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Catherina Tischler

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1 Introduction

1.1 *Problem*

Medical procedures of all kinds are known to be powerful stressors for a majority of patients. Due to the great heterogeneity of the underlying diseases, medical diagnostics, treatments, personal factors, and situational factors, one cannot simply talk about stress in the medical context. Research has to focus on a variety of distinct and specified areas of interest to be able to provide reliable and to some extent generalizable or, ideally, even practically relevant results. (Schmidt, 1992; Schumacher, 2002; Vögele, 1992, 2007)

Carotid artery disease is a condition characterized by the narrowing (stenosis) of the carotid arteries in the neck due to the build-up of plaque in their walls, resulting in reduced blood supply to the brain. Individuals diagnosed with high-grade carotid artery stenosis constitute a group of patients faced with a severe disease that could lead to potentially disabling or even fatal strokes in the near future if not treated adequately and in time. Some of the patients are diagnosed after the occurrence of symptoms such as transient ischemic attacks, whereas others are asymptomatic and diagnosed by chance. Besides medical therapy, patients are either treated with carotid endarterectomy (CEA) or carotid artery stenting (CAS) to achieve revascularization. CEA comprises the surgical removal of the plaque, whereas CAS is a minimally invasive intervention in which a stent is placed inside the artery to increase blood flow. The choice for one of the two alternatives is mostly based on medical characteristics of the patient as well as on the patient's and physician's preference and is complicated by the ongoing scientific debate over their effectiveness. A great number of clinical trials has already addressed the issue of effectiveness of the two procedures, but only very little is known about the psychological stress associated with them. As both techniques can nowadays be performed routinely under local anesthesia (LA), the patient has the advantage of less adverse effects caused by anesthesia, quicker recovery, and shorter hospital stay, but on the other hand has to cope with the stress of consciously witnessing the intraoperative situation. (Biller, et al., 1998; Cao, et al., 2006; Ederle, Featherstone, & Brown, 2008; Levy, et al., 2008; Marrocco-Trischitta, et al., 2004; McCarthy, Trigg, John, Gough, & Horrocks, 2004; Quigley, Ryan, & Morgan, 2000; Richter, Kohrmann, Schwab, & Dorfler, 2008; Ringleb & Hacke, 2007; Society of Vascular Surgery, 2009a; van der Vaart, Meerwaldt, Reijnen, Tio, & Zeebregts, 2008; Yadav, et al., 2004)

The present investigation aims at filling the gap with regard to the subjective experience of both interventions and the psychological and physiological stress associated with them. For this purpose, the patients' subjective and objective stress responses before, during, and after CEA or CAS – both performed under LA – will be assessed against the background of a psychophysiological model that defines stress as an organism's response with emotional, behavioral, and physiological components (Ice & James, 2007).

1.2 *Definitions of Stress and Introduction to Stress Theories*

A great amount of research has been committed to understanding the complex phenomenon of stress – not only because of theoretical interest but also due to the practical relevance of stress in its widest sense. Many disciplines such as the biomedical or social sciences have tried to clarify the various causes, manifestations, and consequences of stress. Due to the complexity of the construct, one distinguishes psychological, biological, medical, social, cultural, or evolutionary approaches among others that each focus on different aspects of the stress process. (Ice & James, 2007)

The widely used term *stress* can lead to confusion as it refers to different aspects of the stress process – in research as well as in common speech. First, it can refer to the stimulus or input (such as a stressful experience like an earthquake), second to the physiological and psychological processing systems, or third to the stress response or output such as physiological markers of the stress response (e.g. rise in blood pressure during or after a stressful stimulus). (Ice & James, 2007; Janke, 1974)

The term stress nowadays mainly refers to the stress response or the whole stress process. Ice and James (Ice & James, 2007, p. 4), for example, defined stress as a “process by which a stimulus elicits an emotional, behavioral and/or physiological response, which is conditioned by an individual's personal, biological and cultural context”. Lazarus and Folkman, on the other hand, proposed that “psychological stress, therefore, is a relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being” (Lazarus & Folkman, 1984, p. 21).

For differentiation purposes, the stimulus or input is named stressor. Generally, a stressor can be any kind of stimulus that elicits a response and thus starts the stress process (Ice & James, 2007). It can be defined as an external event or situation that makes such high demands on a person that it hinders or exceeds adaptation. A popular content-based classification of stressors into five groups dates from Janke (1974) in the 1970s:

- External stressors (e.g. heat, cold, noise, sensory deprivation)
- Hindrance of the satisfaction of primary needs like sleep or food intake (deprivation of primary needs)
- Performance stressors (e.g. excessive demands due to pressure of time, criticism)
- Social stressors (e.g. social isolation, interpersonal conflicts)
- Conflicts (e.g. uncertainty regarding success or failure in efforts to cope, unpredictability)

Stressors can further be categorized based on their temporal course – acute versus chronic stressors –, based on their origin – physical, environmental, or psychosocial stressors –, and based on their intensity – e.g. life events versus daily hassles (Lazarus, 1990). However, these categorizations are artificial and thus only of limited value.

Stress is mostly accompanied by negative emotions of high intensity, though the type of emotion involved (e.g. anxiety or anger) can vary according to individual differences and situational characteristics (Janke, 1974).

Within the several disciplines in the stress field, one distinguishes between two major approaches to stress, namely between *systemic stress* that has its fundamentals in biology and physiology and *psychological stress* that has been developed mainly in cognitive and social psychology (Krohne, 2001). Another distinction categorizes the different theoretical approaches to stress into three types (Jerusalem, 1990; Lyon, 2000): response based, stimulus based, and transactional based.

As the present investigation aims at understanding stress responses in patients undergoing stressful medical procedures from a biopsychosocial model's perspective, the following introductory subsections will look at stress from different angles. Firstly, important physiological concepts of stress that can be subsumed under the term systemic stress will briefly be reprised (see section 1.3). The biomedical perspective of stress will be presented with a special focus on the measurement and interpretation of heart rate variability (HRV) as an indicator for stress (see section 1.3.2). Secondly, the turn to psychological approaches to stress will be outlined and the transactional stress theory formulated by Richard Lazarus will be described in more detail (see section 1.4). At the same time emphasis will be placed on some theoretical constructs of this stress theory that are central for the present investigation, such as coping. Lastly, supporting empirical evidence for an association of HRV and stress or anxiety will be reported (see section 1.5).

1.3 Systemic Stress: The Physiological Stress Response¹

With regard to systemic or response based stress, the beginning of stress research dates back to the early work of the famous physiologist Walter Cannon (1871 – 1945), who coined the so called *fight-or-flight response* to describe an animal's response to threats (Cannon, 1914). The immediate and automatic physiological responses or reflexes in the case of stress have an evolutionary adaptive value as they facilitate the escape of or the fight with an enemy in case of danger. Additionally, Cannon introduced the concept of *homeostasis* to refer to the maintenance of internal stability of the organism's physiological systems in the face of changing environmental conditions.

Based on this fundamental work, the pioneer of stress research, Hans Selye (1907 – 1982), formulated a stress theory that emphasized the non-specific response of the body to diverse stimuli or demands (like heat or cold) which intensely challenge the adaptability of the organism (Selye, 1936). He pointed out that most stimuli have, beside their specific effect depending on their characteristics (regional response, local adaptation syndrome, LAS), a nonspecific effect leading to the stress response of the organism (Selye, 1976). He postulated a stereotypical physiological stress response known as *general adaptation syndrome* (GAS) and described the concomitant somatic changes or damages in detail (Selye, 1936). The chronological development of the response to long lasting stressors that affect the whole body, the so called systemic stress, proceeds in three stages: the alarm reaction, the stage of resistance, and the stage of exhaustion (Selye, 1950). The former constitutes a phase in which the organism reacts to challenging demands by activating the hypothalamic pituitary adrenal (HPA) axis. With the help of the release of epinephrine by the adrenal medulla and the production of glucocorticoids by the adrenal cortex, the body tries to restore homeostasis. In the stage of resistance, the organism succeeds in adapting to the stimuli and restores homeostasis. In case of prolonged exposure to noxious stimuli, the organism's adaptive responses and resistance fail and the stage of exhaustion sets in. Consequently, irreversible tissue damage leads to illness (the so called diseases of adaptation) and with ongoing noxious stimulation and depletion of the individual's adaptive energy, the organism's death ultimately comes about. In his later work, Selye

¹ Chapter 1.3 is based on chapter 1 of Ice, G. H., & James, G. D. (2007). Measuring stress in humans. A practical guide for the field. Cambridge, England: University Press.

(1976) coined the popular terms *eustress*, referring to the healthy and beneficial aspect of the experience of stress, and *distress*, referring to the disagreeable and possibly pathogenic stress response.

Selye's approach to stress is response based, treats stress as a dependent variable (in the sense of a disruption caused by a certain stimulus), and is restricted to physiological aspects of stress. His stress concept popularized the term stress, inspired stress research in many disciplines and had a great impact especially on biomedical and neurological research. Some aspects of his theory were, however, questioned by subsequent researchers. Mason (1971; 1975), for example, criticized among others the postulation of a non-specific causation of the GAS. A body of research showed variation in the response of the HPA axis to diverse stressors and thus demonstrated the importance of the type of stressor and the experimental condition. Moreover, Mason pointed out that many stressors used in Selye's research on animals share the common feature of uncertainty, thus provoking feelings of helplessness and of lack of control in the organisms studied (Ice & James, 2007). As a consequence, this psychological component of the physical stimuli influences the GAS responses and the influences of the stimuli as such are confounded with the influence of the emotional state of the organism. Furthermore, recent research showed that the stress response described by Selye doesn't apply equally to both sexes (McEwen, 2005): gender differences manifest themselves in diverse perceptions of stressors and behavioral responses to them, as well as in physiological differences in the regulation of the hormones involved in the stress response. Another critical issue in Selye's model of stress is the concept of homeostasis and the conclusion that stress somehow represents a disruption of homeostasis by stressors.

McEwen (2005) argued for a change in terminology in favor of the term *allostasis*, which was introduced by Peter Sterling and Joseph Eyer in the late 1980s (Sterling & Eyer, 1988). He pointed out that the concept of homeostasis only fits to some physiological variables like pH or body temperature. In order to maintain life, these and a limited number of others have to be kept within a narrow range of their set-points. Allostasis, however, describes the process of achieving stability through change. In case of confrontation with stressors, the so called alarm reaction described by Selye is the process of regaining allostasis or adaptation with the help of primary mediators like hormones of the HPA axis, catecholamines, and cytokines. The successful adaptation to the stressor in Selye's resistance stage demonstrates the protective effects of the primary mediators. McEwen (2005) further introduced the term *allostatic state* to describe an imbalance of the primary mediators of the stress response due to their excessive or inadequate production in the face of ongoing environmental demands or

challenges. When in such a way altered activity levels of the primary mediators cumulatively produce wear and tear on the regulatory systems of the brain and the body, *allostatic load* results. A further dramatic increase brings about *allostatic overload* which is regarded as a risk factor for diseases. Referring to Selye's stage of exhaustion, an ongoing alarm reaction due to prolonged exposure to stressors leads to an allostatic state and consequently to allostatic overload, which ultimately brings about pathophysiological change.

1.3.1 *Physiological Stress Reactions*

The rapid response to a stressor as described in the fight-or-flight response is primarily mediated by the autonomic nervous system (ANS) in conjunction with the hormone system, leading to a variety of cardiovascular, respiratory, gastrointestinal, renal, and endocrine changes.

The visceral or autonomic nervous system (ANS), a subdivision of the peripheral nervous system (PNS), regulates the functioning of the inner organs mostly without voluntary or conscious control and sensation. It consists of two major branches, the *sympathetic nervous system* (SNS) and the *parasympathetic nervous system* (PSNS), and of the enteric nervous system (ENS) which directly controls the gastrointestinal system. The centre of the ANS in the central nervous system (CNS) is primarily located in the diencephalon (above all in the hypothalamus), in the medulla oblongata, and in the cerebellum. The ANS is mainly responsible for the maintenance of the *inner milieu* – a term coined by the famous physiologist Claude Bernard (1813 – 1878) – or, in other words, the internal homeostasis of the vital functions like heartbeat, respiration, and blood pressure. Although the two main subdivisions of the ANS – the SNS and the PSNS – mostly act antagonistically, they represent a functional unity with the inner organs, the blood vessels, the skin, and the adenoids as effector organs. Most organs are innervated by both branches of the ANS which characteristically have complementary effects (see Figure 1). However, in form of a functional synergism they realize a perfect adaptation to the momentary situation or needs of the organism. (See e.g. Birbaumer & Schmidt, 2003; Deetjen, Speckmann, & Hescheler, 2005)

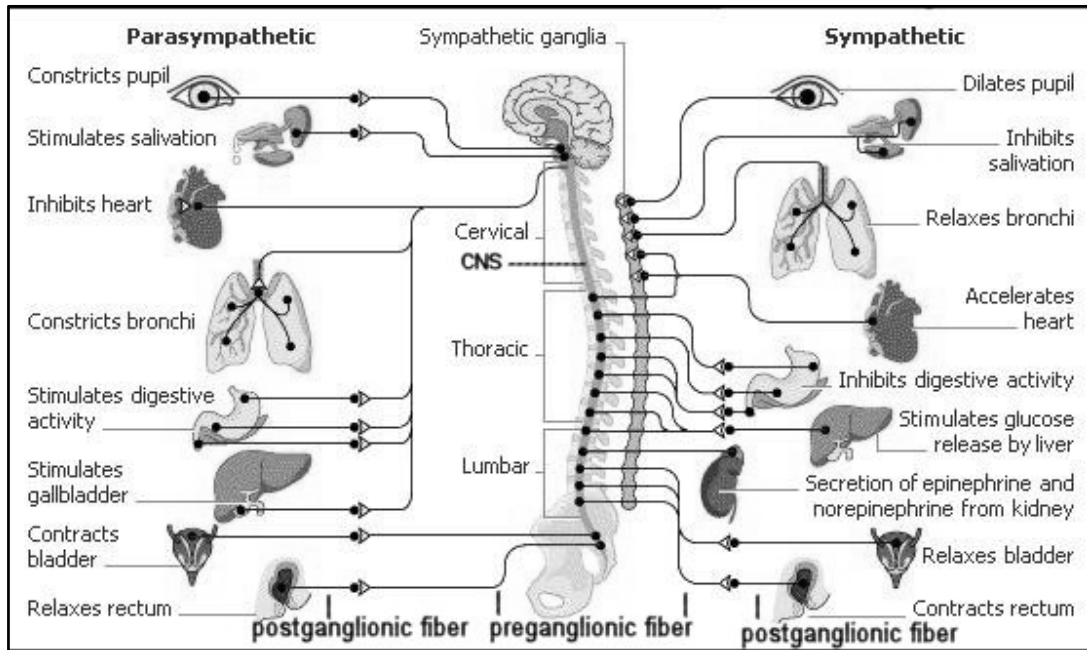


Figure 1. Pivotal effects of the parasympathetic (left side) and sympathetic (right side) nervous system on target organs. *Note.* From Autonomic Nervous System. Retrieved January 21, 2009, from <http://universe-review.ca/R10-16-ANS.htm>.

In case of heightened external demands (e.g. while doing sports or during mental efforts), the SNS influences the inner organs in terms of increasing blood pressure, body temperature, cardiac output, blood sugar level, and widening of the pupils among other effects. This so called ergotropic reaction state corresponds to the “fight-or-flight response” described by Cannon (1914) and aims at adaptation and optimization of the organism in the face of heightened demands or threat. The trophotropic reaction state, on the other side, relates to an increased parasympathetic activity, and constitutes a phase of relaxation and regeneration. For example by decreasing the pulse frequency and increasing the peristalsis, the body has the opportunity to regenerate and refill his reserves. (Fahrenberg, 2001)

One can differentiate two main pathways involved in the stress response: the *sympathetic-adrenomedullary* (SAM) system and the *hypothalamic-pituitary-adrenocortical* (HPA) axis (Schandry, 1998). The former enhances the functioning of the effector organs by releasing catecholamines from the adrenal medulla. Adrenaline (epinephrine) leads to an increase in heart rate and stroke volume as well as to an increased release of glucose. Noradrenaline (norepinephrine) regulates the blood pressure via vasoconstriction, augments respiration depth, dilates the bronchioles of the lung, and represses digestion. The initial point of the second pathway, the HPA axis, is the hypothalamus, which constitutes the highest organ that integrates vegetative functioning. It is an important interface between the neural and the

endocrine system. By secreting the corticotrophin-releasing hormone (CRH) into the pituitary portal system of the adenohypophysis, the hypothalamus regulates the release of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary into the bloodstream. This hormone, in turn, influences the metabolism and stimulates the adrenal cortex to increase the production of cortisol, the most important representative of the glucocorticoids and a central hormone for the maintenance of homeostasis in case of stress. Cortisol itself increases blood pressure and glucose concentrations in blood through a variety of processes, reduces immune responses, and has, among many others, anti-inflammatory effects. A variety of feedback loops regulates the action of the HPA axis. In case of prolonged exposure to stressors, the ongoing heightened concentration of cortisol can have detrimental effects on many systems (e.g. elevated blood pressure, infertility, diabetes, inhibition of growth, immunosuppressive effects). (Schandry, 1998)

In studies investigating the stress response, measurements of hormonal variation in the SAM system or the HPA axis, changes in the cardiovascular system, and enhanced immune responses can serve as markers of the physiological stress response (Ice & James, 2007; White & Porth, 2000). As the ANS plays an important role, direct measures of autonomic activity can provide insight into the stress response. The stress response is characterized by an increase of sympathetic activity and withdrawal of parasympathetic activity, thus resulting in a sort of temporary imbalance of the two vegetative subdivisions. Measurements of heart rate, respiratory rate, blood pressure, heart rate variability, cardiac output, electrodermal activity, rate pressure product, and impedance cardiography all serve as indicators of the stress response mediated by autonomic activity (White & Porth, 2000).

In this context, the analysis of *heart rate variability* (HRV) has been established as an informative, non-invasive marker of autonomic activity and has been applied frequently in research on stress. As this marker of the stress response will be used in the present study, the basics of HRV, measurement methods, and interpretation will be briefly described in the following section (section 1.3.2).

1.3.2 *Heart Rate Variability (HRV)*

HRV refers to the characteristic of the heart rhythm of mammals to habitually show variation in the time between two consecutive heart beats. Thus, there is a sort of “natural arrhythmia”, and under rest the heart rate is never completely constant. This variability results from a variety of overlapping biological rhythms like respiration, blood

pressure regulation, or thermal regulation, and from the influence of the autonomic nervous system (ANS).

The heart has an automatic rhythm that is primarily generated by the sinus node (SA node), the heart's most important natural pacemaker. The electrical impulse generated in the SA node stimulates the atria to contract and spreads to the AV-node, the heart's second pacemaker. The stimulus is then conducted through the bundle of His to the Purkinje fibers and the endocardium at the apex of the heart. It then finally spreads to the ventricular epicardium and initiates its contraction. Figure 2 illustrates the cardiac conduction system. (See e.g. Deetjen, et al., 2005)

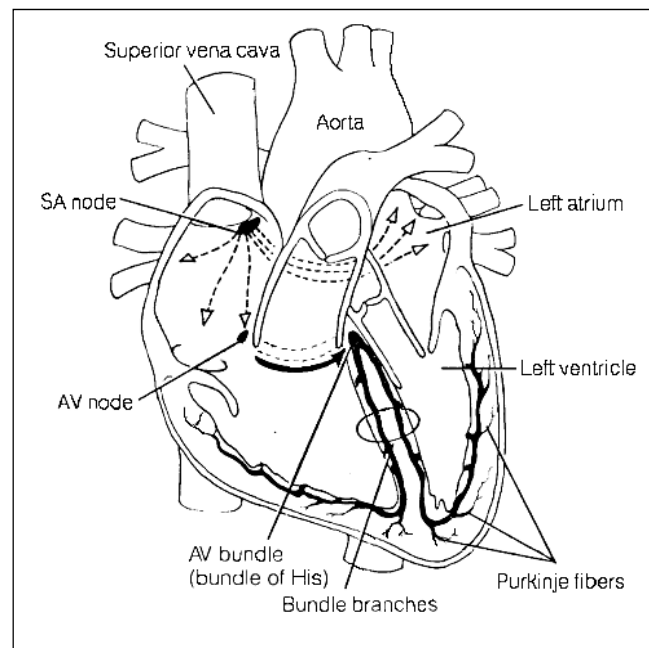


Figure 2. The heart's conduction system. *Note.* From Shardo, J. (2006). Heart electrical activity.

Retrieved July 8, 2009, from

http://frank.mtsu.edu/~jshardo/bly2020/cardiovascular/heart_electric.html.

However, besides the automaticity due to pacemakers, the electrical and contractile activity of the heart is substantially modulated by the ANS, thus allowing the organism to quickly and effectively adapt to changing internal or external demands. HRV analysis quantifies these cyclical fluctuations in ANS control of the SA node. (Berntson, et al., 1997)

- The parasympathetic innervation of the sinus node of the heart is realized via the release of acetylcholine by the vagus nerve, which decreases heart rate, reduces the heart's contractility and excitability, increases HRV, and slows down the conduction from the SA node to the AV-node and in the AV-node itself. Due to

these vagal influences, the resting HR is substantially lower than the intrinsic rate of the pacemaker (SA node).

- The sympathetic innervation, on the other hand, is realized by the release of epinephrine and norepinephrine, which results in an increase in heart rate, shortening of the conduction times, and reduction of HRV. Analysis of HRV thus provides insight into autonomic tone and allows indirect measurements of cardiovascular responsiveness to changing ANS reactivity (White & Porth, 2000).

In healthy individuals one observes continuous variations of HR that reflect a balanced sympathovagal state. Diminished HRV, though, indicates sympathovagal imbalance and is frequently observed in diseases (e.g. diabetes) or in damaged hearts (e.g. due to myocardial infarction). (Sztajzel, 2004)

1.3.2.1 *Electrocardiogram.*

HRV can be measured by the use of the electrocardiogram (ECG) that records the heart's electrical activity over time. Each recurrent segment in the ECG describes a cardiac cycle and consists of a characteristic sequence of waves: P-wave, QRS-complex, T-wave and – not always visible – U-wave. Figure 3 illustrates the characteristic waves and intervals visible in an ECG recording and Table 1 explains the physiological processes they represent.

