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

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Chapter 2: *Prolonged Stress-Related Cardiovascular Activation: Is There Any?*

ABSTRACT

***Background**: Prolonged physiological activation before or after stressors has gained recognition as a decisive element in theories that explain the link between stress and disease, specifically cardiovascular (CV) disease. This view is opposed to the conventional reactivity hypothesis that emphasizes responses during stressors.*

***Purpose**: 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.*

***Methods**: An overview of this evidence is lacking and is provided in this article.*

***Results**: The combined data from the reviewed studies suggest that discrete and chronic stress sources, as well as negative emotional episodes and dispositions, are related to prolonged CV activity of various durations, including sleep periods. On the other hand, evidence supporting the assumption that prolonged stress-related activation predicts disease is still very modest.*

***Conclusions**: In this article we suggest that future research of prolonged activation should give priority to (a) the establishment of clear beginnings and endings of stressful events, (b) the prediction of disease by prolonged activation, and (c) potential psychological mediators of stress-related prolonged activation. These mediators may include, for example, worry and rumination, or other processes characterized by perseverative cognition, including unconscious processes.*

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INTRODUCTION

Psychosocial stress or stress factors have been found to be related to cardiovascular disease (CVD) outcomes such as myocardial infarction (1), coronary artery disease (2,3), stroke (4), and hypertension (5,6). These sources of stress include discrete work-related and domestic events, as well as stressors with a less easily discernable beginning or ending, such as chronic job strain, episodes of depression or anxiety, and stable dispositions to experience a high level of stress, such as hostility or anxiety. They are known to influence many physical diseases, but their influence on CVD is especially well documented. Still, it remains largely unclear which underlying psychophysiological mechanisms are specifically responsible for these CVD outcomes and how psychosocial stressors trigger these mechanisms. More precisely, although the physiological pathogenic pathway appears to be well understood (7,8), the psychophysiological factors that lead from stressors to this pathogenic pathway are not.

Several authors (9,10) have pointed out that the explanatory models for these factors are insufficient. Most theories and studies have focussed on the so-called reactivity model, which suggests that individuals with a tendency to respond to stressful events with increased cardiovascular (CV) reactivity have an increased risk for CVD. Large and frequent increases in CV response would lead to changes in physiological balance, such as increased platelet aggregation and coronary vasoconstriction, which would finally lead to various CVD outcomes. Even though there are animal studies that provide convincing evidence for the reactivity model (11,12), human studies on reactivity have yielded inconsistent results and have had various methodological difficulties, such as lack of stability of the stress response over time and over tasks, inconsistent prediction of CVD, and failure to generalize reactivity in the laboratory to reactivity in daily life (13). Recently, Schwartz and colleagues (10) pointed out that these issues have still not been solved. More important, the reactivity model itself seems to be lacking because it overlooks the duration of the stress response, such as physiological activation after termination of a stressor or in anticipation of a stressor (9,10,14-16). The reactivity hypothesis generally pertains to states of short duration that, even if they are frequent and intense, cannot explain the development of the chronic pathogenic state that leads to CVD (9,14). However, it seems obvious that people whose physiological levels remain elevated for long periods of time following stress may be at greater risk than those who show similar reactivity but recover more promptly. The same goes for people who show anticipatory activation far ahead of a stressor. Thus, psychological factors may only have a detrimental effect on CV health if they result in prolonged states of physiological activity rather than in only short elevations of activity, however high their magnitude. Therefore, the duration of the stress response, rather than its magnitude, may be an important element in causing CVD disease.

Because of the relative novelty of this insight, only a modest amount of CV stress research has explicitly addressed the issue of prolonged activity. However, several studies have measured the duration of stress responses, often as an issue of secondary interest. There is no review available of these potentially important findings with the notable exception of laboratory findings of stress recovery. The latter have been summarized and discussed elsewhere (9,14), and the results suggest that emotional tasks lead to slower recovery than nonemotional tasks (9)

and that recovery is accelerated when there is an opportunity to cope with the source of stress (14).

Laboratory studies are limited with respect to the time scope that is necessary to enable an ecologically valid study of prolonged activity. In contrast, ambulatory field studies provide a larger time scope. In this article we provide a review of findings from ambulatory studies testing the hypothesis that various stress sources can have prolonged CV effects. In addition, we discuss indications from these studies of psychological mechanisms that are responsible for these prolonged effects. Because the stress-disease link has mostly been studied for CVD, and because the reactivity hypothesis is specifically formulated for CV activity, we limited this review to ambulatory field studies that assessed CV variables such as heart rate (HR), blood pressure (BP), and heart rate variability (HRV).

To present an adequate theoretical framework for the review, we first provide a definition and elaborate conceptualization of prolonged activity. Next, we briefly review available evidence for a relationship between prolonged activity and risk for somatic disease. Then, we discuss the few stress-disease theories that have recognized prolonged activation as an essential element. Thereafter, we address possible mechanisms by which psychosocial stressors can bring about prolonged activity. Finally, in the remainder of the article we review and discuss ambulatory field studies that measured prolonged cardiovascular activation.

