, and therefore the associated physiological activation and stress experience.

CARDIAC EFFECTS OF WORRY

To be a possible mediator, worry should have cardiac effects independent of the effects of stressors. Several laboratory studies show that worry is associated with simultaneous (that is, during worry itself) physiological effects (Chapter 3). Only one previous study (6) indicates that worry is related to toxic cardiac levels in daily life and results show that worry especially worry duration is related to elevated HR and decreased HRV during daytime, as well as during the nocturnal sleep period. For the study presented in Chapter 3 we measured timing and duration of stressful events more precisely and could therefore accurately match these with simultaneously occurring cardiac activity. Thus, the results replicate and extend the previously attained findings (6) by showing that worry is related to simultaneous HR and HRV levels, and independent from the effects of stressful events. Additionally, the results indicate that worry duration is longer than stressors duration, which indicates that the net cardiac effects of worry might be even more substantial than those of stressful events. Based on these findings we conclude that worry is a noteworthy source of cardiac elevations, even lasting longer than those of stressors.

The results of this study are consistent with experimental findings of worry (Chapter 3) and show that these latter findings are potentially generalizable to the real world. Real world studies, however, are less adequate in clarifying which of the characteristics of worry are actually responsible for its cardiac effects. Only a few laboratory studies have attempted to do this so far. Oathes et al. (40) found that worry was associated with larger corticospinal motor responses than an arithmetic task with high mental load. The authors reason that this finding supports the role of action preparation in worry; this is in line with the idea that perseverative cognitions continuously induce physiological preparation for action intending to change or escape an unwanted situation ('fight – flight') and this action preparation is thought to be associated with physiological activation, which explains why worry induces more physical effects than mere mental activity that is needed for a mental arithmetic task. On the other hand, Verkuil et al. (41) from our group recently found that while worry elicits higher HR and lower HRV than during relaxation, cardiac levels are similar to those elicited during a cognitive problem solving task concerning moral dilemmas that were not personally relevant. This finding seems to contradict the findings by Oathes et al. (40). The cognitive problem solving task used by

Verkuil et al. (41) however, was designed to resemble cognitive activity during worrying (jumping from one problem to the next) without inducing negative emotions related to personal relevance of the presented problems. As such, this task was more complex and therefore required more mental effort than the mental arithmetic task used by Oathes et al. (40). Verkuil et al. (41) conclude the feature of 'prolonging mental load' instead of the prolonged emotional aspects to be responsible for the adverse effects of worry on health.

CONTENT OF WORRY AND CARDIAC EFFECTS

Instead of focussing on the characteristics of worry, we have concentrated on the content of worry. Results reported in Chapter 4 show that cardiac effects were more pronounced during work-related worry and worry about anticipated future stress than during worry about other topics, which is a new finding in the field. The effects of work-relatedness of worry suggest that the reported effects of work stress on CV health (42) might be – at least partially – mediated by immediate effects of worry about work. It leaves unexplained, however, why work-related worries have a stronger cardiac effect than worries related to other problems. The second content-related finding, concerning future-related worries, underscores the importance of measuring anticipatory stress, by indicating that worry about future stressful events is superior to worry about other topics, by inducing a mean HR that is 4.79 beats/min higher. Thus, worrying about stressful events that might happen in the future can cause considerable anticipatory cardiac activation irrespective of its actual later occurrence. This finding is particularly relevant since there is evidence that this is possibly the most frequently occurring form of worry (43), thus again enlarging its effects. This aspect has been neglected in conventional stress measurements (life event questionnaires, work stress, daily hassles), which are restricted to stress in the past neglecting anticipated stressors. The question why future-related worry has stronger effects than past-related worry is perhaps easier to answer than the earlier question about work-related worry. Worry about the future concerns fear, while worry about the past mostly concerns regret and sadness. Fear is known to trigger stronger physiological effects than regret and sadness (44). This finding seems to urge future studies not only to re-evaluate the reactivity principles but also to include stressors that are feared although they need not actually occur.

