Chapter 14
Psychiatry

Introduction

Emotional regulation has been related to HRV patterns (Thayer 2000; Appelhans and Luecken 2008). Emotion regulation ability has been operationalized and associated with lower or higher HRV (Appelhans and Luecken 2008; Thayer and Fischer 2009; Thayer et al. 2009). Thus, a meta-analysis proposed that "HRV is important not so much for what it tells us about the state of the heart as much as it is important for what it tells us about the state of the brain" (Thayer et al. 2012).

Depression

Depression has a prevalence of between 8 and 12 % around the world (Andrade et al. 2003). It is expected that depression will have the biggest health impact after cardiovascular disorders by 2020 (Murray and Lopez 1997; Kemp et al. 2010). Interesting enough, depression and cardiovascular disease do not develop independently. Rather, there is a clear association between depression and cardiovascular disease. Twenty to forty percent of patients with CVD have at the same time depression (Woltz et al. 2012). The relation is bidirectional – it seems that patients with depression can develop CVD more readily and patients with CVD can develop depression more readily (Pratt et al. 1996; Woltz et al. 2012). HRV changes are well documented both in CVD and in depression. Here some recent theories regarding the genesis of depression will be introduced. In a second part the relation between depression and heart disease will be examined and the findings of HRV changes in relation to depression will be discussed in greater detail.

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Pathophysiology of Depressive Disorders

Major depressive disorder is the official denomination of the malady commonly called depression. The idea of depression includes a wide variety of disorders. A cursory look at concomitant ICD codes reveal depressive symptoms in bipolar affective disorders, depressive episodes, recurrent depressive disorders, and anxiety disorders, not to mention several kind of somatization disorders where depressive symptoms might be more or less existent. One problem is gradation to differentiate between mild, moderate, and severe depression. Another problem regards diagnosis. It is, for instance, a well-known problem that several symptoms related to advanced cancer disease (e.g., anorexia, fatigue, sleep problems) might be due to the original disease, a coexistent depression, or a combination of both. Similar problems exist in the combination of severe cardiac diseases and depression. While at least diagnostic instruments can make it easier to collect a unitary group of study patients, it is far more difficult to agree on the pathophysiology of depressive disorders, in case there is just one.

Major depressive disorder (MDD) is regarded as a familial disorder and some scientists argue that its familiarity is due to genetic factors, suggesting that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed. However, there is no solid evidence for specific genes and specific gene-by-environment interactions in the pathogenesis of MDD (Hasler 2010). The influence of genetic factors might be up to 40 %. Non-genetic factors, explaining the remaining 60 % of the variance in susceptibility to MDD, are individual-specific environmental effects mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce (Sullivan et al. 2000; Kendler et al. 2002, 2006; Hasler 2010), that is, if it is at all possible to find clear causal links. The point here is that, due to its genetic origin, depression probably cannot be circumvented, but once it manifests, several psychosocial concomitant circumstances can be used to control the symptoms.

Today's ideas around the pathophysiology of depressive disorders focus on stress and maladaptive responses of the HPA axis, pathological changes in endogenous monoamines, the neurotrophic hypothesis, ideas around altered glutamatergic and GABAergic subsystems, and combinations of those theories. I summarize them here only briefly with a main focus on theories that include similar brain structures as those involved in generating of HRV.

Stress Reactions and Immune System

There is a long history of discussion of the role of the endogenous stress system and its relation to depression. Stress response differs between genders; men have a higher stress response regarding achievement challenges, whereas women develop

more stress responses related to social situations. Generally, women show higher stress responses, which would match the higher prevalence of depression in women. Not matching are numerous studies that do not show impaired HPA patterns in MDD (Pariante and Lightman 2008). It is unclear whether HPA dysfunctions have an impact on the effect of antidepressive drugs (Schule 2007). One possible role of the endogenous stress system exists in depressed subjects with a history of childhood trauma. Several lines of evidence, in other animal, experimental and clinical studies suggest an influence of the HPA system on the disorders. Most recently, this is based on newer epigenetical ideas indicating that the effects of genes switched off (or on) as a consequence of trauma in childhood can be transferred to the following generations without changed genes.

