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

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Chapter 1: *General Introduction*

Cardiovascular disease (CVD) is the leading cause of death in western countries, which is why numerous studies have focussed on mechanisms, risk factors and possible intervention and prevention strategies. In the past decades, the relationship between psychosocial stress factors and cardiovascular disease (CVD) outcomes has been extensively studied (1-3). However, it remains unclear which underlying psychophysiological mechanisms are responsible for the development of CVD and how psychosocial stressors trigger these mechanisms. More precisely, although the physiological pathogenic pathways appear to be well understood, the *psycho*-physiological factors that lead from stressors to these physiological pathways are not. To be able to design successful interventions, it is crucial to have complete knowledge of these pathogenic pathways.

During the past decades, most studies investigating this stress-disease link have focussed on the *reactivity* model. In this model exaggerated cardiovascular (CV) response is a risk factor for the development of CVD. Large and frequent increases in CV response during exposure to stressors would lead to changes in physiological balance, such as increased platelet aggregation and coronary vasoconstriction. These changes would finally lead to various CVD outcomes (4). However, human studies indicated that reactivity has poor power to predict CVD and several authors (5-9) have pointed out that the reactivity model is conceptually insufficient as an explanation for the relationship between stress and disease.

One important insufficiency is that the reactivity model focuses only on states in which a stressor is present and ignores what happens before or after this period. As such, the reactivity model is related to states of such short duration that these states -regardless of their frequency and intensity- cannot explain the development of chronic pathogenic states that lead to CVD. It seems obvious that people whose physiological levels remain elevated for long periods of time following a stressor may be at greater risk than those who show similar reactivity but recover more promptly. Thus, psychological factors may only have a detrimental effect on CV health if resulting in prolonged states of physiological activity rather than in short elevations, however high their magnitude. Thus, the duration of the stress response, rather than its magnitude, seems to be an important element which has been overlooked in the reactivity model.

Indeed, despite the dominance of the reactivity hypothesis, it has long been recognised (10, 11) that *prolonged* CV responses of stressors and not so much the relatively short responses *during* stressors (i.e. reactivity), strain and wear out the CV system to the extent that they may lead to CVD. The *prolonged activity model* states that the duration of the stress response, rather than its magnitude, is an important element in inducing CVD disease (Chapters 2 and 3). Indeed, several studies have shown that delayed cardiac recovery from stressors is predictive of adverse cardiac outcomes (see Chapter 2 for a review (14)). However, these studies mostly focussed on relatively short-term cardiac stress recovery in the laboratory. Laboratory studies are limited with respect to the large time scope that is necessary to enable the ecologically valid study of prolonged activity. On the contrary, ambulatory field studies provide a larger time scope ánd the possibility to measure real-time stressors; therefore, testing prolonged effects of stressors in an ambulatory design is essential for testing the prolonged activation model. However, only a few ambulatory studies have investigated prolonged effects of stressors (see Chapter 2 for a review (14)). For these reasons, the present dissertation focuses on the prolonged cardiac

effects of daily life stressors and compares them to the immediate effects in an ambulatory design.

Additionally, it remains unclear why some stressors lead to prolonged activation, while others do not. It was recently suggested (12-14) (Chapters 2 and 3) that perseverative cognitions, such as worry or rumination prolong physiological activation beyond the actual occurrence of a stressor. When a stressor cannot be readily coped with, perseverative cognitive processes will keep the cognitive representation of the stressor active along with its negative emotional and physiological concomitants. As a result, the body will remain in a state of behavioral readiness and physiological activation will be prolonged (Chapters 2 and 3). Indeed, recent laboratory studies and one ambulatory study suggest that perseverative cognitions might act directly on somatic disease including CV disease via enhanced activation of the cardiovascular, immune, endocrine and neurovisceral systems (14-22) (Chapters 2-6). Support for this hypothesis is based on only a few laboratory studies. In this dissertation, we investigate the cardiac effects of perseverative cognition in daily life. In our opinion, this is particularly relevant; if we do find that perseverative cognitions induce cardiac effects in daily life, this would open up the possibility of designing an intervention which works specifically on reducing these cognitions.

In general, the present dissertation investigates the prolonged cardiac effects of stressors in daily life and whether perseverative cognitions mediate this relationship. More specifically, three main objectives were investigated.

At first, we reviewed available ambulatory studies for evidence of a relationship between stressors and prolonged CV activation. If prolonged activity is to be an etiological factor it is important to demonstrate that it exists in the first place. We also searched the studies for indications of psychological mechanisms that are responsible for these prolonged effects.

Our second objective was to build the argument that perseverative cognition mediates the health consequences of stressors because it may prolong stress-related affective and physiological activation, both in advance of and following stressors. Additionally, we reviewed evidence that worry, rumination, and anticipatory stress are associated with enhanced cardiovascular, endocrinological, immunological, and neurovisceral activity. Again, it is important to collect evidence, in this case whether perseverative cognition indeed has physiological consequences. If not, it could never have been the topic of the empirical work presented in this dissertation (Chapters 4, 5 and 6), that is, the mediator of stressor effects on health or health parameters.

Thirdly, we conducted an extensive daily life study to investigate the effects of stressful events and worry on simultaneous cardiac activity, prolonged cardiac activity at various durations during the day and prolonged activity during sleep. Since sleep is the primary rest period of most animals including humans, it seems crucial for our model to show prolonged effects during sleep. A previous study from our group suggested that stressors have prolonged effects on sleep and that those effects are mediated by worry (15). We attempted to replicate and expand upon the previous results. We also investigated whether worry mediates prolonged effects of stressful events, as well as negative emotional traits (trait hostility, depression, anxiety and worry) and stress-related factors (job strain). Negative traits and job strain were included because they have been documented previously as risk factors

for CVD (23-28). It is important to investigate whether they have simultaneous as well as prolonged cardiac effects in daily life and during sleep, and whether these effects are mediated by worry.

Thesis outline

Prolonged activity has not often been an explicit research goal of real-life stress studies. Nevertheless**,** a growing number of these studies have provided evidence for prolonged activity as a secondary research goal. In Chapter 2, we review these findings and discuss indications of psychological mechanisms responsible for prolonged effects. In Chapter 3, we plea that perseverative cognition is a mediator of the health consequences of stressors and we review studies that showed an association between worry, rumination, and anticipatory stress on the one hand and enhanced CV, endocrinological, immunological, and neurovisceral activity on the other hand. In Chapter 4, the direct cardiac effects of worry episodes are compared with those of stressful events and neutral events in daily life. Cardiac effects of worry have not been systematically studied in real life. Additionally, we test whether cardiac effects of negative emotional traits (i.e. trait hostility, depression, anxiety and worry) or stress-related beliefs (i.e. job strain) are mediated by momentary worry. In Chapter 5, using a completely different analytical strategy, the hypothesis of prolonged stressor effects in periods of various durations is tested *against* the reactivity hypothesis that involves effects during stressors only; this method enabled us to study whether stressors cause prolonged cardiac activation, how long this activation continues and whether worry effects this process, a question which has not been answered before. In Chapter 6, the effects of daily stressors and worry on cardiac activity during waking and the subsequent nocturnal sleep period are evaluated. This study is a replication of the effects of a previous study (15), which found a relationship between increased daytime stressful events and worry on the one hand and increased mean levels of cardiac activity during daytime and sleep on the other hand. We attempted to replicate these findings in a more elaborate design. In Chapter 7, we provide a summary and general discussion of the integrated results.

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