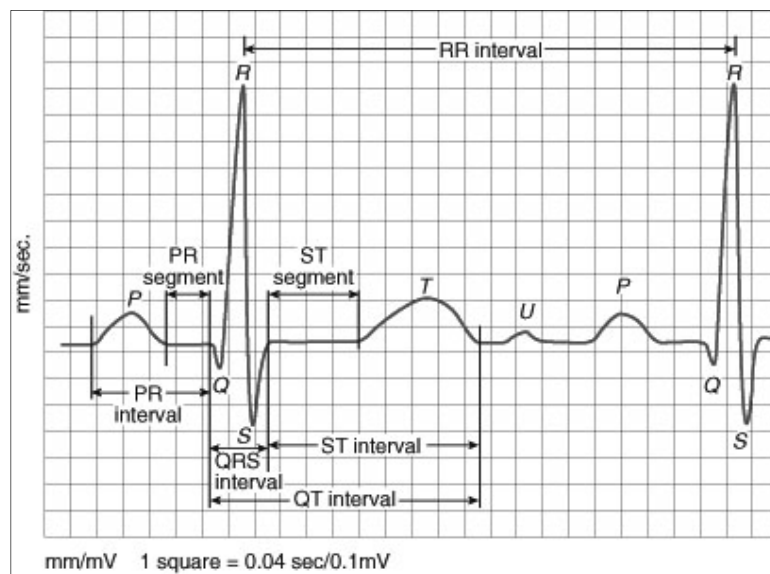


Figure 3. ECG waves and intervals. *Note.* From Merck (2005). Electrocardiography (ECG). Retrieved January 18, 2009, from <http://www.merck.com/mmpe/sec07/ch070/ch070e.html>.

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The interval between two heart beats is mostly defined as the time between two consecutive R-waves (of the QRS-complex), and is called RR interval or NN interval (normal to normal). For HRV-analysis purposes, the morphology of each QRS complex of an ECG recording must be identified and examined, and only sinus complexes are used for HRV analyses.

Table 1. ECG waves and intervals*.

P wave	represents the wave of depolarization that spreads from the SA node throughout the atria; duration of approximately 0.08 to 0.1 seconds
PR interval	period of time from the onset of the P wave (onset of atrial depolarization) to the beginning of the QRS complex (onset of ventricular depolarization); ranges from 0.12 to 0.20 seconds in duration
QRS complex	represents ventricular depolarization; the R wave is the point when half of the ventricular myocardium has been depolarized; duration of approximately 0.06 to 0.1 seconds
ST segment	this isoelectric period following the QRS is the time at which the entire ventricle is depolarized and roughly corresponds to the plateau phase of the ventricular action potential
T wave	represents ventricular repolarization and is longer in duration than depolarization
U wave	a small positive U wave may be seen following the T wave, representing after-depolarization (relaxation) of the ventricles
QT interval	represents the time between the onset of ventricular depolarization and the end of ventricular repolarization and therefore roughly estimates the duration of an average ventricular action potential; ranges from 0.2 to 0.4 seconds in duration depending upon heart rate
PP interval	duration of an atrial cycle; indicator of atrial rate
RR (or NN) interval	time between two QRS complexes

Note. *Adapted from Merck (2005). Electrocardiography (ECG). Retrieved January 18, 2009, from <http://www.merck.com/mmpe/sec07/ch070/ch070e.html>. Copyright 1995 – 2009 by Merck & Co., Inc., and Klabunde, R. E. (2007). Electrocardiogram. Retrieved January 18, 2009, from <http://www.cvphysiology.com/Arrhythmias/A009.htm>, Copyright 1998 – 2009 by R. E. Klabunde.

1.3.2.2 Measurement of HRV.

In 1996, the Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) published

guidelines for the analysis of HRV with a focus on measurement methods, analysis, interpretation, and clinical use. The measurement of HRV can be performed non-invasively by *Holter recordings* (long-term recording, e.g. 24 hours) or by short-term ECG-recordings (e.g. intervals of five minutes). With regard to HRV analysis, one differentiates time domain indices, frequency domain indices, geometric indices, and nonlinear indices, all of which serve as informative clinical parameters. As the present study uses the most frequently employed time domain and frequency domain indices of HRV, these methods of analysis as well as their most important parameters will be described briefly.

- *Time domain measures* of HRV are based on the determination of instantaneous HR or interval lengths between consecutive QRS complexes (NN intervals), resulting from depolarization of the SA node. In the context of time domain measures, one distinguishes between indices either derived from direct measurements of interbeat (NN) intervals or derived from comparisons of adjacent cycle lengths (NN intervals). (Task Force, 1996)
 - The former category reflects both short-term (e.g. respiration) and long-term (e.g. circadian rhythms) variation and is thus influenced by a broad range of factors. Typical indices are the standard deviation of all normal sinus RR intervals (SDNN) – sensitive to short- and long-term variations – and the standard deviation of 5-minute mean heart periods during a 24-hour period (SDANN) – sensitive only to long-term variations. As the total variance of HRV increases with the length of the analyzed recording period, SDNN reflects the cyclic components responsible for variability in a certain time period, and the SDNN measures thus vary according to the chosen time interval. (Task Force, 1996)
 - Indices of the second category mainly reflect short-term variation and predominantly vagally mediated alterations in autonomic tone. The proportion of adjacent normal sinus RR intervals of more than 50 ms (pNN50) and the root mean square difference of successive normal sinus RR intervals (rMSSD) are sensitive and highly correlated indices of vagal influences (high frequency component of HRV). However, other pNN thresholds substantially lower than 50 ms have shown to better discriminate between various groups (e.g. old versus young and healthy versus sick people) compared to the standard threshold of 50 ms (Mietus, Peng, Henry, Goldsmith, & Goldberger, 2002). See Table 2 for a compilation of the just

described and other frequently employed time domain indices. (Task Force, 1996)

Table 2. Selected time domain indices of Heart rate variability (Task Force, 1996, p. 358).

Statistical measures		
Variables	Units	Description
SDNN	ms	Standard deviation of all NN intervals
SDANN	ms	Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording
SDSD	ms	Standard deviation of differences between adjacent NN intervals
NN50 count	ms	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer
pNN50	%	NN50 count divided by the total number of all NN intervals

Note. NN interval (normal to normal) refers to the interval between two heart beats, and is mostly defined as the time between two consecutive R-waves of the QRS-complex, as measured by electrocardiogram. Table adapted from "Heart rate variability: standards of measurement, physiological interpretation and clinical use", by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, *European Heart Journal*, 17, p. 358 (Table 1). Copyright 1996 by the American Heart Association, Inc.

- *Frequency domain methods*, on the other side, refer to the analysis of the power spectral density (PSD), which provides information on how power or variance distributes as a function of frequency (Task Force, 1996). In other words, PSD decomposes the periodic oscillations in HR into their component frequencies, and the power or amplitude of each oscillation is plotted over a range of frequencies (White & Porth, 2000). Spectral power for a certain frequency band can be quantified by deriving the area under the spectral density function within the chosen frequency range (Berntson, et al., 1997). One distinguishes between the rather simple and rapid nonparametric methods like the fast Fourier transform (FFT) and the more complex parametric methods like the autoregressive (AR) approach

(Malliani, Lombardi, & Pagani, 1994). Both methods, however, basically provide comparable results (Pitzalis, et al., 1996). In short-term recordings of HR, three frequencies of HR oscillations can be detected that contain most of the HR power within a frequency range of 0 to 0.5 Hz: very low frequency (VLF), low frequency (LF), and high frequency (HF) oscillations. Long-term recordings (e.g. 24-hour Holter recordings) additionally allow the detection of an ultra low frequency (ULF) component. Figure 4 shows a screenshot from the analysis program medilog® Darwin (Schiller AG) from one patient of the present study sample for a certain time-point of the recording. On the x-axis of the diagram the frequency in Hz and on the y-axis the power in ms^2 is plotted. The ULF/VLF, LF, and HF oscillations are marked, and in the diagram underneath the normal heart beats are displayed and the NN interval is marked. One can see that in this sequence most power distributes in the ULF, VLF, and LF bands with a peak around 0.04 Hz, and only very little power distributes in the HF band.

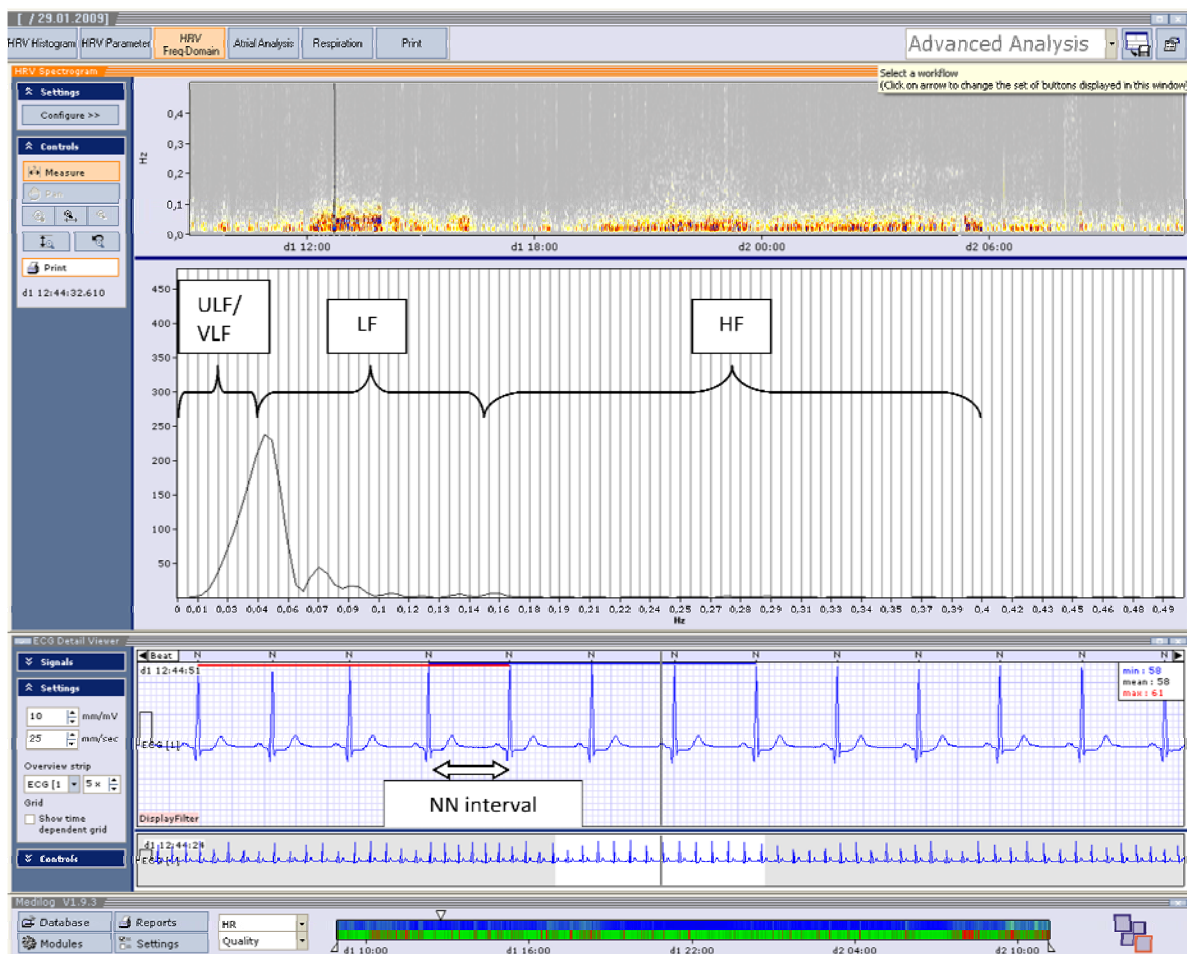


Figure 4. Screenshot of the HRV frequency domain in medilog® Darwin. The frequency bands ULF/VLF, LF, and HF are marked in the diagram [x-axis: frequency (Hz), y-axis: power (ms^2)].

The diagram beneath displays the normal heart beats and the NN interval is marked.

The total power (TP) of RR interval variability is the total variance corresponding to all four frequency bands. Besides reporting the total power for a certain time period (e.g. 5-min TP), one can report the power of the ULF, VLF, LF, and HF components in ms or – for short-term recordings – LF and HF in normalized units (nu) to express the relative value of each power component in proportion to the TP minus the VLF component (Malliani, et al., 1994). This measure gives a better picture of the influence of the two branches of the ANS (Task Force, 1996). See Table 3 for a summary of the most frequently employed frequency domain indices of HRV.

Table 3. Selected frequency domain indices of Heart rate variability for short- and long-term recordings of heart rate (Task Force, 1996, p. 360).

Variable	Units	Description	Frequency range
Analysis of short-term recordings (5-min)			
5-min TP	ms ²	The variance of NN intervals over the temporal segment	$\approx \leq 0.4$ Hz
VLF	ms ²	Power in VLF range	≤ 0.04 Hz
LF	ms ²	Power in LF range	0.04 - 0.15 Hz
LF norm	nu	LF power in normalized units LF / (TP-VLF) x 100	
HF	ms ²	Power in HF range	0.15 - 0.4 Hz
HF norm	nu	HF power in normalized units HF / (TP-VLF) x 100	
LF/HF		Ratio LF [ms ²] / HF[ms ²]	
Analysis of entire 24 hours			
TP	ms ²	Variance of all NN intervals	$\approx \leq 0.4$ Hz
ULF	ms ²	Power in the ULF range	≤ 0.003 Hz
VLF	ms ²	Power in the VLF range	0.003 - 0.04 Hz

Variable	Units	Description	Frequency range
LF	ms ²	Power in the LF range	0.04 - 0.15 Hz
HF	ms ²	Power in the HF range	0.15 - 0.4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	$\approx \leq 0.04$ Hz

Note. NN interval (normal to normal) refers to the interval between two heart beats, and is mostly defined as the time between two consecutive R-waves of the QRS-complex, as measured by electrocardiogram. ULF = ultra low frequency; VLF = very low frequency; LF = low frequency; HF = high frequency; TP = total power; nu = normalized units; Hz = hertz. Table adapted from “Heart rate variability: standards of measurement, physiological interpretation and clinical use”, by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, *European Heart Journal*, 17, p. 360 (Table 2). Copyright 1996 by the American Heart Association, Inc.

The Task Force (1996) gave detailed recommendations for technical and recording requirements and algorithmic standards to guarantee a reliable spectral analysis of HRV. In order to achieve a certain degree of standardization of HRV-studies, it suggested the analysis of short-term recordings of 5 minutes under physiologically stable conditions by frequency domain methods and the analysis of 24-hour recordings by the use of time domain methods.

Furthermore, there is a high correlation between time and frequency domain measures over a 24-hour recording period. SDNN, for example, corresponds greatly with TP, SDANN corresponds with ULF, and rMSSD and pNN50 are highly correlated with the HF component (Task Force, 1996).

With regard to stability and reproducibility of HRV measures, the results of short- and long-term time and frequency domain measures in normal participants as well as in diseased populations (e.g. patients with diabetes mellitus or symptomatic myocardial ischemia) are satisfactory (De Meersman & Stein, 2007; Nolan, et al., 1996; Pitzalis, et al., 1996; Task Force, 1996). Dependent on the analyzed condition like rest, controlled respiration, or tilt-tests, the degree of reproducibility of frequency domain parameters varies, however (Pitzalis, et al., 1996).

1.3.2.3 *Physiological correlates of HRV.*

Although the two subsystems of the ANS constantly interact to achieve a fine tuning and optimal HR dependent on internal and external demands, vagal tone prevails under resting conditions. Vagal activity provokes a rapid cardiac response,

while sympathetic influences are characterized by a time delay and slower response (Berntson, et al., 1997). Efferent sympathetic and vagal influences on the sinus node are characterized by discharge that is to a great extent synchronous with each cardiac cycle (Task Force, 1996). Central (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators generate rhythmic fluctuations in the efferent discharge that consequently manifest as short- and long-term oscillations in the heart period. By analyzing these periodic oscillations, one can draw conclusions on the state and function of the central oscillators, the sympathetic and vagal efferent activity, humoral factors, and the sinus node.

Researchers gain insight into the interplay or relative contribution of the two branches of the ANS to HRV by conducting different types of studies: (a) animal studies that reveal changes in HRV after blockade, amplification, or selective interference with autonomic cardiovascular regulation, (b) human studies in which drug administration or laboratory stimulations manipulate autonomic cardiovascular control and thus alter HRV, and (c) studies with patients suffering from various diseases (e.g. diabetes mellitus, acute myocardial infarction) that primarily or indirectly affect the ANS and consequently alter HRV (Parati, Mancina, Di Rienzo, & Castiglioni, 2006).

- Regarding the HF component (0.15-0.4 Hz), there is – based on clinical and experimental observations of autonomic maneuvers, such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy – a consensus that high frequency cardiac rhythms are predominantly mediated by vagal modulation of the SA node (Task Force, 1996). Parasympathetic blockade by atropine eliminates most fluctuations in the HF band, whereas it only partly reduces those in the LF band. Cardiac sympathetic blockade (e.g. by propranolol), on the other hand, has practically no influence on HR fluctuations in the HF band, but decreases those of the LF component (Parati, et al., 2006). The so called *respiratory sinus arrhythmia* (RSA) is a major contributor to the HF component of HRV. It describes cyclical fluctuations in HR that correspond to changing respiratory phases in the sense that HR increases during inspiration and decreases during expiration (del Paso, Langewitz, Robles, & Pérez, 1996). In humans, RSA normally ranges from about 0.15 Hz to 0.4 Hz, and though it is a multiply determined index (Berntson, Cacioppo, & Grossman, 2007), it is predominantly mediated by fluctuations of vagal activity on the SA node, thus constituting an indication of basal levels of vagal cardiac nerve traffic (Berntson, et al., 1997). The frequency of RSA varies with respiration frequency in the sense that it is markedly greater during slow than during fast breathing. Recent data suggested that the amplitude of RSA, however, is not dependent

on respiration frequency in baseline conditions (Denver, Reed, & Porges, 2007). There is an ongoing controversy whether it is necessary to monitor respiration when measuring RSA. While some researchers argued that monitoring respiration is important to ensure that the respiratory power falls wholly within the specified frequency band in order to prevent confounds (Berntson, et al., 2007; Grossman & Taylor, 2007), others stressed that it is statistically inappropriate to use analysis of covariance (ANCOVA) with the aim of “controlling” effects of respiration, and that one should therefore not use respiration frequency as a covariate to try to accurately quantify RSA amplitude during baseline measures (Denver, et al., 2007). Besides respiration, baroreceptor reflexes substantially contribute to the HF band, as they can operate within high frequency ranges.

- The interpretation of the LF component with a center frequency of about 0.1 Hz is more controversial. Whereas some investigators argued that it reflects mainly fluctuations of sympathetic traffic to the SA node (especially when expressed in normalized units), there generally now prevails the opinion that these rhythms reflect fluctuations of both branches of the ANS (Malliani, et al., 1994). Consistent to this latter view, parasympathetic as well as sympathetic blockade reduce HR fluctuations in the LF band (Parati, et al., 2006). Baroreceptors and chemoreceptors evidently contribute to the oscillations in the LF band. Additionally, when respiration rate is lower than 10 breaths per minute, the LF band is contaminated by RSA. There is furthermore a disagreement of whether one can consider the LF/HF ratio as an index of sympathovagal balance or not. Eckberg (1997), for example, seriously questioned the physiological foundations of the construct of sympathovagal balance, and argued that “calculations of sympathovagal balance may obscure rather than illuminate human physiology and pathophysiology”. Many investigators, nevertheless, rely on this ratio as a marker of autonomic balance, especially when determining alterations in sympathovagal balance across different conditions (Malliani, et al., 1994; Malliani, Pagani, Montano, & Mela, 1998).
- Spectral analysis of long-term recordings revealed that both LF and HF (expressed in normalized units) exhibit a circadian pattern with higher values of LF during the day and HF at night (Task Force, 1996). Together these two components account for only about 5% of the TP in long-term recordings. However, the physiological correlates of the major contributors – ULF and VLF – are still not fully understood and need further clarification. The ULF is believed to mirror circadian and neuroendocrine rhythms, while the VLF component

seems to reflect thermoregulatory feedback mechanisms, renin-angiotensin activity, hemodynamic feedback delays, and circulating neurohormone levels (Berntson, et al., 1997). Moreover, research indicated that parasympathetic tone substantially contributes not only to the high and low frequency RR-interval variability, but also to very low frequency oscillations (Taylor, Carr, Myers, & Eckberg, 1998).

Generally, one has to bear in mind that HRV-analysis measures fluctuations in autonomic inputs to the heart rather than the mean level of autonomic inputs. Consequently, autonomic withdrawal as well as a high level of sympathetic input can both contribute to a reduction in HRV (Task Force, 1996). Nowadays, autonomic activity is no longer conceptualized in terms of reciprocity between the PSNS and the SNS, but rather as two autonomic branches that can vary reciprocally, independently, or coactively, thus implying that sympathetic stimulation of the heart can be accompanied by either an increase or by a decrease in vagal modulation of the heart (Berntson, Cacioppo, & Quigley, 1993).

1.3.2.4 Associations of individual characteristics and HRV.

A variety of factors such as gender, age, circadian rhythm, HR, respiration, body position, physical activity, and smoking may influence HRV and thus have to be controlled to achieve reliable and comparable results across studies.

Generally, HRV decreases with advancing age and with increasing mean HR (Antelmi, et al., 2004; De Meersman & Stein, 2007; Horsten, et al., 1999; Masi, Hawkey, Rickett, & Cacioppo, 2007; Tsuji, et al., 1996). While HRV significantly decreases with aging in all 24-hour time domain measures, the patterns of decline are age- and measure-dependent (Antelmi, et al., 2004), and it is worth mentioning that normal aging can lower HRV to such an extent that the values fall below the cut-off-points associated with increased risk of mortality (Umetani, Singer, McCraty, & Atkinson, 1998). These observations could be attributed to reduced baseline vagal tone with age, which in turn causes lesser vagal control of the cardiovascular system. Thus, cardiac responses to sympathetic stimulation as well as parasympathetic withdrawal are attenuated with aging, as is manifested by differences in HR, blood pressure, and cardiac output responses to vagal withdrawal after administration of atropine (Stratton, et al., 2003).

With regard to exercise, numerous studies provided evidence for a beneficial effect of maintaining or increasing fitness with the aim of slowing the decline of the parasympathetic control of HR with normal aging (De Meersman & Stein, 2007).

Besides the favorable consequences of exercise on HRV, weight reduction in obese subjects has also shown to alter HRV by increasing vagally-modulated indices and thus improving parasympathetic modulation (De Meersman & Stein, 2007). However, a large cohort study revealed no differences in either time domain or frequency domain indices of HRV between normal, overweight, and obese men and women (Antelmi, et al., 2004), and whereas some researchers reported a significant and negative association between BMI and HRV indices (Horsten, et al., 1999), others failed to find a significant correlation between RSA and BMI (Masi, et al., 2007).

Concerning body position, standing is accompanied by significantly smaller RR interval, lower HF power, higher LF power, and a higher LF/HF ratio compared to sitting or reclining (Lucini, Norbiato, Clerici, & Pagani, 2002; Sloan, et al., 1994).