Some sickness behavior, for instance that related to influenza, is well known to mimic several traits of depression. It shares many symptoms with depression, including fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Recent theories (Maier and Watkins 1998; Dantzer et al. 2008; Raedler 2011) focus on brain systems that might be activated in association to this sickness behavior. The behavioral changes are mediated by pro-inflammatory cytokines such as interleukin-1α, tumor necrosis factor-α, and interleukin-6, which activate the HPA axis and impair the central serotonin system. Depressive symptoms all the way up to suicide are a well-known serious adverse effect of treatment with immunological active substances like interferon. Some studies report drugs like aspirin and celecoxib with known effects on the synthesis of prostaglandins caused by inflammation might have inherent or increase effects of antidepressive drugs (Rahola 2012). Depression, so the idea, might be induced by an inflammatory process, which is extended in the brain causing depressive effects.

Monoamines

Most of the noradrenergic and dopaminergic neurons are located in midbrain and brain stem nuclei and project to large areas of the entire brain. Their role is similar to that other nuclei with specific receptors projecting to most of the brain – to have influence reactive patterns and to trigger general responses such as cholinergic or opioidergic neurons. All these systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition. This led early on to the idea that deficiencies in the monoaminergic neurons could cause depression. The well-known properties of antidepressive drugs, to modify and mainly increase the release or the stay of monoamines in the synaptic gap, supported apparently this idea. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (Belmaker and Agam 2008; Hasler 2010). Serotonin is the most important candidate receptor. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD. Despite several experimental approaches supporting this idea,

there are also conflicting results and the overall evidence is still contradictory (Hasler 2010; Rahola 2012). Also dysfunction of the central noradrenergic system has been discussed, but in part because of difficulties in depleting isolated central noradrenaline, its role is unclear.

Almost all established antidepressants target noradrenaline or serotonin receptors. However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Antidepressive drugs have far more effects than only on the monoaminergic receptor, among others also effects on the brain immune system and intracellular translation mechanisms. Despite these limitations, the monoamine deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression until today. The monoamine hypothesis is particularly interesting for the interpretation of HRV because it is also related to the function of the ANS. In addition (as discussed above and below), several antidepressant drugs have profound effects on HRV.

Glutamate and GABA Receptors

Gamma-aminobutyric acid (GABA) and glutamate are two further ubiquitous-appearing transmitter–receptor systems in the brain. While gamma-aminobutyric acid has a generally inhibitory effect, glutamate is exhibitory and has effects on long-term changes in neurons as well. Changed GABA concentrations and diminished GABA receptor function has been reported in depressive patients. Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms (Birkenhager et al. 1995).

The role of the glutamate system received more attention recently when several studies showed decreased depressive symptoms short after application of ketamine, a glutamate receptor antagonist in depressed patients. Glutamate release inhibitors have also shown antidepressive effects. Additionally, abnormal NMDA (a glutamate receptor subtype) function has been shown in depressive patients. All this suggests that this theory is promising and might offer a new therapeutic approach.

Neurotrophic Theory

The continuing function of (brain) neurons is dependent on the regular release of neurotrophic factors. Dysfunctions of neurotrophic systems have been shown in chronic pain and psychiatric diseases (Martinowich et al. 2007). Brain-derived neurotrophic factor (BDNF) has been studied most. Preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in

hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment (Martinowich et al. 2007; Hasler 2010). The administration of ATDs normalizes the levels of BDNF as has been observed both in studies with animals and in postmortem studies on human brains of people suffering from mood disorders (Rahola 2012). A different argumentation is based on the recently discovered phenomena that even in the adult brain cell division occur in at least two places, among them the hippocampal subgranular zone (SGZ). This is interesting in depression where the hippocampus is one of the involved brain regions. Blockade of hippocampal neurogenesis slightly inhibits the effect of antidepressant treatments in rodents (Kempermann 2008) and antidepressant treatments increase the concentrations of different hippocampal growth factors that influence neurogenesis (Rahola 2012). This is significant because neural progenitors of the hippocampal subgranular zone (SGZ), which differentiate and integrate into the dentate gyrus, need about 2–3 weeks to reach the hippocampus, fitting with the number of weeks antidepressive drugs normally need to have an effect.