DEFINITION AND CONCEPTUALIZATION OF PROLONGED ACTIVITY

To avoid confusion, it is important to be clear about what exactly we mean by *prolonged activity*. Therefore, we define three types of prolonged activation, according to the time period in which prolonged activation occurs in relation to the stressor. The first and most frequently studied type is prolonged physiological activity immediately after termination of the stressor, which is often referred to as *recovery*. In ambulatory studies, stressors are often reported over predefined periods (e.g., hours), whereas CV variables or other physiological variables are measured continuously. Some of these studies have in addition analyzed the relationships between these stressors and physiological activity in the subsequent time period. The second type can *reoccur* after initial recovery, when the stressor is so-called mentally re-created -for example when a person ruminates about it at a later point in time (17). This reoccurrence of physiological activity can be found in studies that measured activity during typical restorative periods, such as non-work time, evening, and night. A third type of prolonged activity can take place in *anticipation* of a potential stressor. Anticipatory experience of stress has been occasionally studied but seldom clearly hypothesized as a source of stress-related physiological activity.

In summary, we review psychosocial stressors and stress sources that influence three types of prolonged activity. These three types are defined as (a) slow recovery after stressors or acute prolonged activity, (b) reoccurring prolonged activity after initial recovery, and (c) anticipatory prolonged activity in advance of a stressor. Theoretically, reoccurring as well as anticipatory activity may occur at any time preceding or following a stressful event. We discuss studies that have related prolonged activation to CVD risk in the next section.

PROLONGED ACTIVITY AND RISK FOR CVD: IS THERE EVIDENCE?

Several studies have yielded evidence that prolonged duration of physiological activity during recovery phases is related to CVD outcomes. One study found that slow HR recovery, aggregated over physical and emotional tasks, predicted enhanced rest HR 4 years later when corrected for weight (18). In addition, several studies have shown that prolonged CV activity is an independent or better predictor of disease than reactivity. Delayed systolic BP (SBP) recovery after a cognitive task was found to be more strongly related with hypertension 5 years later than reactivity during the task (19). Similarly, delayed HR recovery during the first minute after physical exercise was found to be predictive of overall mortality 6 years later, independent of reactivity during the exercise and controlled for age, gender, and exercise capacity (20). In addition, slow BP recovery from physical stressors (cold pressor and tourniquet ischemia) was related to elevated BP 3 years later, again after adjustment for reactivity values and controlled for differences due to age, body mass index (BMI), and parental history of hypertension (21). Furthermore, elevated BP during anticipation of physical exercise predicts the development of hypertension 4 years later after adjusting for BP levels during exercise, corrected for smoking, alcohol consumption, physical activity, BMI, and parental history of hypertension (22). In addition, exaggerated anticipatory BP responses to bicycle exercise were cross-sectionally related to incremental increase of left ventricular hypertrophy, which is a risk factor for CVD. This relation remained significant after adjustment for age (23).

Together, these studies seem to provide convincing evidence for a relationship between prolonged stress-related activity and CVD outcomes. An explanation for these findings is that short-term delayed recovery and anticipation reflect a more pervasive and general tendency to recuperate slowly after stress or to anticipate long in advance. Such a tendency might extend the total load on the organism over time, and in that way constitute a risk factor for CVD. Alternatively, prolonged activation might be the consequence of other CVD risk factors and, as such, has no direct effect on disease outcomes. Indeed, delayed CV recovery was found to be related with several of these risk factors, such as parental history of hypertension, low fitness level (for reviews see 24,25), smoking (26), caffeine intake (27), and elevated BMI (28). In the review that follows, we note which factors are controlled. We also discuss several theories in which prolonged activity is an essential element in the relationship between stress and somatic disease.

PROLONGED ACTIVITY AS AN ESSENTIAL ELEMENT IN STRESS-DISEASE THEORIES

As far back as half a century ago, Selye's (29) general adaptation syndrome already included the central element of duration. Even though the importance of prolonged activation was already acknowledged at such an early stage in history of the stress concept, it does not appear to have led to a great deal of attention in later theories and research. There are a few exceptions, however. In the 1980s, Ursin (30) emphasized the crucial role of sustained activation in the effect of psychological stressors on somatic health. In his view, increased physiological activation during a stressful event is experienced as a strain, which the individual is urged to reduce. If the individual would succeed in coping with the stressor (by establishing the expectation to be able to change, eliminate, or avoid it), tonic physiological activation would subsequently be reduced. In contrast, if such an expectation is not

established, the stressful experience would be prolonged and physiological activation would be sustained, which in the long run would be detrimental for physical health. Ursin and Eriksen (31) postulated that activation is sustained by negative outcome expectancies, such as helplessness and hopelessness.

In the late 1990s, several other theorists revived prolonged activation as a cornerstone of stress theory. McEwen (32), in a currently popular theory, proposed the term *allostatic load* to refer to the wear and tear on the body due to repeated efforts to keep it in physiological balance in the face of an external stressor. This theory suggests that there are several types of situations that lead to allostatic load, including repeatedly experiencing novel events causing repeated elevations of stress over long periods of time and failure to habituate or adapt to a specific stressor. According to McEwen, high physiological levels are maintained by a prolonged stress experience.

Linden and colleagues (9) showed that recovery issues seemed to have been neglected in stress studies and that it was necessary to rehabilitate the concept as a subject of crucial theoretical and ecological significance. In their review of laboratory stress studies, they revealed that although recovery was being increasingly measured in stress experiments, it was only being reported in a minority of these cases. They also showed that even in the limited time span typical for laboratory stress experiments, the measurement of recovery yielded findings that were not apparent when only reactivity was taken into account. For example, attenuated recovery but not elevated reactivity was found in persons with a low fitness level, in caregivers, and in anger-provoked participants. The authors postulated that slow recovery after stressors is due to prolonged negative affect.