Gender is another factor influencing HRV in terms of significantly lower HRV in women under 30 years compared to men, but these differences seem to disappear by age 50 and also depend on the HRV measure used (Antelmi, et al., 2004; De Meersman & Stein, 2007; Umetani, et al., 1998). Some reported that HRV indices reflecting parasympathetic modulation like HF, rMSSD, and pNN50 are higher in women, whereas indices like LF, VLF, and LF/HF ratio are higher in men (Antelmi, et al., 2004).

Moreover, cigarette use is negatively associated with RSA (Masi, et al., 2007).

1.3.2.5 *Associations of diseases, medication, and HRV.*

A possible impact of medication on HRV has to be considered. Beta-blockers and diuretic drugs, for example, have been shown to fractionally reduce HRV (Tsuji, et al., 1996), particularly the LF component (Elghozi, Girard, & Laude, 2001). Administration of anticholinergic drugs, such as atropine or ipratropium, blocks vagal activity, and thus HR increases while HRV almost entirely disappears (Curtis & O'Keefe, 2002; Stratton, et al., 2003; Taylor, et al., 1998).

Especially the hemodynamic regulation during anesthesia is a topic of interest. HRV has been increasingly used for noninvasively monitoring the ANS and gaining insight into the short-term effects of anesthesia induction.

With respect to the synthetic opioid fentanyl, its administration has shown to cause significant decreases in mean arterial pressure, heart rate, TP, and LF power, but no change in high frequency power, LF (nu), HF (nu), and the LF/HF ratio. The additional administration of the hypnotic thiopental caused further significant reductions of TP, HF, HF (nu), and LF power, and significant increases of heart rate, LF (nu), and the LF/HF ratio, thus pointing at a simultaneous reduction in sympathetic activity and –

more intensely – vagal activity. The additional administration of the hypnotic propofol, on the other side, caused significant decreases of blood pressure and HF power, but not LF power, and a significant increase of the LF/HF ratio, thus indicating a greater reduction of cardiac parasympathetic tone than sympathetic activity. The benzodiazepine midazolam, a frequently administered premedication with amnesic and anxiolytic effects, has been shown to only slightly reduce LF and HF power, without changing the LF/HF ratio. (Riznyk, Fijalkowska, & Przesmycki, 2005) In another study on short-term effects of general anesthesia (GA) induction (Zickmann, et al., 1996), the combined administration of fentanyl, midazolam, and pancuronium (muscle relaxant) in three different dosages and injection speeds seemed to selectively decrease sympathetic activity, without significantly affecting parasympathetic activity. The authors explained the reductions in sympathetic activity with the depression of the baroreflex function by the benzodiazepine midazolam and the abolishment of the patients' preoperative stress response by anesthesia induction.

In general, anesthesia has shown to immediately decrease heart rate, total and individual powers in all three frequency bands of the HRV spectrum, and the LF/HF ratio, indicating primarily a depression of sympathetic autonomic nervous system activity with only mild decreases of parasympathetic autonomic nervous system activity (Galletly, Westenberg, Robinson, & Corfiatis, 1994; Riznyk, et al., 2005; Vettorello, Colombo, De Grandis, Costantini, & Raimondi, 2008; Zickmann, et al., 1996). However, the problem with studies concerning the effects of anesthesia on ANS modulation is the diversity of the administered drugs, their combination, dosage, and induction speed, and the fact that mostly only short-term effects are studied. Thus, due to a variety of confounding variables, such as the patient's health and age, current medication, premedication or concomitant administration of other drugs, one cannot easily and accurately predict changes in HRV after the administration of a certain drug.

In their review of autonomic tone as a cardiovascular risk factor, Curtis & O'Keefe (2002) underlined the importance of taking the impact of medical therapies on autonomic function into account when prescribing medication. They argued that sympathomimetic drugs can have detrimental effects especially in patients suffering from cardiovascular disease, whereas other interventions like lifestyle modifications (e.g. exercise, smoking cessation, or weight loss) or medication such as β -blockers or angiotensin-converting enzyme (ACE) inhibitors seem to have beneficial effects in terms of autonomic function and other outcomes in patients with CHD.

An extensive amount of research has been dedicated to investigating possible changes of HRV in several diseases or pathologies like myocardial infarction, diabetic

neuropathy, cardiac transplantation, or myocardial dysfunction (Masi, et al., 2007; Task Force, 1996), or in psychological disorders like depression (Rottenberg, 2007; Rottenberg, Clift, Bolden, & Salomon, 2007) or anxiety disorders (Friedman, 2007; Friedman & Thayer, 1998). Furthermore, depressed HRV has proven to be a useful predictor of risk after acute myocardial infarction (it constitutes an independent predictor of mortality and arrhythmic complications) and an early warning sign of diabetic neuropathy (Task Force, 1996). Additionally, many investigations aim at establishing HRV as a clinical measure for risk stratification in a variety of diseases or more generally as a prognostic value linking reduced HRV to increased cardiovascular morbidity and mortality (see e.g. Curtis & O'Keefe, 2002).

1.3.2.6 *Autonomic activity and stress: The polyvagal theory.*

One theory explicitly linking HRV and stress was proposed by Stephen W. Porges in the 90s (1995a). He argued that the concepts of stress and homeostasis are interdependent and demonstrated by the activity of the PSNS. The author suggested that homeostasis is characterized by an autonomic state that fosters visceral needs without external challenge and by a high level of parasympathetic tone. In this context, stress is defined as a disruption of homeostasis because of depressed vagal tone, reflecting the repression of internal needs in response to external needs. By quantifying RSA as an index of vagal tone, the degree of stress can be ascertained, and the chronic autonomic state before a stressful event is assumed to provide insight into an individual's vulnerability to stress.

Within this framework, the sympathetic state that primarily responds to external challenges is not a necessary component of stress, although the withdrawal of parasympathetic activity can occasionally be accompanied by an increase in sympathetic activity.

Porges (1995a) further emphasized the role of the brainstem in regulating autonomic processes and consequently behavioral and physiological reactivity to stress. The vagus, originating in the brainstem, constitutes a complex bidirectional system with myelinated branches that link the brainstem to many target organs and thus enable rapid communication and feedback between brain structures and specific organs with the aim of regulating and maintaining homeostasis. The two source nuclei of the two branches of the vagus have fibers that originate either in the dorsal motor nucleus (DMN) or in the nucleus ambiguus (NA). Porges (1995a) argued that situations of acute stress are characterized by a rapid withdrawal of vagal efferent outflow from the NA, which is primarily responsible for the regulation of HR by innervating the

sinoatrial node. In phases of chronic stress, on the contrary, the vagal system is permanently depressed. He illustrated his theory by the example of monitoring the vagal tone of high-risk neonates as a sensitive index of stress vulnerability.

Subsequently, Porges extended the theoretical framework and postulated the phylogenetically based “polyvagal theory” (Porges, 2001). In separation from approaches that describe the ANS as a linear arousal system with emphasis on the SNS or as a balance system with opposing influences from the SNS and PSNS branches (paired antagonism), he stressed that the function of the ANS is hierarchically organized and phylogenetically determined (Porges, 2007). He distinguished between three sequential functional subsystems or neural constructs that are each linked to a specific response strategy aiming at specific adaptive functions (see Table 4). The proposed hierarchy refers to the response strategy of the ANS in the face of challenge that starts with the newest structures and falls back on the more primitive systems only when everything else fails.

Table 4. The three phylogenetic stages, functional subsystems, ANS components, lower motor neurons, and behavioral functions of the neural control of the heart proposed by the polyvagal theory (Porges, 2001, p. 127).

Phylogenetic stage	Functional subsystem	ANS component	Lower motor neurons	Behavioral function
III	Ventral vagal complex (VVC)	Myelinated or “smart” vagus	Nucleus ambiguus	Mammalian signaling system for motion, emotion, and social communication to signal with minimal energy expense; inhibition of sympathetic-adrenal influences
II	Sympathetic nervous system (SNS)	Sympathetic-adrenal	Spinal cord	Adaptive mobilization system supporting fight or flight behaviors to mobilize in order to obtain metabolic resources; active avoidance; inhibition of the visceral vagus
I	Dorsal vagal complex (DVC)	Unmyelinated or “vegetative” vagus	Dorsal motor nucleus of the vagus	Vestigial immobilization system to immobilize and conserve metabolic resources; passive avoidance

Note. Adapted from “The polyvagal theory: phylogenetic substrates of a social nervous system”, by S. W. Porges, 2001, *International Journal of Psychophysiology*, 42, p. 127 (Table 1).

Within this framework, social behavior can be described from a neurophysiological point of view that focuses on a phylogenetically based hierarchical sequence of adaptive responses. The ventral vagal complex, that is unique to humans, functions as an active vagal brake that is able to rapidly regulate cardiac output through the myelinated vagus in order to foster engagement (behavioral mobilization) or disengagement (self-soothe and calm an individual) with the environment. It is directly connected to the cranial nerves that regulate social engagement by facial expression (regulation of the striated muscles of the face) and vocalization. According to the polyvagal theory, the so called social engagement system modulates the physiological state in order to support positive social behavior by oppressing the SNS (Porges, 2001). The respective physiological state limits the range of behavior and personal experience. This social nervous system in its wider sense is believed to involve neurophysiological interactions with the HPA axis, the neuropeptides oxytocin and vasopressin, and the immune system with regard to social interaction and response to stress.

Porges (2007) argued for an avoidance of the, in his opinion, antiquated construct of cardiac vagal tone and advocated, based on recent neurophysiological and neuroanatomical research, the distinction between the functional outflow of the two primary vagal efferent pathways that innervate the sinoatrial node. In this context, RSA is presumed to mirror the dynamic regulation of the nucleus ambiguus-vagal circuit without disrupting the natural functioning of the system and is observed as periodic changes in HR restricted to the frequencies associated with spontaneous breathing.

The polyvagal theory has inspired research in a variety of topics related to emotion, emotion development, psychopathology, and health (Chambers & Allen, 2007), like anxiety (Friedman, 2007) and depression (Rottenberg, et al., 2007). Other researchers, however, questioned the distinction between the NA and DMN as source nuclei and argued that the physiological foundation for describing separate pathways for vagal cardiac control is presently not elaborated enough (Berntson, et al., 2007). Consequently, they dismissed inferences of distinct influences of the two pathways on psychophysiological functioning and on human behavior as speculative. Moreover, they emphasized the multiple determination of RSA and thus expressed their concern with regard to utilizing RSA as a measure of vagal control of the heart without taking other determinants like respiratory frequency and depth into consideration (Grossman & Taylor, 2007). They thus suggested being cautious when applying RSA as a marker of behavioral processes. They appreciated, however, the attempt to integrate physiology, behavior, and psychosocial processes within a systems perspective in a unified framework (Berntson, et al., 2007).

Summing up, the polyvagal theory provides a framework within which HRV can be understood from a physiological, psychological, and behavioral perspective (Porges, 1995a, 2001, 2007). It emphasizes the role of the PSNS and especially the phylogenetically rather new myelinated vagus in social interaction and engagement or disengagement with the environment. Stress is described as a disruption of homeostasis characterized by depressed vagal tone, and RSA, that is presumed to mirror the dynamic regulation of the nucleus ambiguus-vagal circuit, is proposed as an index of stress.

1.4 *Psychological Stress: A Transactional Model of Stress*

In opposition to the biomedical approach to stress that primarily focused on physical stressors and conducted research on animals, some researchers started to pay attention to the impact of psychosocial stressors in humans. They particularly emphasized the role of major life events and explored the relation between the experience of critical life events (e.g. death of a loved person or divorce) and the human stress response as well as the possible association with illness (Filipp, 1981). In the 1960s Holmes and Rahe (1967, as cited in Lyon, 2000) published the so called “The Social Readjustment Rating Scale” that allowed for the allegedly objective measurement of stress. Underlying is the assumption that negative and also positive critical life events induce changes in life that require a certain amount of readjustment and thus cause different degrees of stress. Criticism of this stimulus based model addressed, among other aspects, the theory’s basic assumptions that life changes are normative and thus demand the same amount of readjustment from all individuals, that change is associated with stress – independent of the desirability of a specific event for an individual –, and that a certain degree of adaptation leads to illness. (Jerusalem, 1990; Lyon, 2000) Although others advanced the stimulus based model of stress, e.g. development of the Life Experiences Survey, LES, by Sarason, Johnson, and Seigel (1979, as cited in Lyon, 2000), which incorporated the individual desirability and the degree of impact of a certain event on an individual’s life, it didn’t succeed in demonstrating substantial correlations between life event scores and illness (Lyon, 2000).

As the approaches to stress that focus on the stimulus and postulate a non-specific stress reaction – like the life events approach and Selye’s GAS – failed to explain the individually different responses to stress, Richard Lazarus and colleagues developed a transactional model of stress that places emphasis on cognitive processes. Appraisal and coping are central concepts in this psychological stress theory which was postulated in the late 1960s and 1970s (Lazarus, 1966). The former

refers to an individual's cognitive evaluation of the importance of the stressful situation for his or her well-being, and the latter to an individual's cognitive or behavioral efforts to manage the situation or problem at hand.

1.4.1 Appraisal

Within the transactional framework, the stress process is regarded as a transaction between individuals and their environment. An individual constructs relational meaning from this relationship. Thus, a stimulus per se doesn't provoke a stress reaction unless a person cognitively assesses a certain stimulus or situation as relevant to his or her well-being and as a potential threat (Lazarus, 1966; Lazarus & Folkman, 1984).

In this process called primary appraisal a person might judge a situation as irrelevant, benign-positive, or stressful. In the case of stressful appraisals, he or she might regard a situation as a challenge, as a threat (focus on the present and future), or as a loss/harm (focus on the past), or as a combination of the above, depending primarily on the subjective view of the environment (Lazarus & Folkman, 1984). Each type of appraisal leads to a different kind of stress and consequently to specific types of emotional reactions (Lazarus, 1966). Challenge appraisals are above all related to positive emotions like excitement and exhilaration, whereas threat appraisals are primarily characterized by negative emotions like fear, anxiety, and anger (Lazarus & Folkman, 1984).

In the process of secondary appraisal, an individual evaluates his coping resources; that is, he judges the situation or problem at hand depending on resources and personal characteristics like self-efficacy, commitment, existential beliefs, general as well as situational control beliefs, personal goals, moral concepts, social and problem-solving skills, social support, or material resources (Lazarus, 1966; Lazarus & Folkman, 1984). Primary and secondary appraisal can occur simultaneously and influence one another.

The term reappraisal refers to the fact that new information can change a former appraisal, and cognitive appraisal thus constitutes a process in which an individual's view might change over time (Lazarus & Folkman, 1984).

1.4.2 Coping

The concept of coping relates to the way an individual deals with the problem or situation after the process of cognitive appraisal (Lazarus, 1966). Lazarus and Folkman (1984, p. 141) described the coping process as "constantly changing cognitive and

behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person” and distinguished between two primary functions: *problem-focused coping* that aims at a solution to the problem and *emotion-focused coping* that aims at easing distress, regulating emotions, or changing the appraisal of the demanding situation. As a third category, *avoidant coping* has been proposed, which is primarily characterized by denial and ignoring the problem at hand. A further distinction categorizes coping into *active and passive coping efforts*. The former category refers to behavior aiming at resolving a problem, whereas the latter category refers to avoidant behavior such as distraction and denial (Kop, Berlin, & Stretch, 2004). All sorts of coping attempts can have a problem- or emotion-focused function, depending more on the intention than on the action itself, they can rapidly change over time, and different types can appear simultaneously and supplement each other in the course of the process (Lazarus, 2000).

Whereas a great number of specific coping strategies or behaviors have been proposed and investigated by several authors, others argue that *coping flexibility* is more important (Kop, et al., 2004).

Alternatively, a variety of habitual coping styles in the sense of personality traits have been proposed in opposition to state-oriented approaches that focus on actual behavior (Krohne, 2001). For instance, people generally differ in the constructs optimism (Carver & Scheier, 2002; Scheier & Carver, 1992), hardiness (Kobasa, 1979), repression versus sensitization (Byrne, 1961), monitoring versus blunting (Miller, 1987), and vigilance versus cognitive avoidance (Krohne & Egloff, 1999) and thus employ different behaviors across various situations, dependent on their personality. In this context, one has to pay attention to the theoretical distinction between the concepts of coping and coping resources; resources are relatively stable antecedents of appraisal and coping, whereas coping is defined as a process depending on these resources (Schwarzer & Schwarzer, 1996). With respect to the great situational and intraindividual variability in coping behavior, Schwarzer and Schwarzer (1996) argued that coping needs to be conceptualized on multiple levels, with a few stable dimensions (trait-oriented) at a higher level and theoretical connections to specific coping strategies at a lower level (state-oriented).

Coping can be assessed by means of self-report data, direct systematic self-observation in a stressful situation, and external systematic observation. The former data source relies on the subjects’ cognitive representation of their coping behavior in a stressful situation and is subjected to memory effects. Some questionnaires specify a certain type of stressful situation [e.g. Coping with Surgical Stress Scale (Krohne, de-

Bruin, El-Giamal, & Schmukle, 2000)], whereas others ask for general coping tendencies [e.g. Stress Coping Inventory (Janke, Erdmann, & Kallus, 1997)]; some refer to hypothetical situations [e.g. Mainz Coping Inventory (Krohne & Egloff, 1999)], whereas others refer to actually experienced stressful situations in the past or present [e.g. Ways of Coping Questionnaire (Folkman & Lazarus, 1988)]. The Ways of Coping Questionnaire (Folkman & Lazarus, 1988) is a widely known and used instrument for assessing coping and distinguishes eight empirically derived strategies on a macroanalytical level: confrontative coping, distancing, self-controlling, seeking social support, accepting responsibility, escape-avoidance, planful problem solving, and positive reappraisal. See Schwarzer and Schwarzer (1996) for a critical survey of current coping instruments with an emphasis on stability, generalizability, and dimensionality. By assessing coping behaviors, those individuals with a presumable deficit or, on the other side, special competence for dealing with a certain stressful situation can be identified. This identification is not only of scientific interest, but also practically relevant with regard to applications in health, clinical, and organizational psychology, as well as counseling. (Perrez, 2004)

Some criticism on coping research addressed the gap between the transactional and process theories of stress and coping and the methodology used in research that is characterized by between-person, cross-sectional designs (Somerfield & McCrae, 2000; Tennen, Affleck, Armeli, & Carney, 2000; Weber & Laux, 1990). In order to adequately capture the dynamic aspect of adaptation, some researchers turned to within-person research designs and so called daily process approaches (e.g. Tennen, et al., 2000).

Although the term coping only refers to an effort of mastering a situation and not necessarily to a successfully completed act, coping attempts can nevertheless be judged according to their degree of effectiveness. This judgment, however, is very difficult to deliver, subjective, and highly dependent on the selected outcome criteria (e.g. well-being, health, social functioning), their operationalization, and the time perspective (short- versus long-term effects). (Lazarus, 2000; Somerfield & McCrae, 2000) In general, research on coping effectiveness suggested that problem-focused strategies are more effective in case of personal control over the respective situation, whereas avoidant strategies are more effective in situations with reduced control (Kop, et al., 2004). With regard to the selection of adaptational outcomes, some researchers argued – in the tradition of positive psychology – for a consideration of potentially positive outcomes (e.g. benefit finding) and not a sole concentration on negative outcomes (e.g. negative affect) and furthermore for the selection of criteria that also

take the needs and goals of the individual into account (Lazarus, 2000; Somerfield & McCrae, 2000).

A lot of research has so far been dedicated to evaluating the impact of certain coping strategies on physical and mental health, as coping has been postulated as an important psychosocial factor moderating or mediating the relation between stress and disease (Somerfield & McCrae, 2000). It has been assumed that coping affects health and well-being by either altering health-related behavior or by attenuating the physiological stress response through a reduction of the emotional stress response (Kop, et al., 2004). See, for example, Penley, Tomaka, and Wiebe (2002) for a meta-analysis of the association between coping strategies and health-related outcomes in non-clinical adult samples.

Coping research has furthermore demonstrated gender differences and cultural differences in the use of certain coping strategies (Kop, et al., 2004).

Some researchers expressed their disappointment concerning research on coping and argued that the enormous quantity of research on stress and coping and the associated enthusiasm have so far not yielded the promised results of high quality and clinical relevance. Thus, despite of a vast number of studies, a foundation for clinical interventions in stress management is still missing. To come up against these problems, they suggested the investigation of coping strategies specific to stressful events or contexts and of interindividual differences in personality traits that affect the choice of certain strategies. Furthermore, prospective within-subjects longitudinal research designs and an assessment of coping that takes place as close to the real-time occurrence as possible should be frequently implemented. (Lazarus, 2000; Somerfield & McCrae, 2000; Tennen, et al., 2000)

Some findings concerning the role of coping styles in the perioperative period will be reported in section 1.6.1.

1.4.3 *Social Support*

Social support can be either categorized as an external resource or as a coping strategy. It generally refers to the intended provision of any kind of help or assistance to an individual who is faced with a problem or stressful situation. The *sources of support* are in most cases spouses or partners, other family members such as children or parents, friends, or, dependent on the circumstances, also formal providers such as community institutions or hospital staff. Social support is a sort of umbrella term comprising different types of support aiming at assistance with solving the problem at hand or at easing the negative emotions associated with the respective problem. The

specific actions range from reassurance, encouragement, and advice to the provision of material resources or physical help with a task. Social support that is directed at reducing negative emotions and changing beliefs concerning the causation of the problem can be sub-divided into *emotional support*, *esteem support*, and *appraisal support*. Social support that is, on the other hand, directed at solving a problem or changing the stressful circumstances, can be categorized into *information support*, *tangible support*, and *instrumental support*. A popular classification distinguishes just between *emotional*, *instrumental*, and *informational support*. Another support category is *protective buffering* which comprises all sorts of indirect social support aiming at protection of the partner. (Cutrona & Gardner, 2004)

The construct social support is to some extent related to the *social network*, referring to the people someone interacts with or is influenced by. However, the studied correlations between characteristics of the network, such as number of persons in the network and frequency of contact with others, and social support are mostly very small. There is also some overlap between the construct of social support and *social integration*, referring to the size and density of the network, the frequency of contacts, the number of social roles a person holds, and the feeling of embeddedness. The former emphasizes the qualitative-functional aspect and the latter the quantitative-structural aspect of social relationships. (Cutrona & Gardner, 2004; Schwarzer, Knoll, & Rieckmann, 2004)

Some other relevant constructs in the context of social support are the *need for support* with great interpersonal differences and a dependency on the respective situation, and the *mobilization of support* that is conceptualized as an active and adaptive coping strategy (Schwarzer, et al., 2004).