Depression and Heart Disease

Observed as early as 1937 (Maltzberg 1937), clear associations between depression and coronary heart disease have been reported many times (recent review (Nemeroff and Goldschmidt-Clermont 2012)). There is also a clear relationship between the magnitude of depressive symptoms and increased cardiac morbidity. Already low scores in the Beck Depression Inventory of 5–9 are associated with an increased frequency of cardiac events (Sheps and Rozanski 2005; Kunzansky 2005). But there are some interesting details in this relationship that are worth a closer look. First, the association of depression and cardiac problems is robust and has been shown repeatedly with the help of statistical models where further common associated risk factors like smoking, overweight, diabetes, and lack of exercise were taken into consideration. Most studies included patients with major depression. For instance, in one study about 400 patients with clinical depression and 400 matched controls, depressive persons had a two-third increased likelihood to develop serious physical illnesses including cardiac disease (Holahan et al. 2010). Another example is a study of 2,832 adults without history of CAD followed up in mean 12 years. Depressed mood and lack of hope was associated with an increased risk of fatal and nonfatal ischemic heart events (RR 1.5 and 1.6, respectively) in a statistical model taking in other risk factors (Anda et al. 1993). Also bipolar disorders are associated with an increased risk for hospital admission due to ischemic events (Callaghan and Khizar 2010).

Several lines of evidence show the bidirectional effects of depression. Depression in patients with different cardiac diseases has a negative effect on the short- or long-term outcome, so in congestive heart failure (Lesman-Leegte et al. 2009), AF (Frasure-Smith et al. 2009), and after MI (Glassman et al. 2009). Also anhedonia, the incapability to feel pleasure, is strongly associated with fatal outcome after myocardial infarction (Davidson et al. 2010).

However, not all reports are clear without ambiguity. Working in clinical practice, it is not possible to overlook a clear association between risk factors for CVD and depression. Depressive patients smoke, eat too much, exercise too little, and in addition take drugs predisposing them even more to excess weight. In the Heart and Soul study of 1,017 patients with coronary heart disease focused on depression and its consequences, the researchers argue that they were able to identify physical inactivity, non-adherence to medications and other negative behaviors as main reason for cardiac disease (Cohen et al. 2010). The study is excellently conducted but has earned some critical remarks regarding the study population (Nemeroff and Goldschmidt-Clermont 2012).

On the pathophysiological level, several explanations have been proposed that can only be mentioned briefly here. One line of argumentation is based on the common inflammatory properties of both diseases. Depression is characterized by a sustained inflammation (Raedler 2011). As mentioned, some authors argue that depression might mimic a motivational pattern normally associated with peripheral infections ("flu"), where chronic immune signaling to the brain causes enduring depressive symptoms (Dantzer et al. 2008).

As mentioned earlier, depressive symptoms are associated with a wide range of immune system parameters, including increased numbers of peripheral leukocytes (particularly neutrophils and monocytes), decreased lymphocytes, and elevated cytokine production (e.g., IL-6) and acute phase proteins (e.g., CRP). Depressive symptoms are also associated with reduced functional tests such as natural killer cell activity and mitogen-induced lymphocyte stimulation. There is overlap in the characteristic immune system correlates of depression and the immune system-related risk factors for coronary artery disease (e.g., elevated CRP levels, pro-inflammatory cytokines such as IL-6 and TNF-alpha, leukocytes, and increased antibody levels to viruses) (Kop and Gottdiener 2005). Several studies have shown increased CRP, not surprisingly also increased IL-1 and IL-6 (Howren et al. 2009). Evidence is conflicting, however. In one study inflammatory changes could be explained mainly by existing risk factors like diabetes, hypertension, obesity, and smoking (Morris et al. 2011). The relationship between depression and immune system parameters is supposed to be bidirectional: central nervous system correlates of depressive symptoms result in immune system changes and vice versa (Kop and Gottdiener 2005). Administration of pro-inflammatory cytokines results in elevated extracellular cerebral serotonin (Capuron 2004) as well as depressed mood, increased sleep, and general malaise (Maier and Watkins 1998).

Another argumentation line is related to the platelet clotting cascade, whose role in coronary heart disease is well known (Nemeroff and Goldschmidt-Clermont 2012). Platelet activation is increased in patients with depression even without cardiac disease or medicaments (Musselman et al. 1996). The platelet function in depressive patients without coronary disease, with risk factors for it or with coronary disease, is either comparable or even declined compared to patients with coronary heart disease without depression (Bruce and Musselman 2005). There are some evidence that antidepressants of SSRI type have an anticoagulant effect including an increased risk for gastrointestinal bleeding, something that has not

been observed with traditional tricyclics (Bruce and Musselman 2005). Also, endothelial dysfunction (Tomfohr et al. 2008), oxidative stress, and impaired arterial repair (Dome et al. 2009) have been linked with depressive disorders.

As discussed in Chap. 6, some interesting models track the different interacting variables in depression and cardiac disease (Thombs et al. 2008; Stapelberg et al. 2011).