Sluiter, Frings-Dresen, Meijman, and van der Beek (33) focussed on the relationship between work-related factors and incomplete recovery. They argued that individuals who experienced repeated stressful factors at work needed more time to recover from work-related neuroendocrine reactivity. This process started a cycle in which extra psychophysiological effort had to be exerted to maintain optimal performance at work. In turn, the cycle could lead to long-term health problems. Indeed, they found that this cycle leads to increased cortisol and adrenaline excretion during non-work periods, together with increased reports of feelings of chronic fatigue and health complaints. However, their theory leaves unexplained how extra psychophysiological effort in itself would lead to prolonged activity. Physical effort of comparable intensity does not usually lead to sustained activation of muscles, HR, cortisol, and adrenaline for hours, let alone nights and days. Thus, something more than physical effort alone must cause sustained activation after stressful events.

All theories discussed thus far explicitly contain the duration element and, all except the last one, postulate mediating psychological mechanisms such as negative mood (9), negative outcome expectancy (30), and prolonged stress experience (32). In our opinion, these mechanisms are insufficient to account for prolonged physiological activation. It is unlikely that individuals suffering prolonged stress-related activation are in a continuous state of negative expectation or negative mood. At best, internal or external "reminders," such as worry, rumination, or contextual clues frequently trigger such states. These kinds of mechanisms are not specified in the aforementioned theories. The most elaborated of these hypotheses or models (31,32) correspond closely to general self-regulation theories or systems

theories in which an evaluation mechanism detects a discrepancy between an individual's goals (i.e., set values) and reality (i.e., actual values), which is the direct instigator of the stress response. However, the stress theories discussed provide a *static* model of the stress response mechanism, which is a model that can explain the organism's state at any given period in time. Conversely, prolonged activation is best explained using the *dynamic* aspects of this evaluation mechanism, such as frequency, speed, initiation, and lag between feedback and behavior. The models do not seem to sufficiently address these dynamic aspects.

In conclusion, the notion of prolonged activation as a crucial mediator of the effects of stress on health has been recognized early in the field. However, it is used only in a limited number of stress theories with respect to the size and history of the field. These theories do not sufficiently address the psychological mechanisms responsible for prolonged activation. Recently, attempts have been made to theorize about the nature of these mechanisms and to find empirical support for them. We discuss this in the next section.

PSYCHOLOGICAL MECHANISMS UNDERLYING PROLONGED ACTIVATION

In retrospect, the first studies of psychological mechanisms underlying prolonged activation were not genuine stress experiments but instead were anger reduction experiments. Starting with a set of studies in the early 1960s, Megargee and Hokanson (34) and several other investigators have consistently found, in more than 20 different experiments (14), that anger induction without opportunity to counterreact prolongs CV reactivity. In a review of these findings and the explanations proposed to account for them, Brosschot and Thayer (14) proposed a comprehensive model, partly based on emotion theory. According to this model, angry emotions lead to physiological preparation for action to change the anger-provoking situation. When this situation can not be changed -for example, when the angering object is not present or if social rules prohibit anger expression- the organism remains in a state of behavioral readiness, and the psychophysiological preparation phase is sustained. Most angering instances of normal daily social life do not provide an opportunity to express anger, and so hypothetically this preparation phase will be continued regardless of an individual's tendency to express or inhibit anger. A recent experiment suggests that increased duration of the CV response after anger provocation is related to ruminating about the angering situation. Glynn and colleagues (17) found that BP recovery following an anger provoking stressor was significantly slower than that following a nonemotional stressor although the magnitude of BP responses was comparable among the tasks. When participants were distracted after the anger provocation and thus were less able to ruminate, BP recovered more quickly. Thus, this experiment suggests that rumination (or related cognitive processes) might prolong physiological activation due to stress. In line with this, two recent theoretical reviews (35,36) revealed that worry and rumination are associated with activity of several physiological systems, including the CV, endocrinological, and immunological systems. This is true for experimental as well as dispositional worry and rumination, and for other dispositions toward sustained cognitive and emotional engagement, such as John Henryism coping (37).

Thus, several studies, directly or indirectly, suggested that one possible way in which physiological responses to stressors may be prolonged is by cognitive processes, such as rumination and worry. Theoretically, these processes extend the

duration of the action tendency associated with the negative emotions and concomitant psychophysiological activation. The responsible mechanism in these processes has been named *perseverative cognition* (35) and is usually implicated in several negative emotional states, including anger, depression, and anxiety. The advantage of using the notion of perseverative cognition is that it involves a direct trigger of physiological activation, namely, the representation of the original (or expected) stressor and the repeated reevocation of this representation and concomitant stress experience and physiological activation. In contrast, emotional states and other more ambiguous and general concepts such as negative mood, prolonged stress experience, helplessness, or hopelessness are too ambiguous with respect to this precise mechanism. In our view, this makes perseverative cognition a promising candidate as a predictor of prolonged activation related to stress sources. However, support for this hypothesis is based on only a few laboratory studies. In our review of ambulatory real-life studies in the next section, we examine whether there are cues or suggestions for possible psychological and psychosocial mechanisms responsible for the prolonged effects, including indications of perseverative cognition.

REVIEW OF AMBULATORY STUDIES OF STRESS-RELATED PROLONGED ACTIVITY

We indicate whether the findings of the reviewed studies were controlled for health behavior that might have caused reactivity, as well as prolonged activation, such as smoking, and coffee and alcohol intake. Furthermore, we mention all CV parameters that are reported. The studies to be considered can be divided in four groups according to the time scope of the psychosocial stress sources measured. We distinguish between four types: (a) discrete stressful events (stressors with an easily specifiable beginning and ending); (b) chronic stressors, which are characterized by their continuous presence or high frequency; (c) transient negative affective states that can act as temporal stressors; and (d) dispositions to experience negative emotions, such as neuroticism, trait anger, hostility, depression, and anxiety. The last type implies the largest time scope, in many cases effectively acting as a lifetime stressor. Table 1 shows a summary of the characteristics and findings of all studies discussed in the next sections, categorizing the studies according to their own time scope (i.e., discrete, chronic, transient affective state, emotional disposition) and that of prolonged activation (i.e., recovery, anticipation, reoccurring).