In Chapter 5 however, we found no cardiac effects of the expectation of a stressor in the succeeding hour. Some factors might explain this non-finding. Firstly, it is possible that the stressors expected in the next hour were not intense enough to elicit cardiac responses. Secondly, it is possible that the future issues that the subjects worried about were not expected in the succeeding hour, but might appear further in the future or might not even appear at all, indicating that "the succeeding hour" was too limited a time-frame or even a falsely designed frame to measure physiological effects. Moreover, stressors expected in the next hour might have already coped with to a large extent, resolving much of the fear that might be responsible for the cardiac worry effects found in Chapter 4. Interestingly, there is experimental evidence supporting this idea. Anticipation of a concrete and unavoidable stressor induced less intense physiological changes than worrying: Hofmann et al. (45) showed that worry was related to higher HR, lower HRV and greater left frontal activity than during baseline, relaxation or anticipation of a stressful speech task. However, anticipation induced higher skin conductance levels

than worry. Nevertheless, since worrying about the future induces such pronounced cardiac effects (Chapter 4) and is a central element of perseverative cognition (62), future studies should focus on the physiological effects of expecting a stressor and apply a less limited time-frame.

A study by Smyth and colleagues (46) showed that anticipating a stressor in the next hour elevated salivary cortisol levels, which seems to contradict our results. However, as discussed in Chapters 4, 5 and 6, participants in our study reported less stressors and worry than other studies, including Smyth's (46). This points to another explanation: too few stressors were expected in the next hour in this sample. Although our results indicate that worrying about possible stressful events in the future can cause considerable anticipatory cardiac activation irrespective of its actual later occurrence, it is clear that there is a need for replication studies to assess the nature of these effects and their generalizability to other subject groups.

WORRY DOES NOT MEDIATE EFFECTS OF STRESSORS

Contrary to our expectations, we did not find evidence that worry mediates substantial effects of stressors, neither concurrent effects (Chapter 4), effects up to one hour (Chapter 5) nor effects on daytime or night-time levels (Chapter 6). At least one previous ambulatory study (6) found that worry duration mediated the effects of stressors on daytime and nocturnal cardiac levels. Results from at least two laboratory studies suggest that slow BP recovery after emotional stress is mediated by worry or rumination (47, 48). The present study could not confirm these findings. However, we argue that worry is always about stressful events, whether in the past, present or future, and certainly not only about those stressful events confined to the limited time periods in the computer diaries. Thus, worry can be about one or more stressful events possibly occurring in a virtually endlessly larger timeframe than the periods in which we measured actually occurring stressors. In fact, it is likely that by measuring worry episodes we measured the (mediated) aggregated effects of those stressful events which typically involve the most relevant stressors for an individual. Furthermore, the small number of stressful events actually measured were general events, including neutral as well as some emotionally upsetting ones. We reason that subjects worried about events that were mainly emotionally upsetting – otherwise why worry about them? Together, these arguments seem to explain why worry did not mediate the effects of stressful events in these studies. In Chapter 6, we further argue that when stressor experiences in daily life are more numerous, and the definition of worry much broader, as in our study (6), it is possible that mediating effects of worry will be found.

WORRY SHOWS PROLONGED CARDIAC EFFECTS

Initially, we expected worry to have a simultaneous and possibly mediating effect but not a prolonged effect of itself. To our surprise, worry displayed a prolonged cardiac effect that lasted up to two hours which was not due to emotions and life style factors, recovery to psychological laboratory tasks or even worry at a later time point. This is an intriguing new result, for several reasons.

Firstly, the finding that worry is related to simultaneous cardiac elevation (Chapter 2) does not indicate a causal relationship, i.e. it may still be reasoned that high HR and low HRV cause worry and stress perceptions, instead of the other way around. On the other hand, the finding that worry is related to cardiac levels up to

two hours is specifically relevant for the perseverative cognitions model, since it is a *prospective* finding, indicating that worry episodes *precede*, and thus likely induce, high HR and low HRV.