With respect to support assessment, one has to differentiate between perceived available support and actually received social support. Questionnaires asking for *anticipated or perceived available social support* gather information regarding individuals' subjective perceptions of the extent of support provision by members of their social network in times of need. These prospective judgments are highly subjective and are assumed to represent a kind of personality trait. Despite of their probable inaccuracy, perceptions of available support are highly informative and important to well-being and health. Alternatively, *actually received social support* can be assessed by asking about the frequency and type of social support that was provided by the network during a certain time period. These retrospective judgments are less prone to subjectivity but, on the other hand, highly dependent on the assessment period. Moreover, even a lot of received support might not be subjectively

perceived as helpful by the recipient, but, on the contrary, could even cause the feeling of being unable to cope with a problem on one's own. For obvious reasons, perceived available and actually received social support are often only weakly correlated and are believed to have different effects on well-being. As a third, rather time consuming possibility, the provision of support can be observed by evaluating actual support interactions externally and systematically or by daily diary approaches. (Antonucci, Lansford, & Ajrouch, 2007; Cutrona & Gardner, 2004; Schwarzer, et al., 2004)

It is important to note that the provision of social support does not always have beneficial effects for the recipient, but unrequested or not needed support can also lead to interpersonal conflicts, negative feelings, such as personal failure or inadequacy, a sense of indebtedness, and loss of self-esteem (Antonucci, et al., 2007). This underlines the importance of carefully considering the perspective (provider, recipient, or external observer) one is interested in, as all three sources yield different information.

An example for a multi-dimensional coping inventory that simultaneously assesses perceived available social support, actually received social support, need for social support, mobilization of social support, and protective buffering are the Berlin Social Support Scales, BSSS (Schwarzer & Schulz, 2000).

Many research activities concentrated on the association between social support and health or well-being. Large-scale studies have provided support for an association between social integration or support and morbidity and mortality rates. Evidence suggested that perceived available support protects or buffers people to some extent from emotional distress caused by all kinds of stressful life events, such as job loss or death of a loved person. Moreover, people with high perceived social support have been found to engage in health behaviors (e.g. exercise or healthy diet) more often and to report better health and well-being than those with low perceived available support. Research further indicated that social support is associated with lower blood pressure, healthy functioning of the immune system, and reduced cardiovascular reactivity in response to laboratory stressors. The findings concerning the relation between social support and indices of recovery from illness (e.g. pain, mobility, length of hospital stay) are, however, inconsistent (see also section 1.6.1.3). At present, there are two influential theories explaining the impact of social relationships on health. The *direct effects model*, on the one hand, proposes that relationships with other people lead to health benefits in good and bad times because of their influence on emotions, thoughts, and actual behaviors. The *buffering model*, on the other hand, suggests that relationships with other people exert their beneficial influence on health mainly in

stressful times and indirectly through the protection or buffering from the harmful impact of stressful life events on health and well-being. See Uchino (2006) and Uchino, Cacioppo, and Kiecolt Glaser (1996) for reviews of the relationship of social support and health with a special focus on the potentially underlying physiological mechanisms and processes. (Antonucci, et al., 2007; Cutrona & Gardner, 2004; Schwarzer, et al., 2004)

Additionally, there are pronounced gender, age, cultural, and situational differences in the need for support, its mobilization, perception, and receipt that have to be taken into account when planning and interpreting research (Schwarzer, et al., 2004).

Some findings concerning the role of social support in the context of medical procedures will be reported in section 1.6.1.3.

1.4.4 *Anxiety*

There are many parallels between the concepts of stress and anxiety. Whereas the situational perception of threat is the central element in both processes, they also differ from one another as anxiety is just one of many cognitive-emotional response qualities in a situation appraised as threatening (Jerusalem, 1990).

Anxiety can be conceptualized as a response that is characterized by a dysphoric affective state and that is by some researchers subdivided into neurotic anxiety (internal source of danger) and objective (external source of threat) anxiety or fear. However, it can also be regarded as an intervening variable, standing between the observable stimulus and the behavioral response, which activates or motivates responses because of its discomforting or painful nature. Furthermore, anxiety can be theorized as a signal of danger that further mobilizes defense reactions. (Lazarus, 1966)

Some researchers, especially within bio- or neuropsychological conceptualizations, further differentiate between anxiety and fear and propose that fear-related behavior (according to Cannon's fight-or-flight response) occurs when a threat is actually present, whereas anxiety-related behavior (in the sense of risk assessment) occurs when a threat is only potentially present (Blanchard & Blanchard, 1988).

Within the cognitive-transactional stress theory as put forward by Lazarus (1966), anxiety plays a major role in the primary appraisal of threat. Dependent on the many factors involved in the process of secondary appraisal, anxiety or fear can persist or be further transformed into another affect like anger or depression. The kind, degree, and

quality of negative affect states thus depend on the appraisal and coping processes and can vary in the course of the stress process.

One can differentiate between state anxiety that is a transient phenomenon and highly dependent on the specific situation at hand, and, on the other hand, trait anxiety that reflects an individual's characteristic or general disposition to respond with anxiety across a wide range of situations (Lazarus, 1966). Thus, when measuring anxiety, one can refer either to the reaction in the face of a specific set of conditions or to a general personality trait, while the quality or nature of the reaction itself might not vary. A popular and frequently used example for a questionnaire assessing both state and trait anxiety is the State-Trait-Anxiety Inventory (STAI) by Spielberger (Spielberger, Gorsuch, & Lushene, 1983).

A theory-based measurement of stress in line with the transactional multivariate process-oriented approach as formulated by Lazarus (1966; Lazarus & Folkman, 1984) would require the complex assessment of key inputs (e.g. life-events), antecedents (e.g. general beliefs), mediating appraisal and coping processes, and response markers (e.g. subjective, behavioral, and physiological indices of emotions) of the stress process. For obvious reasons, such a measurement confronts researchers with a lot of difficulties. Although some instruments for the assessment of stress have been developed, such as the Hassles and Uplifts Scale (Lazarus & Folkman, 1989) and the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), they fail to measure stress in a process oriented sense, but only take stress as an outcome variable into account. Lazarus (1990) argued for repeated measures of as many variables in the system as possible at carefully selected time points, or, at least, for a simultaneous assessment of coping and the outcome variable stress, without claiming to represent the stress process as a whole as defined in the cognitive-relational theory. He further advocated a turn to the measurement of the quality and intensity of emotions as well as their sources instead of stress, as they are presumably more informative and more easily assessed. In line with these recommendations, anxiety is a frequently measured emotion and indicator of stress. (Lazarus, 1990)

As anxiety is the most prominent and most extensively investigated emotion in the context of medical procedures, it was also assessed in the present investigation. Empirical findings concerning the association of anxiety and autonomic activity will be reported in section 1.5 and findings with regard to the perioperative period will be outlined in section 1.6.1.

1.5 *Autonomic Activity and Stress*

In this section, a growing body of research will be reported that links indices of autonomic activity and especially HRV to the psychological constructs of stress and anxiety and consequently establishes HRV as a marker of stress.

1.5.1 *Findings on the Association of Stress or Anxiety and HRV*

Based on Porges' research (see section 1.3.2.6), Friedman (2007) developed the neurovisceral integration model, a framework that links anxiety to the phenomena of inhibition and perseveration and their central nervous system mechanisms. In line with Porges, he criticized the sole focus on the SNS and the relative neglect of the PSNS, as well as the outdated view of homeostasis, dating back to Cannon, in the context of stress research (Friedman, 2007; Friedman & Thayer, 1998). Friedman (2007), in contrast, argued, consistent with modern chaos theories or non-linear dynamics, that healthy physiology is characterized by high levels of adaptive variability. He further stressed the role of inhibition in self-regulation and suggested a failure of inhibition at various response levels of anxiety. He compiled a great amount of empirical findings to support the theory's prediction of reduced HRV and reduced vagal tone in diverse manifestations of anxiety. In sum, the reviewed research, ranging from challenging laboratory tasks like mental arithmetic or reaction-time/shock avoidance to the recall of stressful events or exposure to traumatic stimuli, indicated that acute stress responses and anxiety are marked by ANS imbalance in the sense of cardiac vagal withdrawal and concomitant increased cardiac sympathetic control. Moreover, chronic or trait anxiety, negative mood, and pathologic worry were found to correlate negatively with cardiac vagal control as indexed by HRV. He further summarized evidence that anxiety disorders like panic disorder and Post Traumatic Stress Disorder (PTSD) are associated with aberrant ANS activity and consequently aberrant HRV features. (Friedman, 2007; Friedman & Thayer, 1998)

Consistent with the findings of Friedman (2007), Watkins, Grossmann, Krishnan, and Sherwood (1998) reported significantly reduced vagal control of the heart in individuals scoring high on trait anxiety, as measured by the State-Trait Anxiety Inventory (STAI) (Spielberger, et al., 1983), compared to individuals scoring low on trait anxiety in a sample of about 90 healthy middle-aged men and women. The difference in cardiac vagal control, as measured by baroreflex control of the heart (BRC) and respiratory sinus arrhythmia (RSA), was maintained even after covarying for potential confounders such as age, BMI, or blood pressure.

Jönsson (2007), on the contrary, found no significant correlation between RSA and trait anxiety in a sample of about 80 healthy male and female students. It is worth mentioning, however, that Watkins et al. (1998) reported likewise only modest reductions of RSA with increasing trait anxiety, but at the same time great reductions in BRC, another index associated with vagal control of the heart. Moreover, Watkins et al. (1998) compared individuals with trait anxiety scores in the highest and lowest quartile, whereas Jönsson (2007) compared individuals based on median split of the scores. Nevertheless, with regard to state anxiety, Jönsson (2007) reported significantly higher RSA-magnitude (HF-power) in participants scoring high on state anxiety. The author considered this finding within a neuropsychological framework of anxiety. Gray and McNaughton (Gray, 1982, as cited in Birbaumer & Schmidt, 2003, pp. 660-661) postulated three independent neural systems: (a) the behavioral inhibition system (BIS) that is activated by potential threats, (b) the fight/flight/freezing system that is activated by actual threats, and (c) the behavioral activation system (BAS) that is activated by reward stimuli. The BIS plays a central role in normal as well as pathological anxiety and is primarily located in brain structures like the septo-hippocampal system and the amygdala. It is said to be considerably involved in comparing inputs and reacting to mismatches between an actual and an expected event. In the case of such an approach-avoidance conflict, the BIS inhibits ongoing motor programs and focuses the attention to the perceptual world, and is thus associated with the orienting response (OR) and HR deceleration (Birbaumer & Schmidt, 2003). Therefore, in situations of acute stress, for example after confrontation with a novel or potentially dangerous stimulus, the BIS is supposedly activated and leads to an anxious and attentive state that is accompanied by an initial heart rate deceleration, which represents a vagally mediated OR (Jönsson, 2007). According to Jönsson (2007) the increased vagal tone in individuals reporting high state anxiety could thus be attributed to the activation of the BIS and to increased attention or motor inhibition, processes that might both be accompanied by HR deceleration and possibly RSA increases. Alternatively, the author suggested considering the findings within the framework of the polyvagal theory (Porges, 1995b, 2001). In that case, the increased RSA-magnitude could reflect activation of the so called vagal brake (myelinated vagus) that fosters reasonable behavior patterns in anxious individuals, such as increased attention and engagement with the environment.

In another study that addressed the relationship between trait anxiety and HRV in healthy individuals, the possible influences of age, gender, cardiovascular fitness, and perceived stress during the past week were assessed (Dishman, et al., 2000). The authors reported a small inverse relationship between perceived emotional stress

during the past week, as measured by Cohen's Perceived Stress Scale PSS (Cohen, et al., 1983), and the normalized HF component of HRV, tentatively suggesting attenuated vagal control of the heart in healthy individuals who experienced emotional stress. This relationship was independent of age, gender, cardiovascular fitness, and trait anxiety. Trait anxiety, as measured by the Taylor Manifest Anxiety Scale (TMAS) (Taylor, 1953), was, however, unrelated to all HRV indices.

In an investigation of the association between several psychosocial risk factors and HRV parameters in a large sample of healthy women, Horsten, et al. (1999) found out that a small household size and self-reported lack of social support were significantly related to lower HRV (lower SDNN index, LF, and VLF power) during daily life, as measured by 24-hour Holter recordings. These associations of HRV and social isolation remained significant even after adjusting for age, menopausal status, educational level, exercise and smoking habits, history of hypertension, and BMI. Other researchers, however, failed to find a correlation between social support and HRV (Masi, et al., 2007), but it is worth noting that they only used short-term recordings for the analysis.

1.5.2 *Cardiovascular Reactivity*

Many psychophysiological investigations utilize the paradigm of *cardiovascular reactivity* (CVR) which refers to alterations in relevant physiological parameters such as heart rate or blood pressure in a task- or stress-condition compared to the respective parameter values in a so called baseline-condition (e.g. Turner, 1994). The reactivity of the cardiovascular system thus reflects an individual's response to environmental conditions experienced as stressful. The stressors can be either discrete events such as a public speech, or chronic or repeated stressful conditions such as overwork. People differ from one another in the extent and pattern of their individual responses to stressors, even in the face of allegedly equal external conditions (Turner, 1994). This individual variation is on the one hand interesting per se, on the other hand interesting in connection with the later development of cardiovascular diseases, as pronounced stress responses (e.g. large stress-induced heart rate elevations) are markers of or even hypothesized to play a causal role in the development of diseases such as hypertension (HTN) or coronary artery disease (CAD) (Schwartz, et al., 2003).

Schwartz et al. (2003) addressed several critical points when applying the paradigm of CVR and establishing a link between stress reactivity and the development of diseases.

- First, laboratory assessment of CVR should generalize to stress-induced responses occurring in the natural environment or real world. The authors criticized the questionable ecological validity of many commonly used laboratory tasks such as the cold pressure test and reported limitations in generalizability due to situation and person-by-situation effects. Moreover, they pointed to the hitherto emphasis on the exposure phase and at the same time neglect of the anticipation of and recovery from a stressor. In order to improve generalizability, they suggested using more ecologically valid stressors such as social stressors, aggregating across different tasks to account for person-by-situation effects, and considering anticipatory and recovery responses.
- Second, the authors stressed that it is important to acknowledge that cardiovascular responses to stress cannot be understood adequately by studying single, isolated factors, but only by considering interactions among environmental factors, genetic variation, behaviors, and personality traits. When aiming at investigating disease pathways, one should thus assess interactions between individual predispositions and environmental exposures.
- Third, they emphasized the importance of assessing the frequency and duration of stress responses, beside the magnitude of the response that is commonly measured in laboratory investigations. Real-life responses are often characterized by sustained arousal due to chronic stressful exposures, prolonged anticipatory and recovery phases, and recall of emotional stressors or rumination. Anticipation of a stressor and delayed recovery from it substantially lengthen the period of reaction to a stressor and are hence believed to contribute to the development of cardiovascular disease.

1.5.2.1 *Laboratory Studies of Stress.*

Gregg, James, Matyas, and Thorsteinsson (1999) compared hemodynamic responses in the anticipation phase, during the actual confrontation with a stressor (mental arithmetic and cold pressor test), and in the recovery phase and were able to demonstrate distinct patterns of myocardial and vascular reactivity for each phase. The authors argued that these different hemodynamic patterns should be observed in more detail, as they might play a central role in the development of hypertension. They suggested that anticipatory and recovery reactions might be even more important predictors of cardiovascular risk than the acute reaction to a stressor itself.

With regard to recovery from stress, attenuated vagal reflex activity during recovery has attracted interest as it might be connected to cardiovascular disease.

Within this context, Mezzacappa, Kelsey, Katkin, and Sloan (2001) reported findings from two experiments that aimed at evaluating cardiovascular responses and more specifically sympathetic and parasympathetic reflexes after different stress-inducing conditions (mental arithmetic task, cold pressor task, Stroop color-word task). The authors observed a quick decrease in heart rate below baseline level within one minute after termination of psychological stress that was obviously mediated by a pronounced rebound in vagal activation right after the stress-condition. Additionally, the authors observed a tendency of reduced vagal rebound in participants with a family history of cardiovascular disease. Vagal rebound was calculated as a change score from the maximal rMSSD withdrawal during the task to the first minute of recovery. It seems to constitute a distinct feature in the parasympathetic recovery process and to play an important role in the restoration of cardiovascular homeostasis.

Moses, Luecken, and Eason (2007) addressed person-by-situation effects by investigating CVR in three different situational contexts in the laboratory: an attention task, a cold pressure task, and a speech presentation. Foremost, the authors observed substantial interpersonal variability in the physiological responses across participants. Concerning heart rate, they reported an increasing quadratic tendency during the attention and the speech task, but a decreasing quadratic tendency during the cold pressure task. Concerning HRV, both LF and HF reactivity ratios decreased during the attention task and the speech presentation, but showed distinct reactivity patterns for the cold pressure task. Interestingly, most measurements returned to baseline-values within a recovery period of only five minutes. However, due to a very small sample size ($N = 7$) the results have to be interpreted with caution.

Grossman, Watkins, Wilhelm, Manolakis, and Lown (1996) examined cardiovascular responses to a public-speaking stressor in patients suffering from coronary artery disease with high and low levels of cardiac vagal activity as measured by RSA. The authors demonstrated an association between the level of parasympathetic cardiac control and autonomic responses to stress in the sense that patients with a low level exhibited greater diastolic blood pressure responses, greater increases in total peripheral resistance (an indicator of myocardial oxygen demand) and rate-pressure product, and attenuated baroreflex sensitivity to the stressor. These findings point out that impaired vagal control might constitute a risk factor for cardiovascular diseases through various physiological pathways.

1.5.2.2 *Real-life Studies of Stress.*

As it is still unclear in how far findings from laboratory studies generalize to real-life experiences, some researchers turn to more ecologically valid stressors and investigate reactions to stress in the field.

The assessment of CVR to public speaking as a powerful psychosocial stressor, for example, has shown substantial task-related increases in heart rate, blood pressure, and electrodermal activity (EDA) (Carrillo, et al., 2001; Fichera & Andreassi, 2000).

Moreover, gender differences in reactivity patterns were observed, in the sense that women displayed greater heart rate increases, whereas men showed greater increases in blood pressure (Fichera & Andreassi, 2000). However, in another study no gender differences in heart rate reactivity to public speaking were observed, but women showed greater amplitudes of non-specific skin conductance responses (Carrillo, et al., 2001). Furthermore, the role of psychological dimensions in relation to reactivity was assessed and, interestingly, anxiety and mood states were differently related to cardiovascular and electrodermal indices in men and women (Carrillo, et al., 2001). The heterogeneity of these findings emphasizes the relevance of assessing multiple indicators of stress responses and paying attention to possibly confounding factors such as gender or personality variables.

Sloan et al. (1994) reported significant increases in the LF/HF ratio during stressful episodes of the day as indicated by subjective mood ratings that point to a shift of cardiac autonomic balance towards sympathetic predominance. These stress-induced alterations in the cardiac sympathovagal balance were independent of individual differences and body position.

Lucini, Norbiato, Clerici, and Pagani (2002) tried to capture the impact of real-life stress on human physiology by investigating students' hemodynamic and autonomic adjustments to an important university examination. When comparing a multitude of measurements taken in resting conditions shortly before the examination with those taken at a control day three months afterwards, the authors observed significantly smaller RR intervals and greater systolic arterial pressure (SAP) on the stress day. More specifically, the autonomic control of circulation on the stress day was characterized by significantly higher values of LF (nu) and of the LF/HF ratio, indicating increased sympathetic activity, whereas the HF component was significantly smaller, indicating reduced vagal control of the heart, with the results being independent of respiratory changes. Furthermore, the index α , a marker of the overall gain of the

arterial pressure-heart period baroreflex, was reduced shortly before the examination, pointing likewise to a shift in autonomic balance toward sympathetic predominance and vagal withdrawal. The comparison of immunological markers of the control day to the stress day indicated a pronounced change in cytokine profile, suggesting prolonged activity of the stressor (long-standing preparation for and anticipation of the examination) on humoral homeostasis. With regard to endocrine markers of the stress response, salivary cortisol levels were elevated on the stress day, indicating involvement of the HPA axis, and a significant correlation between cortisol and indices of the autonomic modulation of the SA node was observed. Moreover, the stress response became evident in subjective ratings of stress, and these scores further correlated with the resting values of RR and SAP.

Consistent with these findings, persons suffering from chronic psychosocial stress (high perception of stress and indication of stress-related somatic symptoms) showed increased arterial pressure and impaired autonomic regulation of cardiovascular functions at rest, in the sense of sympathetic dominance, vagal withdrawal, and baroreflex impairment (Lucini, Di Fede, Parati, & Pagani, 2005). It is worth mentioning, that no differences between highly stressed individuals and controls were observed in RR interval variance and absolute values of RR interval LF and HF spectral components. However, the LF component expressed in normalized units (nu) and the LF/HF ratio were significantly higher in stressed individuals, whereas the HF component (in nu) was significantly smaller. Stressed persons furthermore demonstrated a greater LF component of SAP variability and a reduced index α . Moreover, correlations with the subjective stress perception were significant only for those indices expressed in normalized units. The findings of Lucini et al. (2005; 2002) and Dishman et al. (2000) suggested that the analysis of frequency components of HRV expressed in normalized units provides distinctive information compared to absolute values of spectral power and appears to be particularly sensitive to prolonged psychosocial stress.

Worry might play a central role in the prolongation of stress-related cardiovascular reactivity by the continuous cognitive representation of stressors, and thus comes into consideration as a risk factor of cardiovascular diseases (Brosschot, Van Dijk, & Thayer, 2007). Brosschot et al. (2007) investigated the relationship of worry, daily stressors, anxiety, bio-behavioral variables, and indices of HRV during the day and night, to assess whether worry plays a mediating role, and whether possible cardiac activation due to sustained worry during the day has an impact on the subsequent nocturnal sleep. In sum, stressors as well as prolonged worry correlated with high HR and low HRV during waking and sleeping, but worry duration mediated

the effects of the stressors. The effects of trait anxiety on waking HR and HRV, however, could be explained by bio-behavioral factors, such as gender, age, and sleep quality. Hence, the amount of time spent worrying during the day was associated with larger cardiac effects than stressors and even mediated their effect. This points to the importance of taking not only stressors into account, but also factors like worry that potentially sustain the effects of stressors even during nocturnal sleep.