Depression and Changes in HRV

In 17 patients with major depressive disorder, 5-min short-term HRV measurements were conducted before and after treatment with antidepressants using SDNN and RMSSD. Depression was assessed with the Hamilton Rating Scale (HRS). Changes in HRV did correlate with posttreatment HRS and differences of HRS pre- and posttreatment. These relationships were strongest in patients who responded positively to nontricyclic antidepressant medications. HRV before treatment was not predictive of treatment response nor did HRV reliably reflect the severity of depressive symptoms (Balogh et al. 1993). Thirty-two previously not medicated patients with major depression and 32 matched control persons were tested for heart rate variability (SDNN) while resting and during paced breathing. There were no differences between the groups before therapy. The patients were randomly allocated for daily treatment with 150 mg amitriptyline, 150 mg doxepin, 150 mg fluvoxamine, or 20 mg of paroxetine. During treatment with either amitriptyline or doxepin, SDNN had significantly decreased after 14 days, whereas patients treated with fluvoxamine or paroxetine showed no significant changes (Rechlin 1994; Rechlin 1994). In this context it is relevant to point out that SSRI can increase HRV variability (Khaikin et al. 1998), whereas amitriptyline decreases variability (Rechlin 1994; Rechlin 1994).

Medically healthy patients have elevated levels of noradrenaline as result of an increased total body sympathetic activity (Veith et al. 1994). Carney compared 19 depressed and 19 nondepressed CAD patients (with positive angiography) with Holter monitoring. He found a significantly lower SDNN in depressed patients (90 ± 35 vs. 117 ± 26 ms) (Carney et al. 1995).

Patients with depression were tested before and after treatment with imipramine or mirtazapine in a small double-blind randomized study (ten patients in each group). HRV was studied before and after 4 weeks. They calculated LF, MF, and HF. Before treatment, all 20 patients were compared to age-matched controls. Depressed patients showed more suppression of HR variability (both mid- and high-frequency band fluctuations) indicating stronger vagal inhibition and a reduced increase of BP variability (mid-frequency band fluctuations). All patients had a decrease of HRV after 4 weeks of treatment (Tulen et al. 1996).

Regarding the bidirectional relation between immune changes and depression (Kop and Gottdiener 2005), it is interesting to observe that administration of proinflammatory cytokines result in elevated extracellular cerebral serotonin

(Capuron 2004) as well as depressed mood, increased sleep, and general malaise (Maier and Watkins 1998).

Twenty-seven patients after MI and with depressions were randomized to either sertraline 50 mg/day or placebo. Eleven post-MI patients without depression were used as a control group. HRV was taken 1–2 weeks after MI and at 6, 10, 14, 18, and 22 weeks after being randomized. The rate of recovery of HRV was determined by use of a growth curve model based on repeated measures analysis of variance. SDNN increased linearly in the sertraline-treated group in comparison to the control group, in difference to a modest decline in SDNN in the placebo group from 2 to 22 weeks (McFarlane et al. 2001).

Subjects with depressed mood showed greater reductions in HF during a cognitive stress test (speech) and lower reductions in a cold pressure test (an ice bag 3 min on the forehead). This suggests that the parasympathetic tone is diminished in subjects in depressed mood (Hughes and Stoney 2000). Subjects with depression showed lower normalized ULF, VLF, and LF, but not HF after other adjusted risk factors (Carney 2001). Patients with depression treated with fluoxetine or doxepin had an increased SDANN in case of response but a decreased SDANN and SDNN in case of nonresponse in a small study ($n = 13$) (Khaikyn 1998). An interventional therapy with cognitive behavioral therapy reduced heart rate and increased rMSSD, but produced no changes in other time-domain measures (Carney et al. 2000). In a study comparing 21 depressed persons with healthy subjects using Holter ECG and both spectral and time-domain measures, there was no difference between the groups (Sayar et al. 2002).

Depression is a risk factor for medical morbidity and mortality in patients with coronary heart disease. Congestive heart disease patients show low VLF depending on their depressive state – VLF was low in 47 % of those who were moderately to severely depressed, in 29 % of those who were mildly depressed, and in 13 % of those without depression (Stein et al. 2000). Bär conducted a small study including 18 patients with depression (without prior treatment with antidepressants) and 18 matched controls. Before treatment, there were no differences in HRV. Differences developed after the start of treatment with antidepressants (Bär et al. 2004). In 873 patients with stable cardiovascular disease, depression was assessed and found in 195 of them. Holter monitoring using usual time and frequency-domain algorithms did not show any difference between CVD patients with or without depression (Gehi et al. 2005).