Secondly, the finding of prolonged effects of worry seem to point to a form of perseverative cognition not yet identified by our theory. Some other studies suggest a possible mechanism that at least a part of perseverative cognition may act in an unconscious fashion during sleep which is not reported by the subject. For example, anticipating a stressful oral speech to be performed after waking up elicited prolonged low HRV during sleep (49). In the study of our group discussed above prolonged HR and HRV effects during sleep were found following a day of stressful events and worry ((6); see Chapters 2, 3 and 6 for further discussion). Conscious worry evidently does not take place during sleep. Moreover, the majority of cognitive processing operates without awareness, i.e. automatically (50, 51), and a considerable part of normal daily emotional processing - including PC - is likely to be unconscious too (52). Hardly anything is known about the physiological effects of unconscious emotion, except for some brain and some skin conductance effects (53, 54). Therefore, future studies should aim at unravelling the works of unconscious processing of stressful information.

WORRY DOES NOT EFFECT AVERAGE CARDIAC LEVELS DURING DAYTIME OR DURING SLEEP

Although worry and stress had simultaneous cardiac effects and even prolonged effects up to two hours, these effects disappeared when evaluating aggregated mean cardiac levels during daytime and sleep. These findings were in contrast with the previously discussed study by Brosschot et al. (6) in which daily worry and stressors were found to be related to higher average HR and lower average HRV during waking. Subjects that were measured for this thesis reported stressful events and worry episodes less frequently than in Brosschot et al. (6). Possibly the stressful events or worry episodes were not enough to influence the subjects' mean cardiac levels. This might be related to their lower levels of trait worry and trait anxiety. Future studies should assess similar hypotheses in samples with higher trait worry and trait anxiety.

Another aspect might be that the two studies presented their subjects with a slightly different definition of worry. Brosschot et al.'s definition included the aspect of "thinking hard" while the present study focussed more on the emotional negativity of the process. When initially designing the study, we believed that "thinking hard" was a side-effect of a mechanism which continuously keeps negative emotions "on-line". The cardiac effects were supposed to be induced by these negative emotions. This change of design might have resulted in an underreporting of less worrisome cognitive problem solving attempts. However, it can also be argued that this element of "thinking hard" is in fact an essential element for perseverative cognition (55). As was discussed above, the study by Verkuil et al. (41) suggests that mere mental activity and negative emotional perseveration induce comparable cardiac effects. It is possible that the results presented in Chapter 6 failed to find effects of worry on mean daytime and sleep cardiac levels due to the focus away from the element of 'thinking hard' and its cardiac effects. Future studies would do well to employ a much broader operationalization of perseverative cognition, including 'just thinking about problems'.

IMPORTANCE OF MEASURING TRAIT WORRY

Unexpectedly, we found that accumulated worry episodes during the day did not result in elevated cardiac levels during daytime or sleep (Chapter 5). Also, despite studies in the literature that found a relation between depression, hostility, anxiety, job stress and elevated somatic disease, we did not find evidence that these traits are related with cardiac elevations during daytime or sleep. Accordingly, the studies evaluating the effects of negative emotional dispositions or job stress on ambulatory cardiac levels during sleep (see Chapter 2 for a review) and the findings in this thesis (Chapter 4: *effect of PSWQ on HR but disappeared after including biobehavioral parameters*, Chapter 5: *no effects*, Chapter 6: *PSWQ effect on nocturnal HR*) together present an ambiguous picture. On the other hand, we found that a tendency to worry (measured by the PSWQ) induced elevated nocturnal HR activity (Chapter 6). To our knowledge, no study has previously showed such an effect of trait worry, and only one study has found effects of trait worry on risk of CVD (56). Interestingly, our other results on the same sample suggest that elevated tendency to worry does not influence HR or HRV during smaller timeframes (less than 2 hours; Chapter 4 and 5). This seems to indicate that prolonged cardiac activity during sleep alone might mediate this prospective association with CVD (45*).* Since these associations are not mediated by worry or stress or biobehavioral variables, it remains unexplained which underlying psychological mechanism is responsible for the prolonged cardiac effects of hostility and worry. Biobehavioral and emotional factors were controlled for in this thesis. One speculative possibility is that persons with a high tendency to worry are more prone to unconscious perseverative cognitions during sleep, but we have yet no evidence to support this. Nevertheless, this finding is particularly relevant for somatic health. Sleep is the most important period for the body to restore from activations inflicted during daytime. Not recovering from physiological elevations induced by stress, might lead to a situation alike being exposed to a permanent stressor. Being continuously physiologically activated without any restorative break might eventually result in serious health problems. Regarding the limited studies on the CVD risk of worry, our findings stress the importance of measuring tendency to worry when studying risk for CVD.