Prolonged Activity Related to Discrete Stressors

Several studies have measured prolonged CV activation after discrete stressors. Catastrophic stressors or personal traumas, such as earthquakes, hurricanes, nuclear accidents, rapes, and child abuse are associated with a range of psychophysiological consequences, including prolonged BP activity for hours to weeks after the incident (38,39). However, these catastrophic events are relatively rare in the life of the average person and therefore are beyond the scope of this article. Brondolo, Karlin, Alexander, Bobrow, and Schwartz (40) showed that a considerably less intense stressor, such as communication of traffic enforcement agents with the public, was related to increased SBP, but not diastolic BP (DBP) or HR, 15 min after termination of communication, as compared to 15 min after communication with coworkers. The results were adjusted for effects of differences in posture, and only periods in which the agents were not communicating were tested for delayed effects. Another study

showed that a high number of stressors experienced during daytime, measured with 60-min diaries, predicted higher HR, but not HRV, during subsequent nocturnal sleep (41). This effect was independent of health behavior, including smoking, coffee intake, and alcohol intake. More distal past stressors may also influence sleep physiology. Ituarte (42) found that an increased number of stressful events over a 6-month period is related to the absence of the typical decline in HR during subsequent nocturnal sleep, especially among persons with low levels of social support. The results were independent of the effects of age, gender, and BMI.

In addition, prolonged activity during sleep can be observed when anticipating a discrete stressor (43). Participants who were anticipating a stressful oral speech task that had to be performed soon after waking up in the morning showed decreased high-frequency power in their HRV, indicating lower vagal tone, during non-REM (NREM) and REM sleep, as well as an increased ratio of low-to-high frequency power of HRV (mainly indicating high sympathetic tone) during NREM sleep. A control group not anticipating the stressor showed a normal increase of vagal tone and low sympathetic tone across successive NREM cycles. Participants were asked to refrain from exercise, alcohol intake, and caffeine intake prior to and during the experiment, and the authors controlled for stress at baseline and the time that participants were awake during the sleep period.

In conclusion, there is evidence that prolonged CV activation can occur prior to or after a discrete stressor, suggesting that the prolonged experience of a past stressor, as well as the mere expectation of a stressor, are related to sustained or recurrent activation, or anticipatory activation. These results could not be attributed to the effects of unhealthy behavior. None of these studies specifically addressed the possible psychological factors causing the observed prolonged activation. However, the results seem to imply that the participants must have been thinking to some degree about the stressors. The finding of prolonged activation during sleep suggests that at least part of these cognitive processes are continued during sleep in an unconscious fashion, such as during dreaming, and that they still result in prolonged CV activity. We discuss these issues in the last section. The next section addresses the question whether there is evidence that more chronic stressors have prolonged activity effects beyond their actual presence.

Prolonged Activity Related to Chronic Stressors

Chronic stressors are characterized by their frequent occurrence or long duration. In theory, prolonged physiological effects of these stressors are relevant for stress-disease theory. Not only do these stressors and the immediate physiological responses to them last longer, but they might also result in longer periods of prolonged activation than discrete stressors because of their pervasiveness and intensity. Despite what their name suggests, chronic stressors are not necessarily of a continuous nature or "always present". From a prolonged activity perspective, it is of high interest whether they have effects in periods in which they are not present.

An important source of chronic stressors is the work environment. The findings for prolonged activation effects of work stressors are inconsistent. One of the leading theoretical work stress models, Karasek's demand-control model (44), in which high job strain is defined by high psychological workload demands combined with low decision latitude, has been studied relatively frequently in ambulatory designs. Van Egeren (45), in a 24-hr study, found that high job strain, compared

with low job strain, was related to higher SBP, but not DBP, at work and during recovery periods at home in the evening, independent of effects of gender, BMI, or caffeine. Similarly, Steptoe, Cropley, and Joekes (46) found that schoolteachers with low job strain showed larger decreases in SBP and DBP, but not HR, during the evening of a work day than the high-job-strain teachers, controlled for age, BMI, and posture. Remarkebly, these teachers did not differ on BP and HR levels during recovery after stressful job-unrelated tasks in the laboratory, which makes it unlikely that slow recovery is a genetically determined or acquired characteristic of individuals who also report high job stress.

In addition to prolonged activity in the evening, prolonged activity in high-strain workers was also observed during non-work days. Schnall, Schwartz, Landsbergis, Warren, and Pickering (47) found these effects in workers from a diverse range of worksites (newspaper department, health agency, stock firm, liquor shop, hospital, warehouse, insurance company). They also demonstrated that these effects were more pronounced in individuals whose high job strain was stable over a long period. Male workers who reported high job strain during 2 work days, 3 years apart, showed higher SBP and DBP at home in the evening and higher SBP during sleep on both time points than workers who reported high job strain at only one time point, which was corrected for the effect of age, BMI, alcohol consumption, and smoking. In a group of general practitioners with high and low job strain, O'Connor, O'Connor, White, and Bundred (48) found results that seem to point toward recurrent prolonged activity. High-job-strain practitioners had higher HRs during the evening following a work day as well as during a non-work day. Although there were no BP differences during the work day and the following evening, during the subsequent non-work day BP was elevated again in high-strain practitioners, with a trend toward further sustained BP during the evening of that non-work day. There were no gender or age differences between the groups. Because high-strain practitioners did not display higher BP during the evening following work, their high BP during the non-work days could not be caused by delayed recovery from work and may indicate a "re-creation" of the work stressors.