Cross-sectional analysis of a major depression cohort study included 524 controls, 774 patients with a diagnosis of major depression earlier in life (remitted depression), and 1,075 patients with current depression. HRV was recorded over 1.5 h, SDNN and RSA was used. Both depression groups had a lower SDNN and RSA. Anxiety and lifestyle factors in the analysis did not change this effect. Depressed patients who used SRIs, TCAs, or other antidepressants had a significantly lower SDNN and RSA. So most of the HRV reduction was due to medicaments and not due to the illness (Licht et al. 2008).

Holter monitoring in 63 adult depressive but otherwise healthy patients was used to observe HRV changes. In addition, portable devices recorded physical activity,

social interaction, and negative mood. Depression was associated with higher heart rate and negative mood during the day. Persons with higher depression scores tended to have lower HRV. Participants had lower HRV indices while alone and higher HRV indices while in social interaction. The authors discuss whether or not social interaction can buffer adverse health effects of depression (Schwerdtfeger and Friedrich-Mai 2009).

In an intervention study with randomized administration of sertraline or placebo, patients with major depression had initially decreased HRV (Holter monitoring, using frequency-domain values). It had been hypothesized that after 16 weeks of sertraline treatment, HRV would partially recover, which did not occur (Glassman et al. 2007).

The already mentioned seminal "Heart and Soul" study investigated 863 outpatients with stable CHD on depressive syndromes and HRV changes (Holter monitoring, time and frequency domain). It found an association between somatic depressive symptoms and lower HRV, but not with cognitive depressive symptoms. The inverse association of somatic symptoms with HRV was largely explained by differences in comorbidities and lifestyle factors (de Jonge et al. 2007).

Another multicenter study examined depression patients using 15–30 s strips or manual 30 s pulse measurement to calculate SDNN and following patients for over 10 years. The resting heart rate was significantly higher in patients with more severe depressive symptoms. There was no significant association of low HRV and QTc-prolongation with depressive symptoms or mortality. An increase in resting heart rate/SD, adjusted for age, was associated with a 26 % increased risk of cardiovascular mortality (Kamphuis 2007).

In 26 elder patients, short-term HRV (5 min) was conducted: time domain, frequency domain, DFA, sample entropy. The study used Charlson comorbidity index (CCI) and the Yesavage Geriatric Depression Scale (GDS). DFA was correlated with CCI, but not sample entropy. Interestingly, GDS was correlated with higher entropy, thus contradicting the notion that normally lower entropy is related to more severe illness (Blasco-Lafarga et al. 2010). Summarizing these studies, Servant concluded recently that at the moment there is no evidence of a link between decreased HRV and depression independent of CVD (Servant et al. 2009).

In the Cardiovascular Health Study, Kop evaluated 907 persons of an average age of 71 and without clinical symptoms of CVD. The study used a wide range of measures including time domain, frequency domain, DFA, and heart rate turbulence (Holter monitoring) and analyzed these indices together with inflammation parameters like C reactive protein, IL-6, fibrinogen, and white blood cell count. Participants were followed for up to 15 years. One-hundred and thirty-one patients had depressive symptoms at the time of assessment. As expected, depression was associated with increased CVD mortality. Depression was associated with changes in daytime HRV (there with reduced DFA, but no other HRV indices). None of the 24-h parameters were associated with depression. The authors consider the associations as relatively weak. Importantly, ANS reductions correlated with depression and CVD mortality were largely explained with CVD alone (Kop et al. 2010).

In 2010 Kemp published a review and meta-analysis about the impact of both depression and antidepressant treatment on HRV that included 18 published studies.

The review concluded that depressed patients had reduced time domain and HF, increased LF/HF ratio, and decreased nonlinear indices (relative high frequency of largest Lyapunov (sic) exponent, minimum embedding dimension of the QT interval) in drug free individuals in severe depression. Surprisingly, the authors found no differences in pre- and posttreatment measurements with TCA (amitriptyline, doxepin, and imipramine), SSRIs (paroxetine, escitalopram, venlafaxine), mirtazapine, nefazodone, and rTMS. First after secondary analysis, it was shown that, unlike other antidepressive drugs, TCA reduced HRV (Kemp et al. 2010).

Conclusion

I agree with Kemp et al. (2010) that there is clear evidence of an inverse association between depression and HRV parameters and that the effect size is rather small. Several confounders can make interpretation difficult, such as medications and anxiety (Stapelberg et al. 2012).