METHODOLOGICAL CONSIDERATIONS

The studies described in this thesis have several methodological aspects that should be considered. These issues are already discussed in detail in the previous chapters. Below, the most crucial methodological considerations are repeated and elaborated on.

Firstly, the studies in Chapters 4, 5 and 6 are based on multiple analyses performed on the same dataset, which might lead to an increased probability of finding effects that do not exist (57). However, because of their different hypotheses the three studies each used a different statistical approach and slightly different data, which could not be tested together. In the first study (Chapter 4) the starting point of the analysis consisted of stressors and worry episodes and their simultaneous cardiac activity. To correct for differences due to high activities, we included only low-impact activities in the analyses. The second study (Chapter 5) focussed only on cardiac activity during the last 15 minute window of each 60

minute measurement period. This was done because we measured several potential behavioral confounders, such as emotion, physical activity and posture, more specifically in the last 15 minute period. Since we could control for these factors, we did not have to confine ourselves to analyzing only low activities and included high physical activities as well. In the last study (Chapter 6), we analyzed mean HR and HRV levels during daytime and during the sleep period, which was again essentially different from the previous studies and included new elements such as stressful events and worry after 10PM and nocturnal cardiac levels. These analyzing strategies were based on our hypotheses that were all specified before conducting the measurements and thus, we do not feel that multiple comparisons lead to increased "change" findings. However, this important aspect urges these findings to be replicated in future studies, in which the different hypotheses are tested in a different sample. Favorably, we should invest in new statistical methods to investigate the hypotheses at the same time in one sample.

Secondly, one might question the clinical relevance of these findings, since worry and stressors were related to small increases of HR and small decreases of HRV. However, the magnitude of these effects is comparable to the effects of other factors associated with CVD, as reported by a recent consensus report on the effects of elevated HR on CVD risk (58). The report cites two studies finding a 15% increased risk for each 5 bpm HR increase. In addition, Cook et al. (59) report that drugs lowering HR by approximately 5 bpm were associated with an approximately 20% decreased risk of mortality. Few studies exist that have examined HRV measurements using a millisecond metric; however, Antelmi et al. (60) reported that RMSSD decreased approximately 3.6 ms per decade increase in age and HF power decreased 2.1 ms per decade increase in age. It has often been proposed that the effects of worry represent a type of pre-mature aging (61). In addition, the size of the effects for worry and stressful events found in Chapters 4 and 5 were similar in magnitude to those found for smoking in these chapters. The net cardiac effects of worry might even be much more substantial than those of stressful events because the duration of worry episodes is likely to be much longer than that of stressful events, as was indeed found in the present study. The number of stressors and worry episodes is typically low for the healthy sample studied and is not likely to lead to disease. However, for subgroups these changes can accumulate to a level where they start to be potentially pathogenic, especially when combined with the effects of other risk factors, such as smoking, low exercise and hypertension. Thus we feel that the results described in Chapters 4 and 5 are of the same order of magnitude as those that have been shown to be clinically relevant.