Summing up, the paradigm of cardiovascular reactivity (CVR), within which physiological reactions to a variety of stressors can be examined, has been briefly introduced, and the importance of taking into account anticipation of and recovery from stress has been pointed out (Gregg, et al., 1999; Mezzacappa, et al., 2001; Schwartz, et al., 2003; Turner, 1994). Taken together, the reviewed literature, ranging from laboratory studies to investigations of real-life stress, suggests that acute as well as chronic stress responses are marked by a pattern of reduced HRV, vagal withdrawal or depressed vagal tone, as indexed by reduced RSA, HF spectral power, HF (nu) or rMSSD, and at the same time increased sympathetic activity, as demonstrated by enhanced LF spectral power, LF (nu), and LF/HF ratio (Dishman, et al., 2000; Lucini, et al., 2005; Lucini, et al., 2002; Moses, et al., 2007; Sloan, et al., 1994). Moreover, research indicates an association between (different indices of) HRV and psychological dimensions such as anxiety, worry, and mood states, though the findings are sometimes inconsistent and need further clarification (Dishman, et al., 2000; Friedman, 2007; Friedman & Thayer, 1998; Jönsson, 2007; Sloan, et al., 1994; Watkins, et al., 1998).

1.6 *Stressful Medical Procedures*

Medical procedures and examinations of all possible kinds, ranging from taking blood samples to emergency surgeries, constitute stressors that are frequently encountered by many people (Schmidt, 1992; Schumacher, 2002). There is on the one hand great variety in the kind of medical care applied, and on the other hand great heterogeneity in the way people experience and deal with it. One thus has to be aware of the fine line between “psychologizing” and “trivializing” medical procedures at large (Schmidt, 1992). However, there doesn’t seem to be a linear relationship between the severity or riskiness of the medical procedure and the degree of stress people experience (Vögele, 1992). On the contrary, the subjective experience depends on a large number of internal/personal, external/environmental, and interpersonal factors and their interaction, thus suggesting an interactive approach for the investigation of stress (Vögele, 1992). The manifestation, temporal course, and possible mediators and moderators of stress responses in the context of medical procedures have awaked a

lot of interest in both professionals of various disciplines (e.g. psychologists, doctors, nurses, sociologists) and patients or laymen. The practically relevant field of psychological interventions has similarly gained in importance. To narrow the broad field of research down, the focus will henceforth be on surgery, probably the most threatening medical procedure that comprises a lot of unpredictable and uncontrollable features such as anesthesia, postoperative pain, and surgical trauma (Vögele, 2007).

Within the stimulus-based stress conceptualization, some situations or critical life-events are explicitly defined as stressors which require a certain amount of readjustment and thus provoke stress responses. In line with this tradition, serious medical procedures such as surgery can be regarded as a major stressor for a majority of patients (Filipp, 1981). According to Janke's (1974) content-based classification of stressors, medical procedures constitute external stressors that potentially comprise a physical threat. Within the tradition of transactional-based stress theories, some formal characteristics of situations have been identified that possibly contribute to a person's perception of challenge, threat, or loss. Above all, the following characteristics of situations or events are considered as important: novelty, predictability, event uncertainty, temporal conditions (time until the incidence of the stressful event, duration of the event, temporal uncertainty), ambiguity, and timing (Jerusalem, 1990). Applied to the medical context, these formal characteristics of situations can assist in the identification of medical procedures that might be appraised as threatening by many patients. For instance, the degree of stress that a patient awaiting surgery experiences, might vary according to the person's previous experiences with medical procedures (e.g. first stay in a hospital or repeated surgeries), the person's knowledge about the procedure, the duration, possible side-effects et cetera, and temporal factors (e.g. fixed date of surgery or repeated rescheduling; short or long waiting period for surgery), among many other influencing factors.

However, situational characteristics are but one aspect involved in the experience of stress. Also personal factors such as commitments and beliefs (e.g. control beliefs) play a central role in the appraisal and coping processes and can be either regarded as vulnerabilities or as resources (Lazarus & Folkman, 1984). One distinguishes objective resources (e.g. intelligence, knowledge, health, social support) and subjective resources (e.g. dispositional optimism, hardiness) which both determine the employed coping mechanisms (Jerusalem, 1990).

Research confirms that especially the lack of predictability and control contribute significantly to the patient's experience of stress (Krohne, 1992; Vögele, 2007). Because of the restricted behavioral control and instrumental influence prior to surgery,

patients have to turn to primarily cognitive coping strategies (e.g. reinterpretation or attentional diversion) to alter the course of information processing and the appraisal of the situation and subsequently reduce stress in the perioperative period (Krohne, de-Bruin, et al., 2000). Empirical findings concerning the role of personal factors in the context of medical procedures will be reported in more detail in section 1.6.1.

One simple classification of stress in the surgical context differentiates between procedural stress that is stress associated with negative aspects of the medical procedure itself, and outcome stress referring to anxious thoughts about the outcome of the procedure (Vögele, 2007). One can likewise classify anxiety according to the dominant contents, namely anxiety related to anesthesia (worries concerning pain or not waking up again), to the impending surgery (potential negative consequences), and to diseases (possible detection of a severe disease during surgery) (Krohne, 1994). Understandably, the topics related to anxiety change over the perioperative period and therewith the manifestation of anxiety.

Schmidt (1992) developed a framework for the discussion of stress in the context of medical procedures that encompasses a variety of conditions that can be grouped into (a) antecedent conditions, (b) contextual factors, and (c) temporal progress. The former (a) includes a patient's experience with medical procedures, characteristics of the patient such as sociodemographic characteristics, individual differences (e.g. anxiety, aggression, coping, competences, control beliefs), or information and attitudes toward a procedure, and social support. Contextual factors (b) comprise macrosystemic aspects (e.g. insurance issues and laws), aspects of the hospital or practice and organizational factors (e.g. personnel and equipment), the patient's disease, and the particular sort of medical procedure (e.g. diagnostic versus therapeutic and in-patient versus out-patient). The latter group (c) includes the temporal course of the treatment as well as the patient's reactions in the course of time. As there can be a great amount of heterogeneity in all of these factors, it is important to take as many of these into account as possible when planning, conducting, or interpreting research in this context. (Schmidt, 1992)

Schumacher (2002) classified a variety of factors that people encounter in the perioperative period and that might cause strain, into (a) unspecific and (b) specific factors. The former group (a) refers to factors related to the hospital stay (e.g. unfamiliar surroundings, loss of independency, lack of information) and factors related to the respective disease (e.g. pain, loss of physical integrity, unpredictability of the further progress). The latter group (b) includes a possible avoidance-avoidance conflict (neither the surgery, nor the refusal of surgery are attractive options), reduced control

(e.g. reduced control over the situation, reduced predictability of important situational factors), the anticipation of a total loss of control during surgery under GA, and the need for cognitive coping because of reduced possibilities for active coping. (Schumacher, 2002)

Stress or anxiety in the perioperative period can be either operationalized in terms of subjective measurements such as rating scales (e.g. ratings of state anxiety or negative mood), or objective measurements such as physiological parameters (e.g. HR, HRV), or both sources of information can be utilized to get an as realistic picture as possible. In order to evaluate the impact of stress and also of psychological interventions aiming at reducing stress on the patient's medical and psychosocial adaptation, several indices have been proposed (Krohne, 1994): medical criteria (e.g. length of hospital stay, amount of anesthesia and analgesia used, physician's rating of postoperative recovery), self-reports of pain and well-being, criteria of intraoperative adaptation (amount of anesthesia needed, hemodynamic parameters, depth of anesthesia), and psychological or psychosocial criteria (e.g. self-reports of anxiety, depression, anger, compliance). Ideally, several indices should be assessed simultaneously because of the different situational characteristics.

The next section (1.6.1) will focus on stress, anxiety, coping, and social support in the context of medical procedures, whereas the subsequent section (1.6.2) will concentrate on physiological manifestations of stress in the perioperative period. Section 1.6.3 will then describe a surgical (CEA) and a minimally invasive (CAS) method for achieving revascularization in patients with a high-grade stenosis of the carotid artery, as the present investigation focuses on psychological and physiological stress responses in the context of these two interventions. Two subsections (1.6.3.4 and 1.6.3.5) will place emphasis on psychosocial factors associated with CEA and CAS and autonomic activity during both procedures, taking also the influence of anesthesia into account. The broad area of research concerning psychological interventions in the perioperative period (e.g. preparation for surgery) will not be dealt with, however, as it would go beyond the scope of the introduction at hand (for a review see for example Johnston & Vögele, 1992; Schumacher, 2002).

1.6.1 Stress, Anxiety, Coping, and Social Support in the Perioperative Period

Frequently encountered emotional responses in the perioperative period are anxiety, nervousness, depression, anger, sadness, and boredom (Vögele, 2007). Of all possible emotions present in the perioperative period and indicative of stress, anxiety plays a prominent role. The perioperative degree and temporal course of anxiety

depend on personal and situational factors such as the type, severity, and acuteness of the impending surgery, outcome concerns, the underlying disease, dispositional anxiety, and coping styles (Vögele, 1992, 2007). Though stress and anxiety are generally regarded as psychophysiological phenomena with behavioral, physiological, and subjective components, they are nevertheless mostly operationalized in terms of subjective measurements (Krohne, 1994). A great proportion of research dealing with stress in the perioperative period focuses on subjective ratings of anxiety or other emotional responses prior to and after surgery and on their association with coping strategies and outcome criteria (indices of perioperative adaptation and postoperative recovery). *Perioperative adaptation* is a sort of umbrella term referring to several indices such as the occurrence of complications, pain, and length of hospitalization.

1.6.1.1 *Findings on anxiety in the perioperative period.*

Whereas the preoperative level of *anxiety* is generally often elevated compared to anxiety levels in the normal population, the high level does not automatically decline after surgery, but can stay increased for some time, according to the respective situational and personal characteristics (Vögele, 1992, 2007). Prolonged increased anxiety levels in the postoperative period might be indicative of concern regarding the success of surgery, disappointment with the state of health, or ongoing discomfort (Duits, et al., 1998). Karanci and Dirik (2003), on the contrary, reported high levels of preoperative state anxiety, as assessed by a surgery-specific anxiety inventory and the STAI (Spielberger, et al., 1983), and a fast decline postoperatively in a sample of emergency surgery patients, possibly an indicator of sudden relief after surgery. Moreover, women reported preoperatively higher levels and better educated patients postoperatively lower levels of state anxiety, thus indicating that education could be regarded as a personal resource.

Concerning the course of state anxiety in the perioperative period, some researchers provide evidence for a pronounced increase before surgery and a continuous decrease after surgery (de Groot, Boeke, Duivenvoorden, & Bonke, 1996; Gauter-Fleckenstein, et al., 2007; Krohne, 1992; Krohne, de Bruin, Mohiyeddini, Breimer, & Schäfer, 2000; Krohne, Schmukle, & de Bruin, 2005; Krohne & Slangen, 2005). Notably, state anxiety levels are rather high after admission to the hospital, a situation that is experienced as particularly stressful due to the unfamiliar surroundings, separation from family, and anxiety because of impending surgery; they may, however, decrease temporarily after the anesthesiologist's visit before they again increase until surgery (Krohne, 1992, 1994; Krohne & Slangen, 2005).

When subdividing state anxiety into a cognitive (anxious worry, rumination) and an affective (autonomic and somatic reactions) component, evidence suggests distinct courses in terms of a more pronounced increase of the affective component shortly before the operation and a faster decline postoperatively (Krohne, et al., 2005; Slangen, Krohne, Stellrecht, & Kleemann, 1993).

Preoperative state anxiety has been shown to predict postoperative negative affect and pain-related stress (Krohne, de Bruin, et al., 2000; Krohne, et al., 2005), and high postoperative anxiety was associated with a longer postoperative stay in hospital (Krohne & Slangen, 2005).

It is worth mentioning that women generally showed higher anxiety levels across all subscales (cognitive and affective anxiety components) and points in time (Krohne, et al., 2005; Krohne & Slangen, 2005). These gender differences in anxiety were also replicated in a study of CABG surgery patients and extended to depression, with women, too, reporting higher depression levels than men throughout the perioperative period (Duits, et al., 1998).

Gauter-Fleckenstein et al. (2007) demonstrated the importance of taking the underlying disease into account by showing that patients with malign diseases reported significantly higher anxiety levels pre- and postoperatively than patients with benign diseases in a sample of women undergoing elective gynecological surgery.

Kain, Sevarino, Alexander, Pincus, and Mayes (2000) addressed the question whether preoperative anxiety is associated with postoperative pain because research had so far produced conflicting results due to differing research designs and insufficient controlling of confounding variables. In a sample of 53 healthy women undergoing elective abdominal hysterectomy under GA, self-reported anxiety – measured by the STAI (Spielberger, et al., 1983) – and pain – measured by two self-report questionnaires and by analgesic consumption – were assessed several times in the perioperative period and their association with the coping styles monitoring (i.e. information seeking) and blunting (i.e. information avoiding and distraction) – measured by the Miller Behavioral Style Scale MBSS (Miller, 1987) – was investigated. Lower levels of the coping style blunting turned out to be significantly related to higher levels of trait anxiety, preoperative state anxiety, as well as postoperative state anxiety on the ward. As indicated by path analysis, higher levels of preoperative state anxiety significantly predicted higher levels of immediate postoperative pain, pain on the ward, and pain at home one week postoperatively through direct and indirect pathways. The effects of trait anxiety on postoperative pain, however, were mediated through the effects of trait anxiety on preoperative state anxiety. The authors (Kain, et al., 2000)

thus suggested the implementation of preoperative anxiety-reducing strategies in order to decrease pain in the postoperative period.

De Groot et al. (1996), on the other hand, argued that moderate levels of preoperative anxiety might even have beneficial effects on postoperative recovery by leading to preparatory worry and adequate expectations regarding postoperative pain and discomfort.

1.6.1.2 Findings on coping in the perioperative period.

Concerning the relation between *coping* and anxiety in the preoperative period, higher levels of state anxiety were shown to be positively associated with vigilance (increased attention to fear-related stimuli and information seeking) and negatively with cognitive avoidance (avoidance of fear-related stimuli) (Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005), two dispositional coping strategies measured by the Mainz Coping Inventory (Krohne & Egloff, 1999).

In patients undergoing emergency surgery, helplessness and self-blaming in the preoperative period and active coping in the postoperative period were reported as ineffective coping styles in terms of increasing anxiety (Karanci & Dirik, 2003).

In contrast to coping instruments with a dispositional and macroanalytical approach [e.g. vigilance versus cognitive avoidance (Krohne & Egloff, 1999)], Krohne, de-Bruin, El-Giamal, and Schmukle (2000) developed an inventory, the Coping with Surgical Stress Scale (COSS), for assessing the specific coping mechanisms that are frequently employed by patients in the preoperative period. This emphasis on actual surgery-related coping can assist in identifying those psychological preparation or modification programs that are especially suited for a certain patient in a certain situation. Based on empirical data, the authors (Krohne, de-Bruin, et al., 2000) extracted the following five subscales: rumination, optimism and trust, turning to social and religious resources, threat avoidance, and information seeking. They reported substantial gender differences that indicated a differing functional relevance of certain coping strategies for men and women, and thus stressed the importance of considering gender effects in research on coping. In a revised version (COSS-R) of the COSS, seven types of coping with surgical stress were identified: information seeking, rumination, optimism and trust, recourse to personal resources, downward comparison, distraction, and hold in belief and religion (Krohne, et al., 2005). Rumination (worry and persistent speculating about possible negative outcomes) was found to positively correlate with state anxiety, likewise the turn to religion and belief, but recourse to

personal resources, on the other hand, was negatively associated with anxiety (Krohne, et al., 2005).

Within a large-scale project Jordan (1992) tried to get a precise picture of patients' psychological processing on the day before and after a percutaneous transluminal coronary angioplasty (PTCA), a treatment for coronary heart disease performed under LA. The results based on self-ratings and interviews indicated that the majority of patients did practically not suffer from preoperative anxiety, but a gender difference in terms of higher anxiety in women was observed. With regard to coping mechanisms, most patients exhibited a rational, optimistic, and calm attitude on the day before surgery and declared a high degree of trust in medicine, the physicians, and the hospital. Whereas men also tended to trivialize the situation, women's coping was more frequently characterized as emotionally open. On the day after PTCA, the patients mentioned bodily sensations during the procedure as the most inconvenient aspect, but the technical complexity as calming. They would have appreciated more intra-procedural information and indicated a very good doctor-patient-relationship, despite the objectively short and rather impersonal contact with their physician. Similarly to preoperative coping, postoperative coping was characterized by an active, self-disciplined, and concentrated state of mind in combination with positive affect and trustfulness. Hence, PTCA was a rather positive experience for most patients and they generally had adequate coping strategies available.

1.6.1.3 Findings on social support in the perioperative period.

Social support is believed to buffer the experience of stress in the medical context and thus constitutes an important coping strategy (see section 1.4.3). Research on social support often differentiates between emotional support – referring to the expression of sympathy, helpfulness, and concern –, informational support – referring to the information about possibilities of dealing with a problem or stressful situation –, and instrumental support – referring to the provision of services and goods (Krohne, El-Giamal, & Volz, 2003).

To account for the specificity of the perioperative situation, the research group around Krohne developed an inventory, the Emotional and Informational Support Scales – Operations (EISOP), that assessed perceived emotional and perceived informational support, as well as the satisfaction with the provided support in patients awaiting surgery (Krohne, et al., 2003; Krohne & Slangen, 2005). In a revised version of the instrument (EISOP-R) they further differentiated between the source of support and identified the following subscales: perceived support from the hospital staff,

perceived emotional support from the social network, perceived informational support from the social network, and satisfaction with the provided support (Krohne, et al., 2003).

Many studies addressed the impact of social support and its different facets on perioperative adaptation by investigating associations with several indicators of pre-, intra- and postoperative adaptation. For instance, higher levels of social support (especially emotional support) after admission to the ward were associated with a shorter postoperative stay in hospital, taking into account the length planned preoperatively by the hospital staff (Krohne & Slangen, 2005; Slangen, et al., 1993). However, in another study no evidence was found for this relationship when the absolute length of the hospital stay was analyzed (Krohne, et al., 2003). The authors suggested that the found association could be explained either by a beneficial effect of social support on the patient's immune function and wound healing or by a tendency of the medical staff to release those patients earlier that seem to receive a lot of support from their social network (Krohne & Slangen, 2005). Krohne and Slangen (2005) reported high correlations between perceived emotional and informational support, negative correlations between age and support, and generally higher support levels in women. Both informational and emotional support proved to be independent predictors of preoperative anxiety. Whereas high levels of informational support were generally associated with lower levels of anxiety, the influence of emotional support was moderated by gender in the sense that female patients with low support reported the highest anxiety levels and male patients with low support reported the lowest anxiety level (Krohne & Slangen, 2005). High levels of social support were furthermore associated with a better state of health throughout the perioperative period, lower pain intensity, less stress related to pain, and better wound healing as rated by a physician (Krohne, et al., 2003).

1.6.1.4 Conclusions on findings regarding stress, anxiety, coping, and social support in the perioperative period.

With regard to *recovery*, evidence suggests that the observed variability in recovery among patients who received the same treatment might be in part due to psychosocial variables such as anxiety, social support, and coping styles (Vögele, 2007). Broadbent, Petrie, Alley, and Booth (2003) even provided evidence that preoperative psychological stress significantly impairs wound healing at the cellular wound repair level after surgery.

Research indicates that not only parameters of recovery but also indices of *intraoperative adaptation* are associated with psychological variables and unfavorably influenced by high levels of stress and anxiety. The amount of anesthetics required for anesthesia induction and maintenance, for instance, was associated with trait anxiety (Maranets & Kain, 1999), preoperative state anxiety, presurgical coping, and social support and showed a pronounced interaction with gender (Krohne, 1994; Krohne & Slangen, 2005; Slangen, et al., 1993).

Summing up, the findings concerning the degree and course of anxiety are somehow conflicting, with some reporting very low preoperative levels of anxiety (Jordan, 1992), whereas others report high increases preoperatively (Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005; Krohne & Slangen, 2005; Vögele, 1992), and with some reporting a fast decline of anxiety postoperatively (de Groot, et al., 1996; Duits, et al., 1998; Karanci & Dirik, 2003; Krohne, 1992), whereas others report continuously heightened levels postoperatively (Vögele, 1992). One can assume that situational factors such as the type of surgery or disease are not negligible and thus results cannot easily be generalized across different types of patient groups, treatments, and medical procedures. Moreover, anxiety can be mediated by the coping mechanisms employed. In this respect, research provides evidence that avoidant coping is associated with lower levels of preoperative anxiety (Kain, et al., 2000; Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005). Generally, women exhibit higher levels of stress and anxiety in the perioperative period (Duits, et al., 1998; Jordan, 1992; Karanci & Dirik, 2003; Krohne, et al., 2005; Vögele, 1992). Whether women are actually more anxiety prone or whether the results pointing to a gender effect only reflect differences in response styles and social desirability with regard to self-report measures remains unanswered. Self-reported anxiety and observed anxiety as rated by hospital staff showed to be significantly related at a moderate level (de Groot, et al., 1996; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005). Women differ from men not only in their anxiety levels but also in the coping strategies employed (Krohne, de-Bruin, et al., 2000). Social support proved to have an important influence on several indicators of perioperative adaptation such as anxiety, length of hospital stay, pain, self-reported state of health, and narcotics needed for anesthesia induction, but the results were to a large extent moderated by gender (Krohne, et al., 2003; Krohne & Slangen, 2005).

1.6.2 *Physiological Manifestations of Stress in the Perioperative Period*

Some researchers not only take subjective indicators, but also physiological or biochemical parameters of stress and anxiety into account in order to get an idea of the

entire stress response. There is also interest in the intraoperative stress response caused by the surgical trauma itself. The surgical stress response is believed to be involved in the occurrence of non-specific postoperative complications through the activation of the sympathetic-adrenal medullary system. But also psychological stress has been associated with poorer recovery due to physical effects such as increased activation of the SNS. (Pearson, Maddern, & Fitridge, 2005)

In a review of research on perioperative stress, Vögele (1992) summarized that many studies support associations between cardiovascular parameters like BP and HR and psychological variables. He argued that cardiovascular reactions throughout the perioperative period are, however, often difficult to interpret as they are complex and multiple determined. Above all, the impact of the surgery itself with potentially significant physiological alterations has to be considered when comparing pre- to intra- or postoperative levels of physiological parameters as indicators of stress. Additionally, medication and alterations in diet and activity levels possibly influence physiological parameters. The author further criticized the methodological inadequacy of many investigations, as they frequently use very heterogeneous patient samples and employ a wide range of different outcome variables indicating postoperative recovery, like postoperative complications, length of hospital stay, and administration of analgetics or sedatives. (Vögele, 2007)

Vögele (1992) aimed at capturing the stress response in the perioperative period (starting six days before until eight days after surgery) by measuring several psychological and physiological parameters in a rather homogenous sample of 46 patients receiving hip joint endoprosthesis. He reported a significant increase of HR and significant decreases of HRV, BP, and activity of the palmar sweat glands after surgery. Subjective ratings of anxiety, depression, and nervousness reached their maximum and physical activity and concentration their minimum on the first postoperative day, supposedly reflecting the fact that the surgery's success cannot be evaluated until mobilization a few days postoperatively. The results further showed an association between the postoperative increase in HR and negative affect (anxiety, depression, nervousness) and gender differences in terms of higher levels of anxiety, less concentration and activity, and higher HR increases in women compared to men. Taken together, the results clearly demonstrated physiologically and psychologically manifested stress responses and, consistent with the findings of Jordan (1992) and Krohne et al. (2005), the importance of taking gender differences into account.