In contrast with these findings, several studies found no relationship between high job strain and prolonged CV responses. No such results were found for HR and BP in industrial workers concerning aggregated evening and sleep values (independent of age, gender, BMI, and alcohol) (49); for firefighters regarding HR and BP during non-work day (independent of age, BMI, smoking, alcohol intake, and exercise) (50); in nurses regarding HR and BP during evening, sleep, and non-work day (corrected for age, BMI, posture, alcohol intake, and coffee intake) (51); and between high job demands and prolonged BP physiological responses in schoolteachers during the evening (corrected for age, BMI, and physical activity (52)).

Comparable inconsistent results were found using another leading work stress model, that is, Siegrist's effort-reward imbalance model (53), in which high job strain is defined as a high level of extrinsic efforts or demanding work environment combined with low reward such as esteem rewards or momentary gratification. Male white-collar workers with high job strain compared to those with low job strain displayed elevated SBP and HR at work and in the evening at home and lower HRV during the whole measurement period, namely, during work, evening, sleep, and non-work days. These findings were controlled for age, BMI, activity, posture

changes, smoking, and alcohol consumption (54). In contrast, a group of health professionals and office clerks displayed similar differences in BP, HR, and HRV between high- and low-strain workers at work but not during the evening after work. The effects of gender and smoking were controlled (55).

In addition, other more specific occupational stress sources are related to prolonged activation. In a study of general practitioners (56), high feelings of stress specific to general practitioners, such as constant organizational changes and postgraduate education commitments, were related to elevated SBP and DBP during the work day, elevated SBP during the work day evening, and elevated SBP and DBP during the following non-work day, independent of the effects of age and BMI. In a group of various types of workers, low work-related social support was related to higher HR, corrected for age, gender, BMI, smoking, alcohol, and mean physical strain at work (57), but not to higher BP during work, non-work, and sleep periods. The inconsistencies among the findings for prolonged activation related to work stress are difficult to explain at this point in time. One possibility is that the specific stressors that were measured in these studies do not often lead to prolonged activation during non-work hours, because they do not often lead to worry or rumination during these hours or to other mediators of prolonged activation. Unfortunately, none of the discussed studies have measured possible psychological mediators.

Next to chronic work stressors, there is evidence that chronic domestic stressors can also increase activation during typical recovery periods. High marital distress was associated with higher BP, but not HR, at home during the evening in women employed in a variety of occupations. These differences were not visible at work and were not explained by differences in age, BMI, posture, or caffeine consumption (58). Whether the presence of the source of stress, such as the partner, influenced this result was not reported. Thus, it is unclear whether and to what extent the increased activity is reactivity (responses to the presence of the marital stressor) rather than prolonged activity. This interpretational problem also applies to a study by King (59), who compared BP and HR in middle-age female caregivers of an ill relative with age-matched noncaregivers, for either 1 or 2 days. Caregiving has been shown to be an important chronic stressor with many health consequences (60). Although caregivers and noncaregivers displayed similar BPs at work, caregivers displayed elevated BP at home in the evening, a finding that was independent of age and BMI. During these non-work periods, the caregivers were always in the presence of the care recipient. Again, prolonged activity is hard to distinguish from reactivity because it is not clear whether the caregivers would also show prolonged activity in the absence of the care recipient. In both studies, sleep might have been a good period to detect prolonged activity, but the studies did not assess CV values during sleep.

Another, more general chronic stressor, perceived racism, has also been found to be associated with higher BP during waking periods, but not during sleep. This effect was independent from anger expression styles (61).

Finally, there is evidence that chronic work stress in combination with chronic domestic stress can have a synergistic effect on prolonged activity. Brisson (62) showed that among white-collar women, high job strain and high family load were related to increased SBP and DBP during and after work in the evening and during sleep, compared to workers who exhibited high levels of these types of chronic

stress. These results were independent of age, BMI, smoking, alcohol, and mean physical activity.

In conclusion, there is some evidence that chronic stressors can lead to prolonged activity during periods in which the stressor is absent, although in studies focusing on domestic stressors prolonged activation could not be distinguished from "mere" reactivity. The effects of chronic stressors on prolonged activity were independent of the effects of several confounding variables, such as BMI, age, and physical activity. On the other hand, most studies evaluated the effects of these factors on the overall mean of the studied CV variables, instead of evaluating the effects specific for the different time periods. Therefore, it is not always clear whether prolonged activity effects were truly not due to biobehavioral factors. Furthermore, no reported attempts were made in the studies to measure or analyze personal appraisal of the stressors or psychological responses to the stressors, which could have mediated prolonged activation. Next, we review studies that focussed on the physiological effects of negative affective states.