Thirdly, the studies in this thesis focus on effects on cardiac parameters, specifically HR and HRV. An important reason for this is that the reactivity hypothesis, of which prolonged activity is an extension, was originally formulated to specifically explain the relationship between stress and CVD. Nevertheless, prolonged activation is not limited to the CV system and is applicable to various bodily systems and their associated diseases, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters, and so forth. Additionally, there is evidence that perseverative cognitions induce other effects, mainly on somatic complaints, and on endocrinological and immunological parameters (62). Further empirical data on these relations should be gathered and future studies should focus on the mechanisms behind these relations.

Lastly, the sample consisted of high school teachers, who are a highly educated, medium SES subgroup, and the results might not generalize to other groups with lower education and SES. There might also have been a selection bias in the sense that for example teachers responded who experienced a lot of stress, or the opposite, that those with the highest work loads did not respond due to a lack of time. Furthermore, it might be argued that worry and stressors were reported relatively infrequently (only 6-9% of the measured diary entries). However, we did find solid effects of worry and stressors amidst a large pool of neutral episodes which were independent of biobehavioral factors and psychological traits. Additionally, if worry is a key detrimental process that might lead to CV disease in the long run, we do not expect worry to happen often in a healthy population, but is more likely to happen in a population at risk, such as chronic patients, unemployed people, or low SES groups. Nonetheless, future studies should focus on these populations at risk to assess whether the findings of the present dissertation can be replicated. An interesting issue in studying these populations is whether the load on the organism is related to a high number of worries or on a more pronounced level of cardiac activity during worry.

DIRECTIONS FOR FUTURE RESEARCH

The empirical results from this dissertation indicate suggestions for future research. These suggestions have already been formulated in the chapters above and will be summarized below.

In general, future studies should be directed at replication of the findings, taking into consideration the methodological limitations that are raised. More specifically, various hypotheses should be tested without the disadvantage of multiple testing in separate samples. The results should be replicated in different groups of participants, mainly participants at risk for CVD and participants that experience more stress and worry. The prolonged activation model should be extended to other physiological systems, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters.

In Chapters 2 and 3, we reasoned that in comparison to numerous ambiguous processes such as negative mood, prolonged stress experience, helplessness, or hopelessness perseverative cognition is best suited to explain prolonged effects of stressors. This is mainly because perseverative cognition involves a direct trigger of physiological activation, namely, the representation of the original (or expected) stressor, the repeated re-evocation of this representation and concomitant stress experience and physiological activation. Nonetheless, we did not find concrete evidence that worry effects the relation between stressors and (prolonged) cardiac activity. Although our empirical evidence shows that perseverative cognition is a factor with significant cardiac effects, future studies should be directed at elucidating other possible psychological mechanisms that could mediate the relation between stressors and prolonged activation. "Need for recovery" (see above) is an elaborate psychological concept, but its physiological effects are -to our knowledge- not studied yet.

Our results as well as results from other studies (40, 41) indicate that different elements of perseverative cognition might be associated with different levels of physiological cardiac activation in such a manner that presenting different

definitions of worry might even lead to different results. This suggestion urges future studies to elucidate these elements and their ability to induce prolonged activation.

Additionally, we found evidence that specific stressor and worry content lead to more pronounced simultaneous cardiac elevations than others: worry or stress about work or future-related topics were associated with pronounced cardiac elevations, as well as work-related stressors. It is possible that worrying about these topics also leads to more pronounced or longer lasting prolonged activation. However, due to the infrequent reports of stressful events and worry episodes we could not assess this hypothesis. It is worthwhile to direct future studies on testing these suggestions more thoroughly in a larger sample. Additionally, worrying about stressful events that might happen in the future is an aspect that has been neglected in conventional stress measurements, which focus on past stressors. Our findings urge future stress studies to include anticipated stressors or fear of future stressors when evaluating stress.

Additionally, since the results indicate that worry has significant immediate and prolonged cardiac effects, future research should focus on intervention studies designed to reduce frequency and duration of worry. Our group has shown that a simple intervention can reduce the duration of worry (63), but this and other strategies need to be further tested before being incorporated in cardiovascular reduction strategies.