Krohne (1992, 1994) measured cortisol levels and free fatty acids as physiological indicators of stress in the perioperative period in a sample of forty

patients undergoing orthopedic surgery under LA. Both parameters proved to be sensitive indicators of stress as they exhibited a sharp increase preoperatively, remained heightened in the early postoperative period, and showed an interaction with the level of state anxiety and the coping strategies vigilance and cognitive avoidance (Krohne & Egloff, 1999). Those patients who used neither vigilant nor avoidant coping strategies shortly before surgery showed the highest levels of free fatty acids (Krohne, 1992, 1994).

Pearson, Maddern, and Fitridge (2005) also showed significant increases in cortisol and adrenaline, but not in noradrenaline from baseline to surgery in a sample of 39 patients undergoing CEA under LA. Moreover, they reported higher intraoperative cortisol levels in women compared to men. Regression analysis revealed that preoperative state anxiety contributed to 10 percent of the variance in intraoperative cortisol after controlling for demographic and medical variables that explained 45 percent. The association was, however, negative, indicating that higher levels of preoperative state anxiety were related to lower levels of intraoperative cortisol. Additionally, state anxiety significantly contributed (10 percent) to patients' mental functioning but not to their physical functioning one month after surgery after again controlling for demographic and medical variables. Contrary to expectations, the occurrence of postoperative complications was neither associated with intraoperative neuroendocrine responses nor with state anxiety. These findings thus contradict premature assumptions based on a psychophysiological theory of surgical stress that preoperative state anxiety is always associated with increased neuroendocrine responses during surgery and poorer postoperative recovery. The authors suggested viewing the inverse relationship of anxiety and cortisol in light of the high correlations of anxiety and worry, a construct that is not associated with physiological arousal but on the contrary with reductions in cardiovascular activity and HRV in fear-related situations.

Contrary to Pearson, Maddern, and Fitridge (2005) and Krohne (1992, 1994), Gauter-Fleckenstein et al. (2007) found a decrease in cortisol and prolactin levels from the morning of surgery to right before anesthesia induction (GA) and no relationship with anxiety levels as measured by the STAI (Spielberger, et al., 1983). However, the results might have been influenced by the administration of sedative and anxiolytic premedication, which could have blunted the stress response. Moreover, the missing correlation between subjective and objective stress indicators could also be ascribed to the different measurement points, with self-reports filled in the day before surgery and hormone samples collected shortly before surgery. Contrary to Vögele (1992), the

authors (Gauter-Fleckenstein, et al., 2007) further reported an increase in HR before surgery and a decrease postoperatively and a similar trend for SBP.

The rather inconsistent findings concerning physiological indicators of stress responses in the perioperative period can be to a large extent attributed to differences in methodology and situational characteristics, such as the type of surgery or intervention, the anesthetic technique, the underlying disease, the physiological or biochemical parameters investigated, and the measurement points. Moreover, possible interactions of subjective parameters (e.g. anxiety or coping strategies) with objective parameters should be considered when interpreting results. Additionally, the impact of the surgical trauma itself, the potential impact of confounding variables such as medication, gender, and age, and the multiple determination of each physiological or biochemical parameter has to be taken into account.

1.6.3 Carotid Artery Stenosis

Atherosclerosis is a disease of the arteries due to the building up of fatty material on the walls of the arteries. These thickened and hardened substances are called plaque. The plaque deposits narrow the artery, make it less flexible, and consequently make blood flow more difficult (Society of Vascular Surgery, 2009a; U.S. Department of Health & Human Services, n.d.).

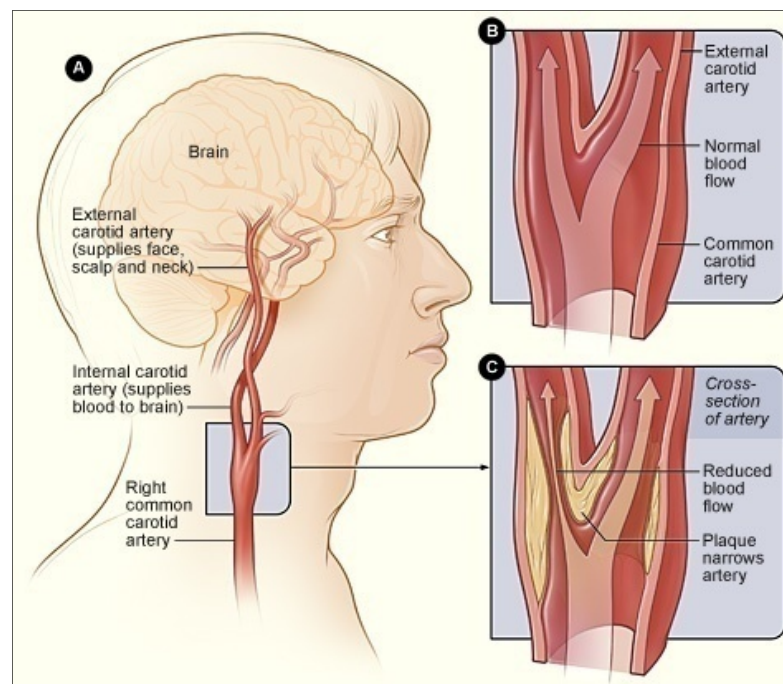


Figure 5. Atherosclerotic plaque in the carotid artery. *Note.* From U.S. Department of Health & Human Services (n.d.). Carotid Arteries. Retrieved October 3, 2009, from http://www.nhlbi.nih.gov/health/dci/Diseases/catd/catd_all.html.

One artery frequently affected by atherosclerosis is the carotid artery. The common carotid artery (CCA), starting at the arch of the aorta, divides into an internal carotid artery (ICA) that supplies the brain, and an external carotid artery (ECA) that supplies the face. The region where the common artery divides into the two branches and the origin of the carotid artery at the aorta are common sites for a buildup of plaque that subsequently narrows the artery and leads to a so called stenosis (see Figure 5). (U.S. Department of Health & Human Services, n.d.)

The degree of occlusion of the carotid artery is usually diagnosed by duplex ultrasound scan and if necessary by further imaging methods like global or selective angiography, magnetic resonance imaging (MRI), or computed tomography (CT). Symptomatic stenoses of about 50% and more are defined as high-grade stenoses and have a prevalence of about 7% in men and 5% in women aged over 65 years (Richter, et al., 2008).

Plaque is sometimes stable without causing any symptoms. There is, however, the constant danger that little particles, so called emboli, break off and move to the brain, where they can cause occlusions of arteries and consequently provoke strokes. These can be either temporary, for example in the form of transient ischemic attacks (TIAs), or permanent. Whereas asymptomatic carotid artery stenosis only leads to a small increase in the risk of strokes (about 2% risk in patients with a stenosis above 70%), symptomatic stenoses that have already caused TIAs, for instance, are accompanied by a great risk of strokes (up to 15% risk, dependent on the degree of occlusion and the latency since the last incidence). (Ringleb & Hacke, 2007) Strokes globally constitute an increasing major public health problem and an enormous financial burden. They can lead to permanent disabilities and are one of the leading causes of death. Strokes due to stenoses of the carotid artery constitute a substantial proportion (about 10 to 20 percent) of all strokes with ischemic origin (Richter, et al., 2008). Consequently, preventive measures make an important contribution to public health and cost-effective solutions are sought.

Symptomatic and also asymptomatic individuals diagnosed with high-grade stenosis of the carotid artery first of all benefit a lot from lifestyle changes (e.g. increasing physical activity, maintain a healthy weight) and control of risk factors (e.g. high blood-pressure, smoking, obesity). Furthermore, they are on the one hand treated with medication, such as anti-hypertensive drugs, antiplatelet drugs (e.g. aspirin), and statins, to reduce inflammation and stabilize the plaque. On the other hand, there are two possible interventions to permanently remove plaque, restore revascularization, and thus substantially reduce the risk of potentially lethal cerebrovascular accidents

(CVAs) as a consequence of thrombo-embolism: surgical methods, carotid endarterectomy (CEA) or eversion carotid endarterectomy (ECEA), and a minimally invasive intervention, named carotid artery stenting (CAS) or carotid percutaneous transluminal angioplasty (PTA) and stenting. (Society of Vascular Surgery, 2009a; U.S. Department of Health & Human Services, n.d.)

1.6.3.1 Carotid endarterectomy (CEA).

CEA is a surgical procedure in which the plaque is directly removed from the artery (e.g. Sigauco-Roussel, et al., 2002).

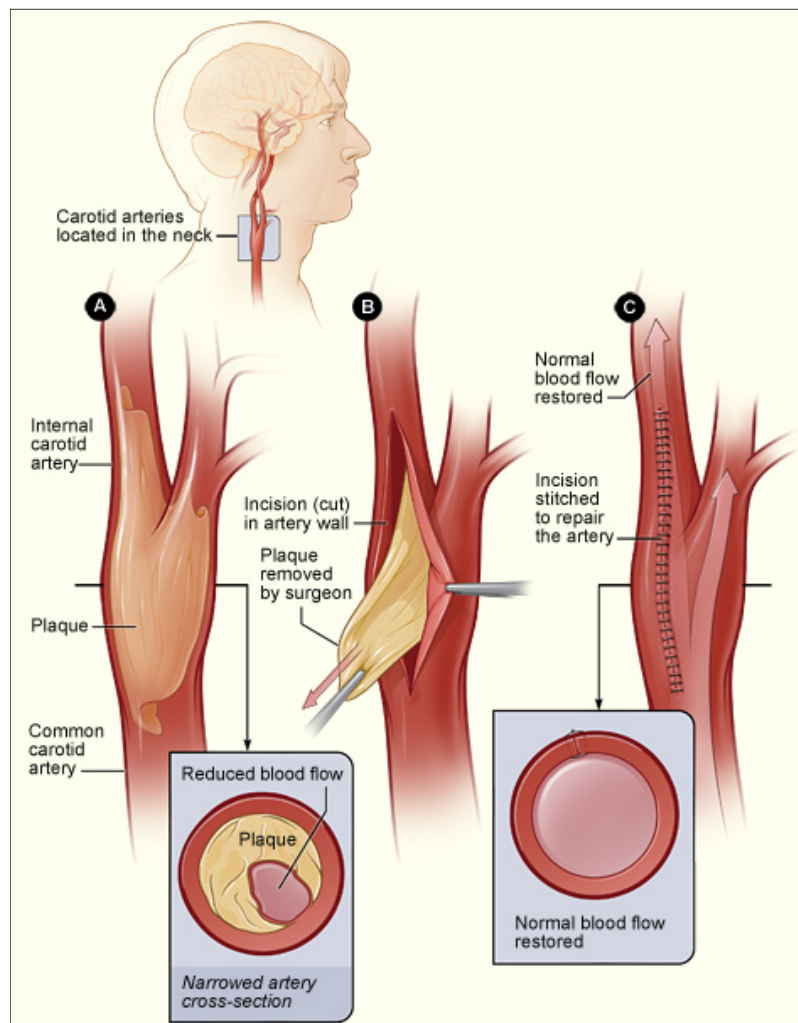


Figure 6. Procedure of carotid endarterectomy. *Note.* From U.S. Department of Health & Human Services (n.d.). Carotid Endarterectomy. Retrieved October 3, 2009, from http://www.nhlbi.nih.gov/health/dci/Diseases/catd/catd_all.html.

For this purpose, the internal, common, and external carotid arteries are clamped, so that the lumen (inner part) of the internal carotid artery can be opened lengthwise (longitudinal arteriotomy) and the plaque deposits can be taken out

(endarterectomy). In order to prevent harm because of the temporary occlusion of the blood flow to the brain, some surgeons lay a so called intraluminal shunt to ensure blood supply during the procedure. Afterwards, the arteriotomy is closed with a patch, the shunt is removed, the arteries are declamped, and the artery and the overlying layers are closed again (see Figure 6). (For an overview see e.g. Society of Vascular Surgery, 2009b)

In addition to this conventional form of carotid endarterectomy, there is an alternative form called eversion carotid endarterectomy (ECEA). This procedure involves the complete transection of the ICA at its origin, removal of the atheroma while the adventitia of the ICA is everted, and reimplantation of the ICA on the common carotid artery. This alternative method is especially useful for patients with severe carotid elongation or kinking. Randomized controlled trials comparing CEA and ECEA indicated that this alternative is as safe and effective as the conventional surgical technique with no differences regarding morbidity and mortality. Thus, the choice of technique so far depends primarily on the experience and familiarity of the individual surgeon and on characteristics of the patient and his or her disease.² (Cao, De Rango, Cieri, & Giordano, 2004; Cao, De Rango, & Zannetti, 2002).

Nowadays, CEA can be either performed under general (GA) or local (LA) anesthesia. The latter option has the advantage that the patient's neurological status can be monitored directly throughout the procedure, and LA seems to be associated with lower morbidity and mortality rates (Assadian, Senekowitsch, & Hagmüller, 2006; Marrocco-Trischitta, et al., 2004; Quigley, et al., 2000). However, a recent multicentre, randomized controlled trial (GALA) comparing carotid endarterectomy performed under GA and LA, found comparable outcomes (relative risks of stroke, cardiac events, and death following CEA) in both groups (Lewis, et al., 2008). They thus suggested to decide individually on the best anesthetic technique for each patient. Possible perioperative complications associated with CEA are for example stroke, myocardial infarction, hypotension, hypertension, wound hematoma, hyperperfusion syndrome, and cranial nerve injuries (Biller, et al., 1998).

² From now on the term CEA will be used to refer to both CEA and ECEA and no further distinction will be drawn between these two surgical techniques.

1.6.3.2 Carotid artery stenting (CAS).

CAS, also known as carotid PTA and stenting, is an alternative prophylactic intervention for stroke prevention (see Figure 7).

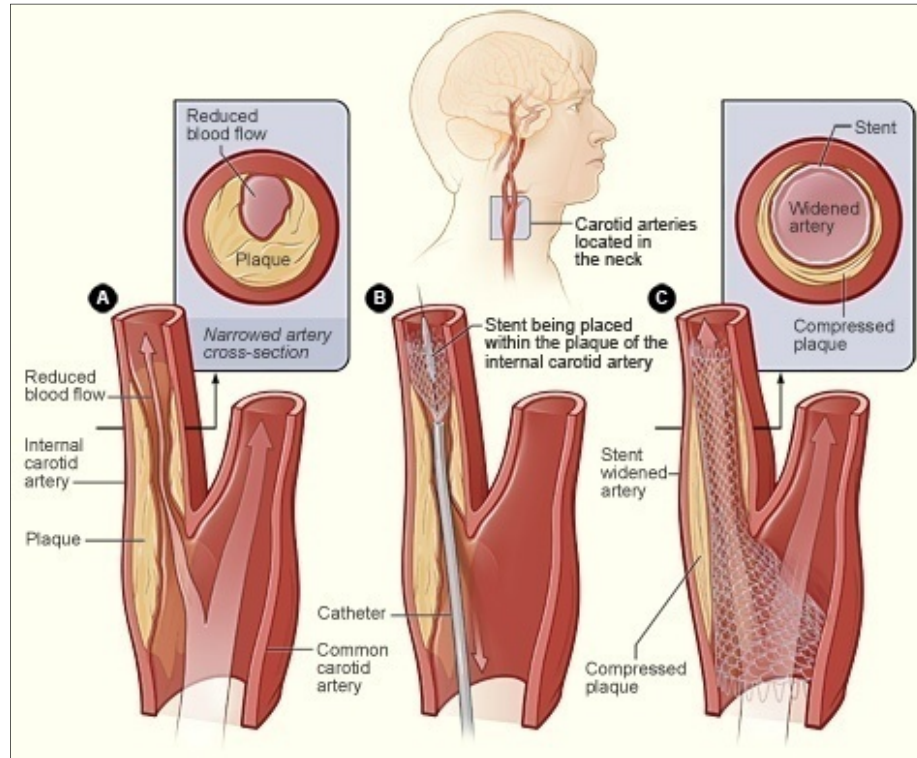


Figure 7. Procedure of carotid artery stenting. *Note.* From U.S. Department of Health & Human Services (n.d.). Carotid Artery Stenting. Retrieved October 3, 2009, from http://www.nhlbi.nih.gov/health/dci/Diseases/catd/catd_all.html.

It is, in contrast to CEA, a non-surgical procedure for unblocking the occlusion of the carotid artery lumen (e.g. Ederle, et al., 2008; van der Vaart, et al., 2008). It starts with a puncture into the femoral artery at the groin (after administration of a local anesthetic) and access through a short sheath. A guidewire is then passed through the aorta and into the arch, while an angiogram is performed simultaneously to monitor the whole procedure. After cannulation of the common carotid artery and placement of a long access sheath, the guidewire is passed through the narrowed region. An embolic protection device, a sort of filter, can be placed above the stenosed area to reduce the risk of microembolisms. If necessary, an angioplasty is then performed, referring to a minimally invasive or percutaneous method of mechanically widening a narrowed blood vessel. This is achieved by introducing a folded balloon into the obstructed region, where it is then distended by the use of water pressure. After this predilatation, a stent (self-expansive or balloon-expandable) is placed in the stenosed area and an angioplasty is performed after stent deployment if required (postdilatation). The stent –

a tiny, mesh or lattice-like coil, which is often made of stainless steel – remains permanently in the artery to support the opening. Eventually, the protection device, the guidewires, and the sheath are removed and the puncture site is taken care of. (For an overview see e.g. Society of Vascular Surgery, 2009c)

1.6.3.3 CEA versus CAS.

Some characteristics predispose a patient for one of the two types of intervention (Levy, et al., 2008). CAS is especially indicated for older (age over 75 years) and so called high risk patients who suffer from one or more anatomical or comorbid risk factors that increase the risk for adverse events during CEA (e.g. contralateral carotid occlusion, previous CEA recurrent stenosis, previous neck radiation or surgery, obese patients with a short neck, congestive heart failure, recent myocardial infarction, unstable angina). Contrariwise, there are several patient characteristics that favor a decision for the surgical intervention (e.g. patients with total occlusion of the target vessel, patients in whom femoral or brachial arterial access is not possible, patients with perforated vessels, heavily calcified plaques, kinked carotid artery, severe elongation of the carotid artery, or filiform stenosis) (Levy, et al., 2008; van der Vaart, et al., 2008).

CEA is an effective treatment of extracranial carotid artery stenosis that is superior to best medical treatment (BMT) for stroke prevention in asymptomatic as well as symptomatic patients, as shown by several large randomized controlled trials (for a review see Levy, et al., 2008; van der Vaart, et al., 2008). It has been regarded as the method of choice or the gold standard for decades and has only recently been challenged by the rapid development of minimally invasive, endovascular techniques that show some advantages, such as shorter duration of the procedure, less invasiveness, and shorter hospital stays compared to CEA (Ederle, et al., 2008). However, the heated debate whether CAS is as effective as CEA in stroke prevention continues to this date. The results of an increasing number of trials comparing both treatments, for example CAVATAS, Wallstent Trial, CaRESS, EVA-3S, SPACE, and SAPPHIRE (for a review see e.g. Cao, et al., 2006; Levy, et al., 2008; Ringleb & Hacke, 2007; Yadav, et al., 2004), still haven't lead to a consensus, partly because of insufficient numbers of patients and test power, varying technical expertise of interventionalists, differing procedures (e.g. angioplasty with or without stents; stenting with or without cerebral protection devices), inability to control important confounding variables (e.g. anatomical characteristics), and conflicting results depending on the selected inclusion criteria and clinical outcomes (Ederle, et al., 2008; Levy, et al., 2008; Ringleb & Hacke, 2007; van der Vaart, et al., 2008). Until presently conducted large

randomized controlled trials such as ICSS, CREST, and ACT I (for a summary see Levy, et al., 2008) shed more light on the question of effectivity, CEA remains the gold standard for treating especially symptomatic carotid artery stenosis (Ringleb & Hacke, 2007). In their review of optimal treatment of carotid artery disease Levy et al. (2008) concluded that, as the two interventions preliminarily seem to be comparably effective, the best outcome for the patient will be achieved when the decision for one of the two treatments is based on individual patient characteristics and personalized risk estimation. Generally, the training and experience of the physician play an important role in terms of outcome, and continuous technological progress contributes to increasing procedural safety (Cao, et al., 2006; Levy, et al., 2008; Richter, et al., 2008; van der Vaart, et al., 2008).

1.6.3.4 Psychosocial factors in the context of CEA and CAS.

Whereas the number of studies evaluating and comparing the effectiveness of the treatments of extracranial carotid stenosis with regard to clinical outcomes is constantly growing, the question how the individual patient experiences either intervention still remains largely unanswered. Although some medical treatments, for instance coronary artery bypass graft surgery (CABG), have inspired lots of research on associated psychological aspects, the findings concerning psychosocial factors in the context of CEA and CAS are still scarce. Psychological variables, though, such as perioperative anxiety or depression, satisfaction with the surgery, aversion to surgery, intraoperative experiences, post-operative well-being and quality of life, and the role of personal vulnerabilities or resources, can make a substantial contribution to the evaluation or improvement of treatments and perioperative care.

Bosworth, Stechuchak, Grambow, and Oddone (2004) addressed the risk evaluation and decision-making process of patients eligible for CEA and shed light at factors explaining patient aversion to surgery. Among a number of clinical, sociodemographic, and personal factors investigated, they demonstrated that patients who were older, African American, had no previous experiences with surgery, reported less trust in their physician, less change locus of control, and less social support showed higher levels of aversion to surgery.

Mlekusch et al. (2006) were interested in the concept of vascular depression that links carotid atherosclerosis to depressive symptoms and reported that patients with high-grade internal carotid artery stenosis showed a significantly higher rate of clinically relevant depressive symptoms, as measured by the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), compared to a control group of patients

diagnosed with peripheral artery disease. Moreover, they observed a significant decrease in depressive symptoms, when comparing the preoperative scores to those measured four weeks after CAS, whereas no reduction was found for the control group undergoing lower-limb PTA. These findings indicate that severe carotid artery stenosis might be associated with depression, and revascularization by a minimally invasive technique might improve the depressive symptoms.

Regarding quality of life, Abelha, Quevedo, and Barros (2008) demonstrated that patients perceived their quality of life six months after CEA as better than before surgery, although they postoperatively suffered from increased dependency in instrumental and personal activities of daily life.