Use of HRV as diagnostic parameter for depression alone might not be appropriate at the moment as long as new studies with more predictive parameters fail to appear. However, reflecting the high comorbidity of CVD and depression, HRV can play nevertheless an important role in a comprehensive evaluation of depressive patients regarding their cardiovascular risk. Prospective intervention studies are lacking. We need studies that address potential preventive treatments in depressive patients with reduced HRV parameters and the effects thereof. Use of HRV in further research can be useful provided that it is part of a research hypothesis and not only one of several parameters. It is important not to confuse HRV as outcome parameter. Increase in HRV does not necessarily signify a better outcome even if associations are reported. I agree with Stapelberg et al. (2012) that HRV is a good starting point to investigate the causal network linking depression and CVD, but the causal relationships have to be discussed cautiously.

Psychosis

Besides suicide and accidents, schizophrenic patients have an up to three times all-cause mortality and SCD has been discussed as important cause (Koponen et al. 2008). HRV has only been used in some few studies. In 23 patients with schizophrenia or schizoaffective disorder, 24-h Holter monitoring demonstrated a bimodal distribution: 11 of 23 patients had a PNN50 of > and = 8.0, and 12 had a PNN50 of < and = 4.0; no subject had a PNN50 value between 4.0 and 8.0. All 12 patients with low cardiovagal tone (vs. only 6/11 of the other patients) had schizophrenia. PNN50 was not associated with present age, gender, smoking, IQ scores, or symptomatology (Malaspina et al. 1997). Same patients in psychotic states show decreased HF without changes in LF, suggesting psychotic states suppressed the parasympathetic

function without affecting the sympathetic function (Toichi et al. 1999). In 53 patients with chronic schizophrenia, no difference was noted between them and a control group regarding HRV. HRV was measured in 17 first-episode patients with psychosis previously not treated with neuroleptics and 21 healthy controls during two tests. RMSSD and HF were significantly reduced in patients and remained unaltered during the tasks; whereas, in controls the HRV diminished with increasing mental stress. The authors conclude that acute psychosis might be characterized by a limited capacity to respond to external demands at the level of the autonomic nervous system (Valkonen-Korhonen et al. 2003). Patients with schizophrenia had decreased frequency-domain patterns compared to controls, especially in LF. This was exacerbated in patients receiving atypical antipsychotics (Mujica-Parodi et al. 2005). Fifteen patients with schizophrenia had lower complexity measures (approximate entropy, compression entropy, fractal dimension) and increased QT-variability compared to matched healthy controls (Bär et al. 2008). Jindal was unable to replicate these results in a group of neuroleptic naive patients with psychosis, except for some minor changes (Jindal et al. 2009).

Phobias

The Normative Aging Study enrolled 581 men between 47 and 86 years old and free of coronary artery disease and diabetes. Symptoms of anxiety were assessed using the Crown-Crisp index, an instrument that in previous prospective studies was a strong predictor of the risk of sudden cardiac death. HRV was assessed with the paced-breathing technique, SDNN. The maximal minus minimal HR over 1 min was calculated. Men with higher levels of phobic anxiety had lower SDNN (Kawachi et al. 1995). Fifty-four flight phobics were assessed with HF and sample entropy (paced breathing and under a fearful sequence of audiovisual stimuli at the end of treatment and at 6 months follow-up) and the results related to treatment outcome. A regression model could only be established when HR entropy was added to the HR variability measure in a second step of the analysis. HR variability alone was not found to be a good outcome predictor (Bornas et al. 2007).

Stress-Related Disorders

Introduction

After Selye introduced the notion of stress, definitions have been debated for many decades. Some distinguish between positive and negative stress; whereas, others focus exclusively on “negative” forms like threats or anticipated perturbations of safety (Thayer et al. 2012). Stress is also discussed as a psychological and somatic

reaction when the adaptive capacity of the individual is exhausted. There is increased interest in this adaptive capacity, also described as resilience, and there is no doubt that it relies on the social, psychological, but also genetic and epigenetic background.

For the mental processing of stress, the amygdale is understood to be a central structure. This brain structure has been characterized as a first responder to potential threats and as an important part of adaptive fear responses (LeDoux 1996). Some argue for a function both for aversive and appetitive stimuli (e.g., Whalen and Phelps 2009), while others conclude on a predominant role in negative stimuli (e.g., Cunninham 2008). The role of prefrontal areas are usually underestimated due to many animal models based on rodents, only more recently newer imaging technology has shifted the focus to humans.