Prolonged Activity Related to Negative Affective States

Being in a negative affective state can be understood as experiencing a stressor. Several studies measured the effect of these states on prolonged physiological activity. Kamarck and colleagues (63) studied the effects of "emotional affect" and "emotional arousal" on BP and HR in male and female participants. In these participants, 45-min periods of high negative affect compared to periods with low negative affect were related to higher BP in the same period, as well as in the next 45-min period, even after adjusting for negative affect during that next period. High arousal was also related to enhanced BP but only during the same period. These results are independent of posture, physical activity, talking, and caffeine and alcohol intake. Brosschot and Thayer (64) demonstrated that high HR related to negative emotions lasted longer than high HR related to positive emotions. Emotional arousal and physical activity predicted simultaneous HR, whereas prolonged HR activation 5 min later was solely predicted by "negative emotional valence", independent of emotional valence at that point in time and initial HR response. Thus, these two studies suggest that prolonged activity seems to be related to negative emotional valence, and not to high emotional arousal or positive emotional valence. In addition to these short-term effects, Shapiro (65) showed that college students who frequently experience daytime angry or sad emotional states displayed elevated BP, whereas frequently experiencing pleasant or happy states was related to decreased BP during sleep, which was independent of differences due to posture or activity. There was no effect on HR. However, it is not clear from this study whether the BP changes were caused by emotions experienced immediately before sleep or by their accumulation during the preceding day.

To conclude, there is some evidence that episodes of negative affect -or the lack of positive affect- are related to slow recovery as well as prolonged activity during sleep. Even though psychological mediators were not measured in these studies, the results are consistent with the view that prolonged activation is produced by some form of cognitive emotional perseveration that extends beyond the presence of the negative emotion itself. From the perspective of studying the contribution of negative emotions to the development of CVD, it is even more important to know the effects of chronically experiencing these negative

psychological states, or, in other words, having a disposition to experience them. The last review section discusses studies that have focussed on the prolonged effects of several of these emotional dispositions.

Prolonged Activity Related to Negative Emotional Dispositions

Dispositions to experience negative emotions such as hostility, depression, and trait anxiety have been found to be predictive of CV and other diseases (66-69). One explanation is that such negative dispositions could lead to the appraisal of more stressful situations, which could in turn have negative influences on the coping process following the stressors. Thus, these personality dispositions cause longer lifetime exposures to stressors and in fact act as exceptionally chronic stressors. These personality traits can be hypothesized as an even more powerful source of prolonged activation than chronic work stressors or domestic stressors because of their pervasiveness. If this theory proves true, prolonged activation may explain a large part of the disease risks associated with negative dispositions.

There is indeed evidence of prolonged activity in persons with hostile, pessimistic or anxious attitudes. Räikkönen, Matthews, Flory, and Owens (70), who measured university employees during working hours and the subsequent evening, found that high hostility, as well as high levels of pessimism and trait anxiety, were related to continuously elevated BP, but not HR. In contrast, participants low on these traits displayed elevated BP only when actually reporting elevated negative mood. These results were independent of effects of age, posture, location, and physical activity.

Most other relevant studies have related emotional dispositions to high CV activity during sleep. Jamner, Shapiro, Goldstein, and Hug (71) measured HR and BP in paramedics during a 24-hr period including work and sleep, finding that participants with high levels of hostility, in contrast to those with low hostility levels, demonstrated elevated SBP, but not DBP or HR, during waking and sleep. In contrast, high "defensive" participants showed only higher awake DBP levels, but not higher sleep DBP levels, compared to low "defensive" participants. The findings were not controlled for biobehavioral variables. Pasic, Shapiro, Motivala, and Hui (72) found that, independent of effects of gender, age, and BMI, highly hostile participants displayed elevated mean SBP during the 3 hours in the morning preceding awakening compared to participants with low hostility, yet no differences were found during the 3 hours following awakening. Because such differences were not found for anxiety, these results seemed to be limited to hostility. Moreover, Shapiro, Goldstein, and Jamner (73) found a relationship between cynical hostility and prolonged SBP, but not HR or DBP, during waking periods and sleep. This relationship was independent of gender and BMI but only found in African American participants. African American participants scoring high on both anxiety and defensiveness displayed higher DBP during waking periods but not during sleep, which is somewhat in line with the results of Jamner et al. (71).

Kario, Schwartz, Davidson, and Pickering (74) showed higher SBP during sleep, but not during waking time, in men high on anxiety or depression, compared to men low on both these traits. However, this was found only when sleep-to-awake ratio of SBP was used, suggesting that these effects were weak. Women in this study showed only higher waking SBP and pulse rate, not DBP, in relation to higher anxiety. Yet, no differences were found during sleep. These results were corrected

for differences in age, gender and mean activity during sleep and awake measurement periods. In contrast, Schneider, Julius, and Karunas (75) and Van Egeren and colleagues (45,76) did not find differential awake or sleep levels for BP and/or HR related to Type A personality. However, these two studies were conducted before it became broadly established that hostility is the most crucial part of Type A personality in terms of predicting CVD. It is possible that only the hostility element was associated with prolonged CV activity during sleep and not the complete Type A behavior pattern.

Collectively, these results indicate that prolonged activity can be observed in participants with negative emotional dispositions, during waking time as well as during sleep. The sleep findings with these dispositions are even more informative than those with the other stress sources. Earlier, we noted the problem of disentangling stress periods from nonstress or restorative periods in chronic stress. This problem is even more severe during waking for persons with dispositional hostility, depression, or anxiety. In a way, they theoretically experience stressors all the time. However, sleeping might be the only period in which their dispositions are not turning harmless events into potentially disturbing ones, at least not consciously. It is the only period in which we can be sure of the absence of a stress source. Thus, whereas high CV activity during waking may be either reactivity or prolonged activity, high CV levels during sleep must be prolonged activity.