Concerning patient satisfaction with CEA, results from a prospective, randomized (McCarthy, et al., 2004) and a non-randomized study (Quigley, et al., 2000) indicated that patients were generally satisfied with the surgical procedure and regarded it as a rather positive experience, independent of the type of anesthesia used. Patients who received LA, however, perceived their postoperative recovery (a score comprising the perception of postoperative nausea, distress, pain, length of stay, and return to normal activities) as significantly better than those who received GA (McCarthy, et al., 2004). Moreover, the data stressed the importance and beneficial effects of a person who attends explicitly to the patient during the surgical procedure under LA (McCarthy, et al., 2004).

In line with these findings, Barnason and Rasmussen (2002) also reported high scores in a global rating of satisfaction with CEA one month postoperatively.

Whereas the findings on psychosocial factors in the context of CEA and CAS are very scarce, a lot of research has been dedicated to neurocognitive changes after carotid revascularization. Due to the many confounding factors, up to now no consensus has been reached regarding the interventions' impact on cognition. See for example De Rango et al. (2008), Berman, Pietrzak, and Mayes (2007), and Sciarroni, Gremigni, and Pedrini (2007) for reviews of the impact of CEA and CAS on cognitive performance.

Altogether, the few findings regarding psychosocial factors in the context of CEA indicated that the majority of patients were satisfied with the surgical procedure independent of the type of anesthesia administered (Barnason & Rasmussen, 2002; McCarthy, et al., 2004; Quigley, et al., 2000), and reported improved quality of life postoperatively (Abelha, et al., 2008). With respect to CAS, evidence suggested that patients suffering from a severe stenosis of the carotid artery showed high levels of depressive symptoms, possibly indicative of a so called vascular depression, that

significantly decreased after the minimally invasive intervention (Mlekusch, et al., 2006). To the knowledge of the author, so far no studies have been published that shed light on the patients' subjective perceptions and experienced stress associated with CEA and CAS. Consequently, the present study aims at filling this gap and at concentrating on the perspective of the patients.

1.6.3.5 *Autonomic activity during CEA and CAS.*

Besides the possible psychological stress a patient being operated on experiences, each surgery leads to physiological alterations and hence some sort of surgical stress. This biological stress reaction, comprising hemodynamic, metabolic, inflammatory, and immunologic changes, is mediated by the HPA-axis through the activation of the autonomic nervous system (Marrocco-Trischitta, et al., 2004). The degree of surgical stress might be related to the type and magnitude of the operation, the duration of the procedure, and the anesthetic technique used. As an intraoperative stress response might have detrimental effects on the patient's health, postoperative recovery, and clinical outcomes, the perioperative monitoring of physiological parameters can provide valuable insight into the stress caused by a procedure. For this purpose, analysis of HRV is particularly suitable as it allows a non-invasive, continuous recording throughout the perioperative period. Regarding CEA and CAS, it is for example of relevance to know whether the minimally invasive technique (CAS) really causes, as supposed, less stress than the surgical procedure (CEA), and what type of anesthesia (LA versus GA) used during CEA goes along with less stress for the patient (Marrocco-Trischitta, et al., 2004).

In the special cases of CEA and CAS the interpretation of alterations in HRV parameters as indicators for stress responses is complicated by the fact that both methods have an impact on the *baroreflex* through intraoperative stimulation of the carotid baroreceptors. These stretch receptors are located in the carotid sinus and play an important regulatory role in the short-term control of BP and HR through changes in vagal and sympathetic neural activity (Yakhou, et al., 2006). The baroreceptor stimulation is believed to be responsible for the occurrence of hemodynamic instability (hypertension, hypotension, or bradycardia) in the perioperative course of the procedures (Landesberg, Adam, Berlatzky, & Akselrod, 1998; Mendelsohn, et al., 1998; Sigauco-Roussel, et al., 2002; Yakhou, et al., 2006). The influence of the interventions on carotid sinus baroreceptor functions and the associated effects are, however, not completely predictable and conflicting results have been observed and published so far.

Hirschl, Kundi, and Blazek (1996) investigated the impact of preoperative-to-postoperative changes in baroreceptor sensitivity after CEA with respect to blood pressure variability, therapeutic interventions, and vascular events during a five-year follow-up period. They demonstrated that an improvement of receptor sensitivity after carotid surgery is related to a long-lasting reduction of blood pressure levels and variability. In detail, patients without a postoperative increase in sensitivity showed significantly higher systolic BP values, higher variability ranges of systolic and diastolic BP, higher ventricular thickness, had more major vascular events, and needed more therapeutic interventions regarding BP shortly after surgery until the end of follow-up compared with those patients showing a postoperative increase. The authors thus concluded that baroreceptor function may serve as an indirect indicator for the later postoperative course.

Concerning CEA performed under LA, HR and BP have been shown to decline right after carotid artery declamping and then stabilize at a lower level (Landesberg, et al., 1998). The authors suggested that the surgical removal of the stiff plaque causes a sudden dilatation and increased pulsatility of the carotid artery. This in turn leads to a step increase in baroreceptor stimulation and to the associated changes in BP and HR through fast adaptation mechanisms as well as slow-reacting components in the baroreflex loop.

Sigaudou-Roussel et al. (2002), on the contrary, investigated the baroreflex in patients receiving CEA under GA and reported a temporary deterioration in baroreflex response after plaque removal, characterized by an immediate increase in BP, and a postoperatively persisting reduction in overall baroreflex gain (ratio between changes in RR interval and in SAP at a certain frequency). Regarding autonomic alterations after CEA, Sigaudou-Roussel et al. (2002) reported a significant reduction of TP of HRV six weeks after the surgery compared to preoperative values. The authors further supposed a sympathetic predominance prior to until two days after CEA, as indicated by higher LF values in contrast to HF values, both expressed in normalized units (nu).

With regard to CAS, the stretching of the sinus baroreceptors might lead to a baroreflex dysfunction and consequently hemodynamic instability.

Yakhou et al. (2006) compared the cardiac baroreflex and autonomic cardiovascular control after CAS and CEA and found an increase in spontaneous cardiac baroreflex sensitivity (SBRs) within the first 24 hours after CAS, but no change after CEA. This index was twofold calculated, using a sequence method (the ratio of change in the RR interval to change in SAP) and a cross-spectral analysis (LF and HF gains), and did not differ between the two groups preoperatively. Moreover, the

patients of the CAS group postoperatively exhibited decreased SAP and DAP and a trend towards lower heart rate, whereas no significant changes emerged in the CEA group. Regarding HRV, the CAS patients postoperatively showed an increase in the HF (nu) component and a decrease of the LF/HF ratio component, as well as a decrease of the LF (nu) component of systolic arterial pressure variability, whereas again no change was observed in CEA patients in any spectral analysis. However, the results of this study have to be treated cautiously as the sample size was very small (ten patients per group) and the patients were not randomly assigned to the treatments.

Demirci et al. (2006), too, addressed possible differences in autonomic cardiovascular control as consequences of CAS or CEA by analyzing parameters of HRV and BP on the day before and on the first three days following surgery. They observed completely different alterations of autonomic balance when comparing the two groups, in terms of a postoperative shift towards sympathetic predominance after CEA [increased LF (nu), decreased HF (nu), increased LF/HF ratio] and, in contrast, a shift towards parasympathetic predominance after CAS [decreased LF (nu), increased HF (nu), decreased LF/HF ratio]. The authors presumed that the shift towards the sympathetic side in the power spectrum after CEA indicates reduced carotid baroreceptor sensitivity, possibly resulting from changes in the mechanical properties of the vessel wall or damage to baroreceptors or the carotid sinus nerve during surgery. Concerning the shift towards the parasympathetic side in CAS patients, they speculated that the compression of plaque into the vessel wall could have increased tension over the baroreceptors. This stimulation might have led to parasympathetic predominance, or, alternatively, the stent could have possibly exerted a continuous force to the vessel wall and thereby increased baroreceptor activity. However, because of biological restorative and compensatory mechanisms these effects were assumed to be temporary. It is worth mentioning that the study's results are based on a small sample size and that the patients were not randomly assigned to the treatments. As CEA was performed under GA and more patients suffering from coronary heart disease were present in the CAS group, the effects and group differences might have been underestimated.

Marrocco-Trischitta et al. (2004) aimed at capturing the physiological stress response by assessing HR, BP, cortisol, ACTH, prolactin, and C-reactive protein (CRP) at several points in time before, during, and after CEA and further compared the impact of the anesthetic technique (LA versus GA) in a non-randomized, prospective study with more than 100 patients. The cortisol and ACTH levels increased sharply from the preoperative baseline to an intraoperative pre-clamping time point and further to post-clamping under both anesthetic techniques, though somewhat more pronounced under

LA. Under GA, however, the values continued to increase until the early postoperative period, while the levels under LA postoperatively quickly returned to baseline. By the morning of the first postoperative day the stress response as indicated by cortisol and ACTH levels was entirely abolished in both groups. The prolactin levels in both groups followed exactly the same pattern as the cortisol and ACTH levels with a significant intraoperative increase and a fast postoperative decrease to baseline values within one day. CRP levels, however, significantly increased equally in both groups and started to decrease not until the third postoperative day, suggesting a systemic inflammation and stress due to surgery. With regard to hemodynamic variability (BP and HR variability), there were similarly no differences between GA and LA at any time. These findings thus indicate that the surgical stress responses are somewhat blunted under GA but rather similar under both anesthetic techniques, and hormonal levels return to baseline within 24 hours.

Summing up, the impact of baroreceptor activity has to be taken into account when interpreting alterations in parameters of autonomic activity during and after CEA and CAS, as both procedures might have an influence on their function (Landesberg, et al., 1998; Mendelsohn, et al., 1998; Sigaudou-Roussel, et al., 2002; Yakhou, et al., 2006). The findings concerning this matter are, however, conflicting and to some extent still speculative. Parameters of HRV nevertheless provide valuable information concerning the stress and physiological effects of the procedures. So far, evidence suggests that CEA leads to a shift towards sympathetic predominance and a reduction of TP of HRV (Demirci, et al., 2006; Sigaudou-Roussel, et al., 2002), whereas CAS is accompanied by a shift towards parasympathetic predominance in the early postoperative period (Demirci, et al., 2006; Yakhou, et al., 2006). With respect to the impact of the anesthetic technique, research indicates that although the intraoperative stress response is somewhat alleviated under GA, there are practically no differences observable in any physiological stress indicators between GA and LA twenty-four hours postoperatively (Marrocco-Trischitta, et al., 2004).

1.7 Research Questions

The present investigation aims at a comprehensive portrayal of the subjective and objective stress responses of patients with carotid artery stenosis undergoing either CEA or CAS (both under LA) for revascularization. The study is insofar unique as it investigates physiological parameters of stress in the pre-, intra-, and postoperative period and thus provides insight into changes of parameter values of HRV throughout the perioperative period. Both techniques are compared with regard to alterations in HRV and the patients' subjective experience of the intraoperative situation. Against the

background of a psychophysiological understanding of stress, the recording of HRV is supplemented by the measurement of pre- and postoperative state anxiety as the most prominent emotional reaction in the stress process in the medical context. In line with the cognitive-relational stress theory as put forward by R. Lazarus, data on important mediators and moderators of the stress process, such as trait anxiety, coping, and social support are additionally collected. Furthermore, associations between the psychosocial variables themselves and between physiological indices of stress (HRV parameters) are investigated in this field study.

1.7.1 *Heart Rate Variability*

- Based on an understanding of stress as a disruption of homeostasis or allostasis (see section 1.3), the stress response due to the stressor surgery is assumed to result in a temporary imbalance of the autonomic nervous system characterized by an increase of sympathetic activity and withdrawal of parasympathetic activity, mediated by the sympathetic-adrenomedullary system and the hypothalamic-pituitary-adrenocortical axis (see section 1.3.1 and 1.6.2). The analysis of HRV allows a non-invasive evaluation of these physiological stress reactions (see section 1.3.2). Research within the paradigm of cardiovascular reactivity, ranging from laboratory studies to investigations of real-life stress, and within the framework of the polyvagal theory (Porges, 1995a, 1995b, 2001, 2007) suggested that stress responses are marked by a pattern of reduced HRV, vagal withdrawal or depressed vagal tone, and possibly at the same time increased sympathetic activity (see section 1.3.2.6 and 1.5) (Dishman, et al., 2000; Lucini, et al., 2005; Lucini, et al., 2002; Moses, et al., 2007; Sloan, et al., 1994). When measuring stress responses in the context of surgery, the physical impact of the procedure as well as intraoperative medication have to be taken into account. With regard to CEA and CAS, especially the influence on the baroreceptor region has to be considered (see section 1.6.3.5) (Landesberg, et al., 1998; Mendelsohn, et al., 1998; Sigaudo-Roussel, et al., 2002; Yakhou, et al., 2006). Whereas both patient groups should not differ in the HRV parameter values in the preoperative period, the stress and the differing physical impact of both techniques are expected to lead to distinct alterations in HRV parameters in the intra- and postoperative periods. The intraoperative situation is expected to be characterized by an increase in sympathetic and decrease in parasympathetic activity relative to the preoperative situation. Based on the findings of Demirci et al. (2006), Yakhou et al. (2006), and Sigaudo-Roussel et al. (2002) it is

hypothesized that parameter values of HRV change in the course of time and interact with the type of treatment. More precisely, a shift towards parasympathetic predominance in the postoperative period after CAS and towards sympathetic predominance after CEA is expected (see section 1.6.3.5).

- Research provides evidence for associations between HRV and psychological variables and thus establishes HRV as a sensitive indicator for stress and negative affect, though the findings are sometimes inconsistent (see section 1.5). It is expected that HRV correlates negatively with state and trait anxiety. In detail, state and trait anxiety are assumed to be associated with reduced variability and a reduced vagal component of HRV. (Dishman, et al., 2000; Friedman, 2007; Friedman & Thayer, 1998; Jönsson, 2007; Lucini, et al., 2005; Lucini, et al., 2002; Moses, et al., 2007; Sloan, et al., 1994; Watkins, et al., 1998)

1.7.2 *Psychological Variables*

Besides the specific alterations of HRV parameters caused by CEA and CAS, the present study focuses on the patients' perceived stress associated with both medical interventions. To get a more precise picture of the patients in the perioperative period, state anxiety and trait anxiety, social support, and coping strategies as important mediators or moderators of stress are additionally assessed. Moreover, their assessment allows for a comparison of both groups with regard to these psychological variables, in order to control their influence on the subjective stress associated with both medical interventions and changes in HRV parameters.

- To the author's knowledge, so far no studies have compared CEA and CAS – both performed under LA – with regard to the patients' subjective experience of the intraoperative situation, although both techniques greatly differ from each other (see section 1.6.3). Research on CEA suggests that patients are generally satisfied with surgery and consider it as a rather positive experience, independent of the type of anesthesia used (McCarthy, et al., 2004; Quigley, et al., 2000). It is, however, hypothesized that patients undergoing CEA regard the medical intervention as more stressful than those undergoing CAS because the surgical intervention takes longer and is more invasive, amongst other things. The duration of the procedure and gender will also be examined as possibly confounding factors.
- Evidence suggests that state anxiety levels are often very high in patients awaiting surgery. These high levels usually quickly return to normal values after

surgery, dependent on personal characteristics such as trait anxiety and situational characteristics such as the type of surgery and disease (see section 1.6.1.1). As patients undergoing CEA or CAS normally don't suffer from complications and rather quickly recover, they should feel a sudden relief after surgery when the threatening event is over. (de Groot, et al., 1996; Duits, et al., 1998; Gauter-Fleckenstein, et al., 2007; Karanci & Dirik, 2003; Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005; Krohne & Slangen, 2005; Vögele, 1992) Thus, it is expected that state anxiety levels are significantly higher in the preoperative period than in the postoperative period. Moreover, gender differences in state anxiety will be examined.

- Habitually anxious persons might explicitly focus on threatening aspects of the intraoperative situation and thus experience higher degrees of stress. Furthermore, patients who have had a stressful experience might still feel uneasy and anxious shortly after the procedure. The relation between the perceived stress associated with the medical interventions and trait and postoperative state anxiety will be illustrated for the present sample.
- Persons who are characterized by habitually high levels of trait anxiety are more likely to show high levels of state anxiety in stressful situations. Research has consistently shown significant correlations of about medium size between indices of trait and of situation-specific anxiety in the hospital setting (Kain, et al., 2000; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005). The relation between trait anxiety and pre- and postoperative state anxiety will be illustrated for the present sample.
- Social support can buffer stress and constitutes a resource especially when faced with stressful or threatening situations. In the medical context, not only social support provided by family and friends, but also support from the hospital staff plays an important role. This is especially true for those who are socially isolated. Providing information and advice concerning the perioperative period and providing emotional support can be both very helpful and reduce distress (see section 1.6.1.3). The relations between social support and anxiety in the pre- and postoperative situation will be illustrated for the present sample. Differences according to gender will also be examined. (Krohne & Slangen, 2005)
- As patients awaiting surgery have to deal with restricted behavioral control and instrumental influence, they profit more from turning to cognitive or emotion-focused coping instead of problem-focused coping, in order to influence the

appraisal of the situation and reduce negative emotions and stress. Research suggests that avoidant coping strategies and recourse to personal resources have an anxiety-reducing effect, whereas vigilant coping, rumination, and the turn to religion are positively associated with anxiety when awaiting surgery (see section 1.6.1.2) (Kain, et al., 2000; Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005). The relations between different coping strategies and preoperative anxiety will be illustrated for the present sample. Differences in the use of coping strategies according to gender will also be examined.

2 Method

2.1 *Study Design*

The study was designed as a prospective, quasi-experimental field study with two treatment groups (group 1: CEA; group 2: CAS) and repeated measurements.

The general linear model for repeated measures (ANOVA) was applied for analyzing differences between both treatment groups (between-factor) in parameters of HRV (within-factor) at several points in time (repeated-factor). Associations between psychological variables and between subjective and objective stress indicators were assessed by correlation analysis.

2.2 *Participants*

The study was conducted in cooperation with the Hanusch Hospital in Vienna, Austria. All persons who were diagnosed with a high-grade stenosis of the carotid artery and who were scheduled for either carotid endarterectomy (CEA) or carotid artery stenting (CAS) were eligible for the study. The sample comprised patients who presented within the period of September 2008 until the end of April 2009 in the Hanusch hospital with the diagnosis of a carotid artery stenosis and who consented to participation. Only men and women of age and competent to personally sign informed consent were included in the study. Those patients suffering from another life-threatening disease at the same time (e.g. cancer) were excluded from participation.

The local Ethics Committee (Medical University of Vienna) approved the study protocol and written informed consent was obtained from all patients (see APPENDIX C: PATIENT INFORMATION for the patient information leaflet). Patients could either agree to the whole protocol or, alternatively, only fill in questionnaires without having their HR recorded.

Patients were assigned to either of the two treatments based on personal (e.g. age) or medical characteristics (e.g. comorbid risk factors), as well as on patients' and physicians' preference (see also section 1.6.3). Thus, patients were not randomly assigned to the treatments, but the assignment was representative for clinical practice. The lacking randomization is on the one hand disadvantageous concerning internal validity, but on the other hand advantageous concerning the study's ecological validity.

Altogether 52 patients (CEA: $n = 28$; CAS: $n = 24$) were investigated during the study period. See Figure 11 for the sample sizes per group and per analysis and section 3.1 for patient characteristics and the comparison of patient data between both treatment groups.

2.3 Operationalization and Instruments

2.3.1 Cardiovascular Recording

A continuous ECG was recorded with a Holter monitor (medilog® AR12, EVO Scientific Biosignal Recorder by Schiller AG), using three disposable ECG chest electrodes (3M™ Red Dot™ Monitoring Electrodes, Micropore plaster, solid gel, Ag/AgCl). One active electrode was placed under the right clavicle, one at the left costal arch, and the reference electrode was placed in the middle of the sternum (see Figure 8).

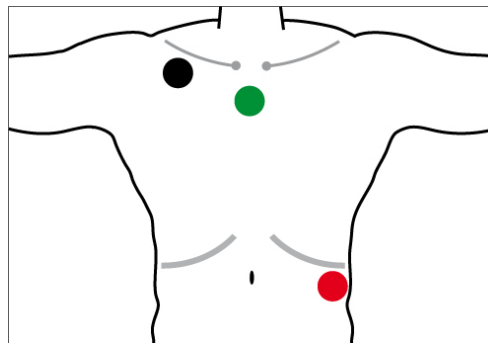


Figure 8. Electrode application.

See section 1.3.2 for general information on HRV and section 2.6.1 for details on the data management and analysis.

2.3.2 Psychological Questionnaire Assessment

- *State and trait anxiety* (variables: state anxiety pre, state anxiety post, trait anxiety): The patients' state as well as trait anxiety were assessed by the German version (Laux, Glanzmann, Schaffner, & Spielberger, 1981) of the

State-Trait Anxiety Inventory (STAI) (Spielberger, et al., 1983). The X1 scale (state anxiety) asks for a person's momentary feelings, whereas the X2 scale (trait anxiety) asks for general feelings. Both subscales consist of 20 items each that have to be answered on a four-point rating scale (X1: 1 = *not at all*, 4 = *very much* so; X2: 1 = almost never, 4 = almost always), with sum scores ranging from 20 to 80 (higher scores indicate greater self-rated anxiety). The STAI is a popular and frequently administered questionnaire with satisfactory reliability and validity. Although Krohne (2000; 2005) criticized its use in the medical setting due to lacking specificity of the questions, it has the advantage of being a quick and economic questionnaire that has also been frequently used in research on stress responses in the perioperative period (e.g. de Groot, et al., 1996; Duits, et al., 1998; Gauter-Fleckenstein, et al., 2007; Kain, et al., 2000; Karanci & Dirik, 2003; Pearson, et al., 2005) and thus enables the comparison of results (see also section 1.6.1). With regard to the present sample, Cronbach's α was .93 for trait anxiety (20 items; scale: $M = 37.51$, $SD = 10.67$, $n = 45$ cases), .94 for preoperative state anxiety (20 items; scale: $M = 40.39$, $SD = 11.53$, $n = 41$ cases), and .91 for postoperative state anxiety (20 items; scale: $M = 33.22$, $SD = 8.44$, $n = 46$ cases).