Our results indicate that worry induces prolonged cardiac activation which last for up to two hours. Together with other studies this suggests that part of perseverative cognition acts in an unconscious fashion. Since there is almost no knowledge on how unconscious processing of stressful information induces physiological effects, this is a challenging new topic for future research.

In conclusion, the results presented in this dissertation stress the importance of perseverative cognitions for the prolonged activation model. More specifically, they extend evidence on cardiac effects of worry from the laboratory to daily life. The findings of prolonged effects of worry and the tendency to worry call for further research on the role of unconscious perseverative cognitions.

REFERENCES

1. Selye H. Stress. Montreal, Canada: 1950.

2. Ursin H. Personality activation, and somatic health. In: Levine S, Ursin H, editors. Coping and Health. New York: Plenum; 1980. p. 259-79.

3. McEwen B. Stress, adaptation, and disease - Allostasis and allostatic load. Annals of the New York Academy of Sciences 1998;840:33-44.

4. Brosschot JF, Pieper S, Thayer JF. Expanding stress theory: prolonged activation and perseverative cognition. Psychoneuroendocrinology 2005;30(10):1043-9.

5. Pieper S, Brosschot JF. Prolonged stress-related cardiovascular activation: is there any? Ann Behav Med 2005;30(2):91-103.

6. Brosschot JF, Van DE, Thayer JF. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. Int J Psychophysiol 2007;63(1):39-47.

7. Stewart JC, Janicki DL, Kamarck TW. Cardiovascular reactivity to and recovery from psychological challenge as predictors of 3-year change in blood pressure. Health Psychol 2006;25(1):111-8.

8. Heponiemi T, Elovainio M, Pulkki L, Puttonen S, Raitakari O, Keltikangas-Jarvinen L. Cardiac autonomic reactivity and recovery in predicting carotid atherosclerosis: the cardiovascular risk in young Finns study. Health Psychol 2007;26(1):13-21.

9. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007;74(2):224-42.

10. Carroll D, Smith GD, Sheffield D, Shipley MJ, Marmot MG. Pressor reactions to psychological stress and prediction of future blood pressure: data from the Whitehall II Study. BMJ 1995;310(6982):771-6.

11. Carroll D, Smith GD, Shipley MJ, Steptoe A, Brunner EJ, Marmot MG. Blood pressure reactions to acute psychological stress and future blood pressure status: a 10-year follow-up of men in the Whitehall II study. Psychosom Med 2001;63(5):737-43.

12. Kamarck TW, Lovallo WR. Cardiovascular reactivity to psychological challenge: conceptual and measurement considerations. Psychosom Med 2003;65(1):9-21.

13. Schwartz AR, Gerin W, Davidson KW, Pickering TG, Brosschot JF, Thayer JF, Christenfeld N, Linden W. Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. Psychosomatic Medicine 2003;65(1):22-35.

14. Trivedi R, Sherwood A, Strauman TJ, Blumenthal JA. Laboratory-based blood pressure recovery is a predictor of ambulatory blood pressure. Biol Psychol 2007.

15. Ottaviani C, Shapiro D, Goldstein IB, Mills PJ. Vascular profile, delayed recovery, inflammatory process, and ambulatory blood pressure: laboratory-to-life generalizability. Int J Psychophysiol 2007;66(1):56-65.

16. Moseley JV, Linden W. Predicting blood pressure and heart rate change with cardiovascular reactivity and recovery: results from 3-year and 10-year follow up. Psychosom Med 2006;68(6):833-43.

17. Brydon L, Wright CE, O'Donnell K, Zachary I, Wardle J, Steptoe A. Stress-induced cytokine responses and central adiposity in young women. Int J Obes (Lond) 2007.

18. Steptoe A, Wardle J. Cardiovascular stress responsivity, body mass and abdominal adiposity. Int J Obes (Lond) 2005;29(11):1329-37.