Psychological stress is more and more identified as an important risk factor, not the least for cardiovascular disease (Steptoe and Kivimäki 2012). Associated to the idea of variability as a sign of the stability of the whole system, higher indices of HRV should indicate robustness against stressors. In fact, this has been shown (Weber et al. 2010) in studies discussed below.

Physiology and Pathophysiology of Stress

Classical stress reactions include hormonal changes, activation of SNS, and decreased activity of PNS. The hormonal pathway is the well-known hypothalamic–pituitary–adrenocortical axis. Stress activates hypothalamic neurons secreting corticotropin-releasing hormone (CRH) and vasopressin. CRH promotes release of the adrenocorticotropic hormone (ACTH), which acts on the adrenal cortex, causing release of glucocorticoids. The released corticoids themselves trigger a negative feedback circle stopping further release of CRH and ACTH (Fig. 14.1).

The SNS activation is associated with increased levels of adrenaline and noradrenaline with the already discussed consequences. In addition, it has effects on the immune system, probably mediated in lymphatic nodes (which are innervated by SNS fibers). Stress has remarkable effects on the immune system. Short stress

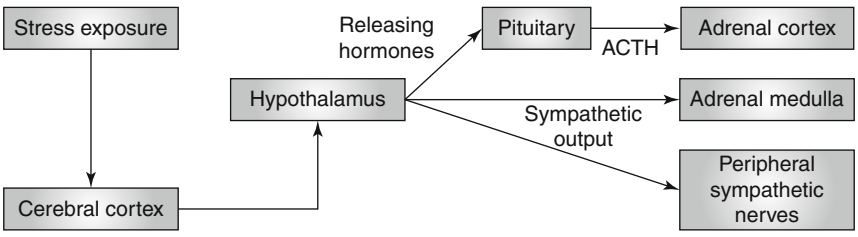

Fig. 14.1 Physiological stress response (Reproduced with friendly permission of Nature publishing group of (Steptoe and Kivimäki 2012))

situations usually trigger augmented immune activity, whereas chronic stress situations lead to immune depression.

A classical cardiologic disease associated with stress is coronary heart disease. The INTERHEART study included patients and controls from 52 countries and used a chronic stress classification that included stress at work, at home, financial problems, lack of control, and depression. The study took into account stress variables in a statistical model and added classical causal factors like apolipoprotein ratio, obesity, smoking, diabetes, hypertension, and others. Independent of other risk factors, the odds ratio for MI was doubled in case of stress. This was independent of gender, nationality, and age (Yusuf et al. 2004). Not surprising, a temporal dose–response pattern between (work related) stress and metabolic factors has been observed (Chandola et al. 2008), as have been clear associations between long working time and CHD (Virtanen et al. 2012).

The pathological factors leading to CHD under chronic stress conditions are still under discussion. Greater morning increase of cortisol and reduced heart rate variability (see below) as a sign for attenuation of ANS and neuroendocrine function have been reported (Chandola et al. 2008). Additionally, an increase of hypertension in relation of stress has been shown (Markovitz 2004), though not always in association with an increased incidence of CHD (Chandola et al. 2008). The association between depression and CHD is well known (Nemeroff and Goldschmidt-Clermont 2012). And there is evidence of an association between chronic stress and depression (Netterstrøm et al. 2008). Other observed factors include the already mentioned suppressed immune function (Cohen et al. 1997), reduced telomere length (Brouilette et al. 2007), and metabolic syndrome (Chandola et al. 2006). Stress triggers health risky behavior like smoking (Kouvonen et al. 2005; Rod et al. 2009), decreased physical activity (Rod et al. 2009), shortened sleep, or sleep disturbances (Virtanen et al. 2009).

Acute stress can indeed cause MI events, as was first shown systematically after a major earthquake in Athens (Trichopoulos 1983), terrorist attacks in the US (Feng et al. 2006), and missile attacks on the population in Israel (Kark et al. 1995). Even after dramatic soccer games, increases of cardiovascular events have been reported (in the Dutch study quoted, only in men) (Witte et al. 2000; Wilbert-Lampen et al. 2011). The biological bases to acute stress-related MI are not completely clear, but procoagulant factors, disturbed rhythm, and transient ischemia have been discussed (Steptoe and Kivimäki 2012).