DISCUSSION

We started this article by stating that although prolonged activity is widely acknowledged as an essential part of basic stress-disease theories, it seems to have been largely neglected as an empirical and theoretical research theme for its own sake. To review the available evidence, we collected ambulatory CV studies that measured prolonged activity in relation to various stress sources, whether or not as a primary research aim. This review suggests that there is some evidence for a relationship between prolonged activity and psychosocial factors spread over studies of different types of stress sources. A handful of studies have shown that discrete stressors of various intensities were related to prolonged activity in preparation for and immediately after the stressor and during sleep. Studies focusing on more chronic stressors, such as work-related stressors or caregiving, have found a relationship with prolonged activity during typical recovery periods, such as evening, sleep, and non-work days. However, consistency was lacking with respect to the work-stress findings. Studies have found that negative affective states were related to prolonged activity, immediately after and during sleep. Negative emotional dispositions, which can be viewed as a more chronic form of experiencing a negative affective state, were related to prolonged activity in between episodes of negative states and during sleep.

On the other hand, strong conclusions concerning stress-related prolonged activation are precluded, because of the lack of methodological requirements. These requirements concern the precise identification of prolonged activity and the nature of the mediators of prolonged activation. Firstly, the establishment of clear beginnings and endings of stressful events is lacking in nearly all studies discussed. This is essential because prolonged activity can occur in any period when the stressor is absent, and thus the stress period ought to be established with high precision. In fact, this type of information can be easily reported in the ambulatory

diaries that are already frequently used. It opens the possibility to assess the actual duration of prolonged activity effects. Theoretically, the longer the duration of physiological activation, the more damage will be inflicted on the system. A related problem is that in a number of ambulatory studies, periods such as the evening, sleep, and non-work days were considered as neutral or stress-free periods, with no attempt being made to control for stressors in these periods. This complicates the interpretation of the data, especially in the studies of chronic stressors and emotional dispositions. For example, there was no information available concerning the presence of the stressor during recovery periods, such as in the form of doing work-related chores. Therefore, it is not possible to establish whether these periods are really neutral and stress-free and whether or not prolonged activity during these periods is, in fact, reactivity.

Secondly, it is necessary to correct for various biobehavioral variables that activate physiology, such as physical activity and caffeine/coffee consumption, to be sure that the observed differences are due to prolonged activity. Controlling for these factors can rule out the alternative "health behavior" explanation. Some persons will engage in more unhealthy behavior, such as smoking, drinking alcohol, or drinking coffee, during neutral periods preceding or following stressful events. Their enhanced CV activity in these neutral periods may be the result of this behavior, instead of actual prolonged activity. Although the vast majority of the reviewed studies controlled for one or more of these health behavior variables, only a minority was complete in this respect.

Significantly, none of the studies operationalized and measured potential psychological mediators of the observed prolonged physiological effects. As we proposed earlier in this article, perseverative cognitive processes, such as worry and rumination, form a logical candidate for such a mediating vehicle. Even though such processes were not measured, several findings do suggest their presence. This is especially the case for findings of prolonged activation before or after stressors with a clear-cut beginning and ending. In these cases the stressor is obviously not present during prolonged activation, and it is highly likely that participants are at least busy processing or thinking about the upcoming or past stressor. Of these, most revealing are perhaps those studies that found that CV levels are higher after negative emotional episodes even when the negative affect itself has already worn away (63,64). These findings make clear that prolonged activation cannot easily be attributed to stress-related emotions, but that something more than "mere emotion" mediates these effects, such as perseverative cognition.

It is likely that at least a part of this perseverative cognition is unconscious. This possibility becomes significant when interpreting the findings of prolonged activation during sleep. Prolonged activity during sleep cannot be accounted for by conscious perseverative cognition. There is evidence for a peak in conscious worry frequency in the first part of the night in healthy participants (77), and this is perhaps continued on a less conscious level during subsequent sleep. The possibility of deficient nocturnal recovery of physiological arousal due to a form of cognitive perseveration may be of predominant significance for health because it leads to a situation not unlike being exposed to a permanent stressor. Being continuously physiologically activated by stress without any natural restorative break might eventually cause serious health consequences.

This review is limited by the fact that only studies measuring CV variables were involved. 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. A more practical reason is that most available ambulatory studies have focussed on the relationship between stress and CVD. Nonetheless, prolonged activation is obviously not limited to the CV system and CVD but is applicable to various physical systems and their associated diseases, such as the endocrine and immune system, muscle tension, glucose blood level, asthma-related parameters, and so forth. For example, there is empirical evidence that prolonged activity occurs in anticipation of a stressor for cortisol (78) and for cortisol and immune parameters (79). This review of CV ambulatory studies hopefully adds to the insights concerning prolonged activation reached by previous reviews on findings from the laboratory (9,35).

In summary, this article suggests that there is some but not sufficient evidence for a relationship between prolonged CV activity and stress-related psychological factors in ambulatory studies. Future studies are needed that explicitly test the prolonged activation hypothesis with more appropriate methodology and with explicit theories and operationalizations of psychological mediators of stress-related prolonged activation. We suggest that anticipatory activation might be given priority as a research object, given its theoretical importance and the surprisingly small amount of attention it has received as a research object.