19. Wright CE, O'Donnell K, Brydon L, Wardle J, Steptoe A. Family history of cardiovascular disease is associated with cardiovascular responses to stress in healthy young men and women. Int J Psychophysiol 2007;63(3):275-82.

20. Steptoe A, Marmot M. Psychosocial, hemostatic, and inflammatory correlates of delayed poststress blood pressure recovery. Psychosom Med 2006;68(4):531-7.

21. Hughes JW, Casey E, Luyster F, Doe VH, Waechter D, Rosneck J, Josephson R. Depression symptoms predict heart rate recovery after treadmill stress testing. Am Heart J 2006;151(5):1122-6.

22. Kubzansky LD, Davidson KW, Rozanski A. The clinical impact of negative psychological states: expanding the spectrum of risk for coronary artery disease. Psychosom Med 2005;67 Suppl 1:S10-S14.

23. Ostir GV, Markides KS, Black SA, Goodwin JS. Emotional well-being predicts subsequent functional independence and survival. J Am Geriatr Soc 2000;48(5):473-8.

24. Ostir GV, Markides KS, Peek MK, Goodwin JS. The association between emotional well-being and the incidence of stroke in older adults. Psychosom Med 2001;63(2):210-5.

25. Blazer DG, Hybels CF. What symptoms of depression predict mortality in community-dwelling elders? J Am Geriatr Soc 2004;52(12):2052-6.

26. Pressman SD, Cohen S. Does positive affect influence health? Psychol Bull 2005;131(6):925-71.

27. Steptoe A, Gibson EL, Hamer M, Wardle J. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. Psychoneuroendocrinology 2007;32(1):56-64.

28. Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status: a mechanism for increased cardiovascular disease risk? Eur Heart J 2002;23(22):1757-63.

29. Steptoe A, Willemsen G, Kunz-Ebrecht SR, Owen N. Socioeconomic status and hemodynamic recovery from mental stress. Psychophysiology 2003;40(2):184-91.

30. Brydon L, Edwards S, Mohamed-Ali V, Steptoe A. Socioeconomic status and stress-induced increases in interleukin-6. Brain Behav Immun 2004;18(3):281-90.

31. Steptoe A, Kunz-Ebrecht SR, Wright C, Feldman PJ. Socioeconomic position and cardiovascular and neuroendocrine responses following cognitive challenge in old age. Biol Psychol 2005;69(2):149-66.

32. Steptoe A, Donald AE, O'Donnell K, Marmot M, Deanfield JE. Delayed blood pressure recovery after psychological stress is associated with carotid intima-media thickness: Whitehall psychobiology study. Arterioscler Thromb Vasc Biol 2006;26(11):2547-51.

33. Sonnentag S. Recovery, work engagement, and proactive behavior: a new look at the interface between nonwork and work. J Appl Psychol 2003;88(3):518-28.

34. Geurts SA, Sonnentag S. Recovery as an explanatory mechanism in the relation between acute stress reactions and chronic health impairment. Scand J Work Environ Health 2006;32(6):482-92.

35. van Amelsvoort LG, Kant IJ, Bultmann U, Swaen GM. Need for recovery after work and the subsequent risk of cardiovascular disease in a working population. Occup Environ Med 2003;60 Suppl 1:i83-i87.

36. Kivimaki M, Leino-Arjas P, Kaila-Kangas L, Luukkonen R, Vahtera J, Elovainio M, Harma M, Kirjonen J. Is incomplete recovery from work a risk marker of cardiovascular death? Prospective evidence from industrial employees. Psychosom Med 2006;68(3):402-7.

37. Sonnentag S, Bayer UV. Switching off mentally: predictors and consequences of psychological detachment from work during off-job time. J Occup Health Psychol 2005;10(4):393-414.

38. van der Klink JJ, Blonk RW, Schene AH, van Dijk FJ. The benefits of interventions for work-related stress. Am J Public Health 2001;91(2):270-6.