HRV Changes in Stress-Related Disorders

Different mental states and their consequences on HRV in laboratory were assessed in healthy normotensive men and women. Spontaneous breathing subjects and subjects under paced breathing showed no changes. Mental distraction (word puzzle) and mental stress (computer quiz) led to decreased HRV (Madden and Savard 1995). HRV was tested to measure stress responses during sleep following a standardized task and showed changes in frequency-domain values (Hall et al. 2004)

Of particular interests are studies investigating the recovery after stress stimuli and their relationship to pretest HRV. Weber and colleagues tested 44 healthy men between 20 and 50 years old. As stress tests they used the manometer test (a test to recognize features on a screen under time pressure) and mental arithmetic tests. They analyzed both frequency domain and time domain (RMSSD), reporting a correlation between RMSSD and HF (of r 0.9). They divided the group by variability of HRV with help of RMSSD (split point 35.5 ms) resulting in one "low group" (with 25.8 ± 6.5 ms) and one "high group" (with 51.7 ± 13.9 ms). These groups did not differ in certain aspects with exception of age (age was consequently used as covariate in further analysis). Most importantly, they observed significant differences between the groups. Subjects with low baseline HRV had a more pronounced increase of diastolic blood pressure under the tests and did not recover in the following 5 min resting phase. The high-HRV group showed decrease of HRV under stress, returning immediately after tests to the pretest level. By contrast, the low-HRV group retained a lower HRV also under resting conditions. Additionally, cortisol decreased more slowly in this group and the recovery of the THF-alpha level was delayed. The authors concluded that the high group showed physiologically better coping of stress (Weber et al. 2010). This can be of importance. Delayed recovery of BP after stress can predict increases in BP several years later (Steptoe and Marmot 2006).

One study focused on the effects of *work stress* on blood pressure, heart rate, and heart rate variability. One-hundred and nine male white collar workers were included and their work stress level was assessed with a paradigm that included job overcommitment (inability to withdraw from job obligations) and imbalance between effort and reward (Siegrist model for work stress). The study used 24 h-ECG and RMSSD as measure for the vagal tone. Men with a high imbalance had higher blood pressure. Overcommitment showed no association with blood pressure. There was a trend, but no significant effect, for the RMSSD to be lower for subjects with imbalance, but not overcommitment. Large standard deviations for RMSSD were observed (Vrijkotte et al. 2000).

Caregivers (of patients with Alzheimer disease) compared to noncaregivers with a similar age and gender showed increased pre-ejection period values, whereas RSA values were not different. The authors regard this as evidence of increased sympathetic activity (Cacioppo et al. 2000).

5-minute heart rate variability in frequency domain was measured in healthy subjects and correlated with self ratings of *trait anxiety and perceived emotional stress*. There was an inverse relationship between emotional stress and HFnu, which was independent of age, gender, trait anxiety, and cardiorespiratory fitness (Dishman et al. 2000).

Mental stress reaction in subjects with several apolipoprotein E phenotypes caused different changes in HRV. Subjects with apoE4/2, 4/3, and 4/4 showed a stress-related decrease in HRV, while E3/2 and E3/3 showed a slight increase (Ravaja et al. 1997)

Short mental stress leads to physiological reactions in individuals. The amount of the stress reaction, however, is different and a study identified different groups characterized either by high sympathetic markers for heart rate, high immunological activation and higher levels of steroids and norepinephrine, or lower reactions in all areas (Cacioppo et al. 1995).

In *generalized anxiety disorders,* diminished heart rate variability, especially in the HF band, has been reported (Thayer et al. 1996; Friedman and Thayer 1998; Cohen et al. 2000a, b, c).

Nine patients with *post-traumatic stress disorder* with fluoxetine treatment, nine PTSD patients without fluoxetine, and nine healthy controls were tested with 15-min HRV measures. In PTSD patients with fluoxetine, HRV measures were normal compared to the untreated PTSD patients (Cohen et al. 2000a, b, c). Six female rape victims with PTSD were treated with CBT. This resulted in decreased HRV during REM sleep in 5 responders, whereas the nonresponder showed an increase (Nishith et al. 2003).

In 59 adults with post-traumatic stress disorder, HRV was taken in a laboratory setting where the subjects were confronted with neutral or trauma-related stimuli. A significant proportion of the group had no elevated basal heart rate. The subgroup with elevated basal HR had significant correlations with RSA. In their conclusion the authors outline a possible association between basal elevated heart rate and parasympathetic alteration independently of sympathetic influences in a subgroup of subjects with PTSD (Hopper et al. 2006).

In pregnant and non-pregnant women, use of a standardized stress model (Trier Social Stress Test) led to decreased HF, increased LF/HF, and in tendency of increased LF. No differences between pregnant and non-pregnant women were recorded, neither differences between pregnancy in second and third trimester (Klinkenberg et al. 2009).

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