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Table 1: Overview of Reviewed Ambulatory Studies and Prolonged Cardiovascular Findings

Stress Source	*Study*	*N*	*Ambulatory Duration*	*Type of Prolonged Activation*	*Specific Stress Factor*	*Prolonged Activation Findings*	*Controlled Biobehavioral Variables*
Discrete	Brondolo et al. (40)	115 (48% men)	8 hr	Recovery	Communication with public	↑ SBP ↕ DBP ↕ HR 15 min after	Posture, activity
	Brosschot et al. (41)	73 (20% men)	± 14 hr	Recovery	Daily stressors	↑ HR ↕ HRV sleep	Smoking, coffee, alcohol
	Ituarte et al. (42)	120 (47% men)	48 hr	Recovery	Stressful events during past 6 months	↑ HR sleep	Age, gender, BMI
	Hall et al. (43)	59 (51% men)	1 night	Anticipatory	Oral speech task after awakening	↓ HF ↑ L/HF sleep	Awaking time, exercise, coffee and alcohol
Chronic	Van Egeren (45)	37 (46% men)	24 hr	Recovery	High demand-control imbalance	↑ SBP ↕ DBP evening after work	BMI, gender, caffeine
	Steptoe et al. (46)	162 (37% men)	13 hr	Recovery	High demand-control imbalance	↑ SBP ↑ DBP ↕ HR evening after work	Gender, age, BMI, posture
	Schnall et al. (47)	195 men	2 x 24 hr	Recovery	High demand-control imbalance measured twice, 3 years apart	↑ SBP ↑ DBP evening after work; ↑ SBP ↕ DBP sleep	Age, BMI, alcohol, smoking
	O'Connor et al. (48)	27 (63% men)	2 x 10-15 hr	Reoccurring	High demand-control imbalance	↕ BP evening after work, ↑ BP non-work day	Age, gender
	Fauvel et al. (49)	70 (22% men)	24 hr		High demand-control imbalance	↕ BP ↕ HR evening after work, sleep	Age, gender, BMI, alcohol
	Steptoe et al. (50)	49 men	2 x 8 hr		High demand-control imbalance	↕ BP↕ HR non-work day	
	Goldstein et al. (51)	138 women	4 x 24 hr		High demand-control imbalance	↕ HR ↕ BP evening after work, sleep, non-work day	Age, BMI, posture, alcohol, caffeine
	Steptoe et al. (52)	104 (36% men)	9 hr		High demand-control imbalance	↕ BP evening after work	Age, BMI, physical activity

	Vrijkotte et al. (54)	109 men	3 x 24 hr	Recovery	High effort-reward imbalance	↓ HRV ↑ SBP ↑ HR ↕ DBP evening after work; ↓ HRV ↕ SBP ↕ HR ↕ DBP sleep, non-work day	Age, BMI, physical activity, posture, smoking, alcohol
	Hanson et al. (55)	70 (44% men)	8-12 hr		High effort-reward imbalance	↕ BP ↕ HR ↕ HRV evening after work	Gender, smoking
	O'Connor et al. (56)	27 (63% men)	2 x 15 hr	Recovery, reoccurring	Stress specific for general practitioners	↑ SBP ↕ DBP evening after work; ↑ SBP ↑ DBP non-work day	Age, BMI
	Unden et al. (57)	148 (79% men)	24 hr (for 93% of the sample)	Recovery	Low work-related social support	↑ HR ↕ BP after work, sleep	Age, gender, BMI, smoking, alcohol, physical strain at work
	Carels et al. (58)	50 women	± 15 hr	Recovery	Marital stress	↑ BP ↕ HR during evening	Age, BMI, posture, caffeine consumption
	King et al. (59)	10 women	1 or 2 days during waking hours	Recovery	Caregiving of ill relative	↑ BP ↕ HR during evening	Age, BMI
	Steffen et al. (61)	69 (43% men)	20 hr		Perceived racism	↕ BP during sleep	Age, gender, BMI
	Brisson et al. (62)	199 women	24 hr	Recovery	↑ Job strain and ↑ family load	↑ SBP ↑ DBP during evening, sleep	Age, BMI, smoking, alcohol, physical activity
Negative affective state	Kamarck et al. (63)	120 (50% men)	2 x 24 hr plus 4 days during waking hours only	Recovery	Negative affect (sad, frustrated, stressed, upset)	↑ BP ↕ HR 45 min later	Gender, race, negative affect at recovery, posture, physical activity, caffeine, alcohol, talking

	Brosschot and Thayer (64)	33 (36% men)	8 hr	Recovery	Arousal and negative valence	↑ HR 5 min later	Age, gender, emotional valence, physical activity at recovery
	Shapiro et al. (65)	197 (50% men)	24 hr	Recovery	Frequent daily anger or sadness	↑ BP ↕ HR during sleep	Posture, activity
Negative emotional dispositions	Räikkönen et al. (70)	100 (50% men)	3 x 8-14 hr	Recovery	Hostility, pessimism, anxiety	Continuously ↑ BP ↕ HR	Age, posture, location, physical activity
	Jamner et al. (71)	33 men	24 hr	Recovery	Hostility	↑ SBP ↕ DBP ↕ HR during sleep	
	Pasic et al. (72)	32 (56% men)	24 hr	Recovery	Hostility Anxiety	↑ SBP ↕ DBP 3 hr preceding awakening -	Gender, age, BMI
	Shapiro et al. (73)	144 (50% men)	24 hr	Recovery	Cynical hostility	↑ SBP ↕ DBP ↕ HR during sleep only in African American	Gender, BMI
	Kario et al. (74)	231 (55% men)	24 hr	Recovery	Anxiety, depression	↑ SBP sleep-to-awake ratio ↕ DBP in men	Age, BMI, physical activity during waking and sleep
	Schneider et al. (75)	33 men	24 hr	Recovery	Type A	↕ HR ↕ BP during sleep	
	Van Egeren and Sparrow (76)	107 (52% men)	2 x 24 hr	Recovery	Type A	↕ HR during sleep	Gender, BMI, caffeine

Note. Parenthetical numbers in the Study column correspond to the reference list numbers. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HRV = heart rate variability; BMI = body mass index; HF = high frequency power; L/HF = low to high frequency power; BP = blood pressure; ↑ = higher; ↓ = lower; ↕ = no difference.