39. Sonnentag, S., Binnewies, C., and Mojza, E. J. Did you have a nice evening? A day-level study on recovery experiences, sleep and affect. Journal of Applied Psychology, 2008;93(3):674-84.

40. Oathes DJ, Bruce JM, Nitschke JB. Worry facilitates corticospinal motor response to transcranial magnetic stimulation. Depress Anxiety 2007.

41. Verkuil, B., Brosschot, J. F., Borkovec, T. D., and Thayer, J. F. Acute autonomic effects of experimental worry and cognitive problem solving: why worry about worry? Submitted.

42. Karasek R. Job strain and the prevalence and outcome of coronary artery disease. Circulation 1996;94(5):1140-1.

43. Davey GCL, Tallis F. Worrying; perspectives on theory, assessment and treatment. Wets Sussex: John Wiley & Sons Ltd; 1994.

44. Cornelius RR. The science of emotions. Upper Saddle River, New Jersey: Prentice Hall; 1996.

45. Hofmann SG, Moscovitch DA, Litz BT, Kim HJ, Davis LL, Pizzagalli DA. The worried mind: autonomic and prefrontal activation during worrying. Emotion 2005;5(4):464-75.

46. Smyth J, Ockenfels MC, Porter L, Kirschbaum C, Hellhammer DH, Stone AA. Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. Psychoneuroendocrinology 1998;23(4):353-70.

47. Gerin W, Davidson KW, Christenfeld NJ, Goyal T, Schwartz JE. The role of angry rumination and distraction in blood pressure recovery from emotional arousal. Psychosom Med 2006;68(1):64-72.

48. Glynn LM, Christenfeld N, Gerin W. The role of rumination in recovery from reactivity: Cardiovascular consequences of emotional states. Psychosomatic Medicine 2002;64(5):714-26.

49. Hall M, Vasko R, Buysse D, Ombao H, Chen QX, Cashmere JD, Kupfer D, Thayer JF. Acute stress affects heart rate variability during sleep. Psychosomatic Medicine 2004;66(1):56-62.

50. Bargh JA, Chartrand TL. The unbearable automaticity of being. American Psychologist 2008;54(7):462-79.

51. Kihlstrom JF. The cognitive unconscious. Science 1987;237(4821):1445-52.

52. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry 2003;54(5):504-14.

53. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000;23:155-84.

54. Morris JS, Ohman A, Dolan RJ. A subcortical pathway to the right amygdala mediating "unseen" fear. Proc Natl Acad Sci U S A 1999;96(4):1680-5.

55. Borkovec TD, Robinson E, Pruzinsky T, DePree JA. Preliminary exploration of worry: some characteristics and processes. Behav Res Ther 1983;21(1):9-16.

56. Kubzansky LD, Kawachi I, Spiro A, III, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation 1997;95(4):818-24.

57. Pocock SJ. Clinical trials with multiple outcomes: a statistical perspective on their design, analysis, and interpretation. Control Clin Trials 1997;18(6):530-45.

58. Palatini P, Dorigatti F, Zaetta V, Mormino P, Mazzer A, Bortolazzi A, D'Este D, Pegoraro F, Milani L, Mos L. Heart rate as a predictor of development of sustained hypertension in subjects screened for stage 1 hypertension: the HARVEST Study. J Hypertens 2006;24(9):1873-80.

59. Cook S, Togni M, Schaub MC, Wenaweser P, Hess OM. High heart rate: a cardiovascular risk factor? Eur Heart J 2006;27(20):2387-93.

60. Antelmi I, De Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. The American Journal of Cardiology 2004;93(3):381-5.

61. Friedman BH, Thayer JF. Autonomic balance revisited: panic anxiety and heart rate variability. J Psychosom Res 1998;44(1):133-51.

62. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation and health. Journal of Psychosomatic Research 2006;60(2):113-24.

63. Brosschot JF, van der Doef M. Daily worrying and somatic health complaints: Testing the effectiveness of a simple worry reduction intervention. Psychology & Health 2006;21(1):19-31.