- *Perceived Medical Intervention Stress*: The patients' subjective experience of CEA and CAS was assessed by a questionnaire that was self-developed based on observations of the intraoperative situation and discussions with patients and doctors. Patients had to indicate their degree of agreement with 23 statements that focus on the specific characteristics and stressful elements of the two treatments on a 4-point rating scale (1 = *not at all*; 4 = *very much*). The average score ranges from 1 to 4 with higher scores indicating greater self-rated stress associated with the procedure. With regard to the present sample, Cronbach's α was .81. See APPENDIX A: QUESTIONNAIRES: 3 for a list of all items and means and standard deviations for the scale as well as each item.
- *Social support (EISOP-modified)*³ (variables: overall support, support from social network, support from hospital staff): The patients' perceived available support was assessed by a shortened and modified version (EISOP-modified)

³ Prof. Dr. Heinz Walter Krohne (personal communication, January 16, 2008, and February 8, 2009) gave his written consent to use the questionnaire EISOP in the present study and to print the items in this thesis.

of the German Emotional and Informational Support Scales – Operations (EISOP) (Krohne, et al., 2003; Krohne & Slangen, 2005). In contrast to general social support inventories, it specifically focuses on the preoperative situation and distinguishes between the type (informational and emotional) and source of support (provided by the social network and provided by the hospital staff) (see also section 1.4.3 and 1.6.1.3). Patients had to indicate their degree of agreement with five statements referring to social support in the current situation on a five-point rating scale ranging from 1 (*not at all*) to 5 (*very much*). An average score was calculated for the patients' overall perceived social support (5 items; $\alpha = .81$), and separately for support provided by the hospital staff (2 items; $\alpha = .71$) and support provided by the social network (3 items; $\alpha = .82$), with all scores ranging from 1 to 5 (higher scores indicate more support). See APPENDIX A: QUESTIONNAIRES: 1 for a list of all items, means and standard deviations for each scale as well as each item per scale, and the internal structure of the questionnaire.

- *Coping (COSS)*⁴: Coping in the preoperative period was assessed by a revised version of the German questionnaire Coping with Surgical Stress, COSS (Krohne, de-Bruin, et al., 2000; Krohne, et al., 2005). The inventory focuses on specific coping strategies of patients awaiting surgery (see also section 1.4.2 and 1.6.1.2). Patients had to express their degree of agreement with 51 statements referring to their coping behavior in the current situation on a 4-point rating scale (1 = *not at all*; 4 = *very much*), with higher values indicating greater agreement. Based on theoretical considerations and optimization of Cronbach's alpha for each scale, eight scales representing different coping strategies in the preoperative situation were then computed: information seeking (9 items; $\alpha = .89$), rumination (9 items; $\alpha = .84$), optimism and trust (10 items; $\alpha = .76$), recourse to personal resources (6 items; $\alpha = .75$), downward comparison (4 items; $\alpha = .89$), distraction (5 items; $\alpha = .64$), belief (2 items; $\alpha = .92$), and seeking social support (5 items; $\alpha = .78$). One item (COSS_16) was excluded from the analyses due to only minor correlations with all other items. See APPENDIX A: QUESTIONNAIRES: 2 for a list of all items and means and

⁴ Prof. Dr. Heinz Walter Krohne (personal communication, January 16, 2008, and February 8, 2009) gave his written consent to use the questionnaire COSS in the present study and to print the items in this thesis.

standard deviations for each scale as well as each item per scale, and a correlation matrix of all COSS scales.

- *General Questionnaire: assessment of potentially confounding variables* (see APPENDIX A: QUESTIONNAIRES: 4 for the whole general questionnaire):
 - o *Patient characteristics*: Patients had to answer several questions regarding socio-demographic (e.g. age and education level) and other possibly confounding variables (e.g. current medication, smoking, physical activity, and prior surgical episodes) on different response formats.
 - o *Health status* (variables: general health status, health status pre, health status post): Patients were asked to indicate their general as well as their current health status before and after surgery on a rating scale ranging from 1 (*perfect*) to 5 (*bad*), with lower values reflecting better self-rated health.
 - o *Subjective well-being* (variables: general well-being, well-being pre, well-being post): Patients were asked to rate their general as well as their current well-being before and after surgery on a rating scale ranging from 1 (*perfect*) to 5 (*bad*), with lower values reflecting better self-rated well-being.
- *Intraoperative data*: Intraoperative information relevant for the study (e.g. length of surgery or intervention, medication, complications, et cetera) was obtained from the medical protocols.

2.4 Statistical Hypotheses

Whereas the hypotheses regarding distinct alterations in HRV in the perioperative course of CEA and CAS, the relation of HRV and anxiety, the comparison of both groups with respect to the perceived medical intervention stress, and the levels of pre- and postoperative state anxiety are the main focus of the present study, interrelations of anxiety and psychological variables are investigated at a descriptive level. A detailed description of the patient sample with regard to anxiety, coping strategies, and social support was intended rather than tests of hypotheses. Moreover, gender differences and differences between the two treatment groups were examined for each psychological variable.

In the following, only alternative hypotheses (H1) relating to the formulated research questions (see section 1.7) will be reported, without repeating the respective

null-hypotheses (H0), stating that all differences or correlations in the data are due to chance.

HRV and CEA/CAS:

- H1.1: There is a significant interaction of intervention (CEA versus CAS) and time (pre- versus postoperative) in time domain indices of HRV: SDNN, pNN50, and rMSSD are expected to be decreased after CEA and increased after CAS.
- H1.2: There is a significant interaction of intervention (CEA versus CAS) and time (pre- versus postoperative) in frequency domain indices of HRV: LF, LF (nu), and LF/HF ratio are expected to be increased and HF, HF (nu), and TP to be decreased after CEA, whereas HF, HF (nu), and TP are expected to be increased and LF/HF ratio, LF, and LF (nu) to be decreased after CAS.

Correlations between HRV and Anxiety:

- H1.3: Trait anxiety, as measured by the STAI X2, correlates negatively with time domain parameters of HRV (SDNN, pNN50, and rMSSD), HF, HF (nu), and TP, and positively with LF, LF (nu), and LF/HF ratio.
- H1.4: Preoperative state anxiety, as measured by the STAI X1, correlates negatively with time domain parameters of HRV (SDNN, pNN50, and rMSSD), HF, HF (nu), and TP, and positively with LF, LF (nu), and LF/HF ratio.

Perceived medical intervention stress:

- H1.5: Patients undergoing CEA have significantly higher values in the perceived stress associated with the medical interventions, as measured by the perceived medical intervention stress questionnaire, than patients undergoing CAS. Moreover, the interventions' duration and patients' gender are examined as possibly confounding variables.

State and trait anxiety:

- H1.6: State anxiety levels, as measured by the STAI X1, are preoperatively significantly higher than postoperatively.

Interrelations of anxiety, perceived medical intervention stress, social support, and coping:

- Relations between the perceived stress associated with the medical interventions, as measured by the perceived medical intervention stress

questionnaire, and trait anxiety, as measured by the STAI X2, and postoperative state anxiety, as measured by the STAI X1, in the postoperative period, are illustrated.

- Relations between trait anxiety, as measured by the STAI X2, and pre- and postoperative state anxiety, as measured by the STAI X1, are illustrated.
- Relations between social support, as measured by the EISOP-modified, and pre- and postoperative state anxiety, as measured by the STAI X1, are illustrated.
- Relations between the coping strategies information seeking, rumination, belief, optimism and trust, recourse to personal resources, downward comparison, seeking social support, and distraction, as measured by the COSS, and preoperative state anxiety, as measured by the STAI X1, are illustrated.

2.5 Procedure

2.5.1 Patient Recruitment and Data Collection

All eligible patients were informed about the study after diagnosis or when scheduling the appointment for CEA or CAS. No requested patient declined participation in the study.

Preoperative assessment: The first contact of the study author and a doctor with the patient and the preoperative assessment took place either on the night before or in the morning of surgery at the ward, dependent on the date and time of the patient's admission to the hospital. After providing detailed information and obtaining informed consent, a doctor equipped the patients with a Holter monitor. Then, patients were requested to fill in several questionnaires (see section 2.3.2): the general questionnaire, STAI X1, STAI X2, COSS, and EISOP-modified. The first assessment took about 30 minutes.

Postoperative assessment: The second assessment took place on the evening of surgery or the day after, dependent on the constitution of the patient and external circumstances. The patients were asked to fill in the questionnaires on the perceived medical intervention stress and once again the STAI X1. Afterwards the Holter monitor was removed. The second assessment took about 15 to 20 minutes.

See Figure 9 for the procedure of data collection in the study period.

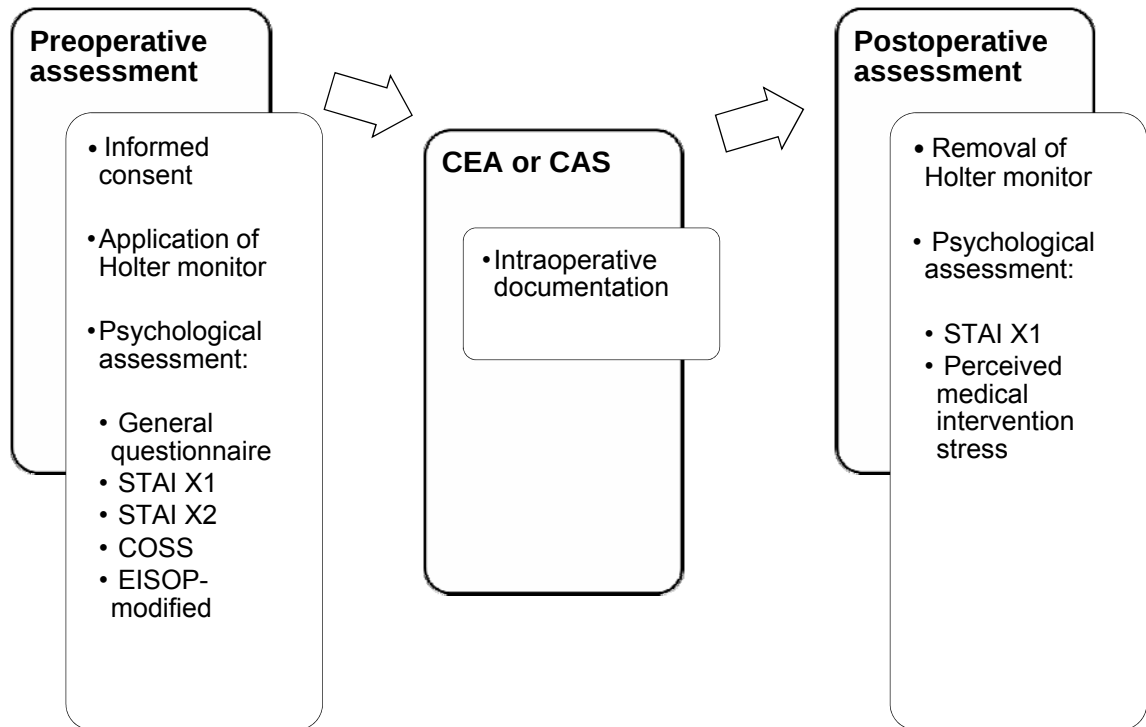


Figure 9. Procedure of data collection.

Altogether 49 recordings with a duration ($M \pm SD$) of $21:56 \pm 06:54$ (hh:mm) were collected. See Table 5 for the time between the preoperative assessment and surgery/intervention, the time between surgery/intervention and the postoperative assessment, and the time between the pre- and postoperative assessment.

Table 5. Time between pre- and postoperative assessments and surgery/intervention for the whole sample and separately for the two subgroups (CEA – CAS).

	Whole sample <i>N</i> = 52		CEA <i>n</i> = 28		CAS <i>n</i> = 24	
	Mdn	Range	Mdn	Range	Mdn	Range
Days between preoperative assessment and intervention	0	3	1	3	0	1
Days between postoperative assessment and intervention	1	5	1	5	1	2
Days between pre- and postoperative assessment	1	6	2	6	1	2

Note. MD = missing data.

In case of more than one day between the first assessment and surgery/intervention, surgery was unexpectedly rescheduled due to medical or organizational reasons. In these cases however, patients hadn't yet been informed about the deviation of schedule at the time of the first assessment and thus believed that the treatment would take place either in the following morning or a few hours afterwards. In case of more than one day between surgery/intervention and the second assessment, either the patient's medical condition or organizational reasons made it necessary to delay the questionnaire assessment, although the Holter monitor was removed at the predefined time.

2.5.2 Medical Treatment

Patients were usually admitted to the hospital the night before or in the morning of surgery and stayed in hospital for about three to six days in case of no complications. The patients diagnosed with carotid artery stenosis were routinely treated either by surgeons (CEA) or interventionalists (CAS). All patients were operated on ante meridiem, and monitored in a post-anesthesia care unit for a few hours after surgery before they returned to the ward.

Concerning CEA, the whole procedure, including primary incision and removal of the plaque from inside the artery, was performed under both deep and superficial cervical plexus block supplemented with fentanyl and propofol infusion. Genuine heparin was administered before artery clamping. All patients were mildly sedated (e.g. midazolam) before surgery. Supplemental doses of sedatives (e.g. midazolam) or pain medication (e.g. fentanyl, metamizol, piritramid) were administered intraoperatively if necessary. During surgery, HR, DBP, SBP, oxygen saturation, and temperature were monitored and the patients' status was continuously evaluated with regard to the occurrence of any neurological changes. A prophylactic shunt was placed in all surgeries. In the case of two patients, GA became necessary and was induced by the administration of propofol, fentanyl, and sevoflurane.

Concerning CAS, all interventions were performed with self-expanding stents (Abbott Diagnostics) that were introduced via the femoral artery after the administration of a local anesthetic. Prophylactic atropine (1/2 ampoule) was administered routinely shortly before balloon inflation in order to prevent bradycardia or asystole, and the intervention was routinely performed with cerebral protection devices. Predilatation was conducted when necessary. Patients were preoperatively only sedated by request at the ward.

In case of intraoperative hypotension patients were treated with etilefrine and in case of intraoperative hypertension with clonidine, urapidil, metoprolol, or verapamil.

All patients were maintained on their normal schedule of medication prior to surgery and their revised schedule after surgery. With respect to CAS, treatment with acetylsalicylic acid (Thrombo ASS®) was started immediately after diagnosis and all patients received clopidogrel (Plavix®) for three months and low-molecular-weight heparin (Lovenox®) for three days postprocedurally. With respect to CEA, all patients received analgetics (e.g. piritramid: Dipidolor®) and low-molecular-weight heparin (Lovenox®) in the early postsurgical period. The study thus did not influence the patients' treatment in any way, but reflected the actual situation.

For a more detailed description of the two treatments see sections 1.6.3.1 and 1.6.3.2 and for an outline of the impact of medication on HRV see section 1.3.2.5.

2.6 *Data Management and Statistical Analysis*

2.6.1 *Data Management of Physiological Recordings and Questionnaires*

All patient data were made anonymous after data collection and only the study author kept the classification of patients to IDs.

HRV was measured and calculated according to the standards suggested by the Task Force (1996). The conversion of analog to digital data was performed at a sampling rate of 4096 Hz. Data of ECG recordings were recorded on a compact flash memory card (ScanDisk Inc.) in the portable ECG (Holter) recorder (see section 2.3.1). After recording, data were stored on a personal computer and imported into the medilog® Darwin analysis program (Schiller AG) for offline analysis. After template analysis, the QRS complex and arrhythmia classification provided by the program was additionally visually inspected and all complexes identified as noise, ectopic beats, or other arrhythmias were excluded from the HRV analysis. Only normal beats were included. The fast Fourier transform (FFT) algorithm (linear detrending by Welch-method) was used for computing spectral densities of RR interval variability in 5-min intervals. See Figure 4 for a screenshot of the medilog® Darwin analysis program of the frequency domain analysis. The TP and spectral power of HF and LF were calculated in absolute units (ms^2) as well as normalized units [LF (nu), HF (nu)] and the LF/HF ratio was calculated (see section 1.3.2.2). Regarding HRV time domain analysis, the parameters SDNN (ms), rMSSD (ms), and pNN50 (%) were calculated (see section 1.3.2.2). The HRV parameter values for the recording periods of question were exported into Microsoft Excel files and once again checked for suspicious and missing

data. The Excel files of all patients were then assembled into one file for further analysis.

See Figure 10 for a screenshot of the medilog® Darwin analysis program for the 24-hour recording of one patient of the present study sample. The diagram on the top displays the patient's mean (red line), maximal (blue line), and minimal (green line) heart rate over the whole recording period. The right (blue) and middle (red) HRV-interval histograms beneath indicate the time lag between two consecutive heart beats. In the scatterplot on the right each beat interval in ms (x-axis) is plotted against the preceding interval (y-axis). The diagram underneath displays the patient's ECG for a certain time period.

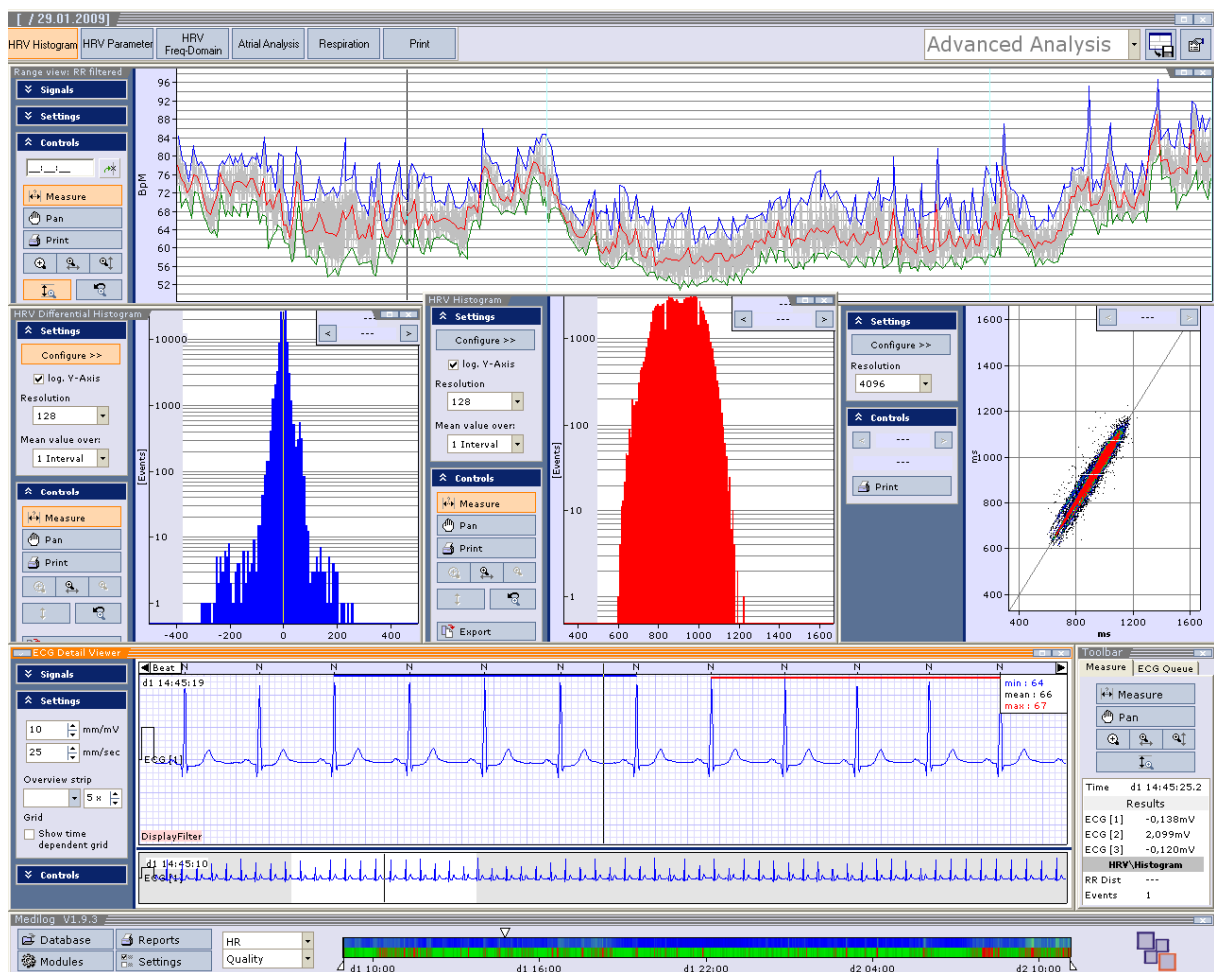


Figure 10. Screenshot of the medilog® Darwin analysis program of a 24-hour recording.

All paper-pencil questionnaires (see section 2.3.2) were manually entered into Microsoft Excel and then imported into SPSS, where scales were computed. In case of single missing values (less than 20% of the items per questionnaire), the missing data were substituted by the Expectation-Maximization (EM) algorithm (see for example

Howell, 2007). For further analysis, the physiological and psychological data were combined in one file.

2.6.2 *Statistical Analysis and Power Analysis*

Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences, Version 17.0, SPSS Inc. Chicago, IL) and STATISTICA (Version 7, StatSoft Europe GmbH, Germany, Hamburg).

The normal distribution of variables was tested with the Kolmogorov-Smirnov test (K-S test) and with standardized values (z-scores) of skewness and kurtosis (absolute values greater than 2.58 were considered significant at $p < .01$). Prior to each statistical analysis, the parameters' distributions were tested and parameters that were not normally distributed in the respective sample were log transformed to reduce the skewness of their distribution (Field, 2005), as frequently done in HRV research (e.g. Demirci, et al., 2006; Maunder, Lancee, Nolan, Hunter, & Tannenbaum, 2006). As it is not possible to get a log value of zero, a constant of 1 was added to the pNN50 values before log transformation.

To analyze the interaction of time (pre- versus postoperative) and intervention (CEA versus CAS) in HRV parameters, analysis of variance for repeated measures with the HRV parameters SDNN, pNN50, rMSSD, LF, LF (nu), HF, HF (nu), LF/HF ratio, and TP as dependent variables, treatment group (CEA versus CAS) as the independent variable, and the means of three preoperative and three postoperative time intervals as repeated measures was conducted. For each analysis post hoc tests (Tukey's HSD for unequal n) were performed for significant main effects or interactions.

Concerning the preoperative time intervals, three 5-min intervals starting 15, 10, and 5 minutes before the start of the surgical or minimally invasive intervention were chosen for calculating a preoperative mean. At this time all patients were in a comparable situation, as they were all being prepared for the surgical or minimally invasive intervention. Concerning the postoperative time intervals, three 5-min intervals starting 295, 300, and 305 minutes after the end of the medical intervention were chosen for calculating a postoperative mean. Five hours after the procedure all patients were resting in the post-anesthesia care unit and the effects of procedure specific medication (e.g. sedation) should have mostly ceased. For instance, the administration of atropine during CAS, known for abolishing practically all RR-interval spectral power at all frequencies (Taylor, et al., 1998), only has short-term effects that shouldn't have any impact on HRV more than five hours after the drug administration. Moreover, the selection of the just described time intervals ruled out potential influences of physical

activity, posture, and to some extent breathing frequency on HRV, as all patients were in the supine position during the chosen time intervals.

To assess associations between variables, Pearson's correlation coefficient or Spearman's rank correlation coefficient were used, dependent on the respective data levels and fulfillment of assumptions.

With regard to the correlation between preoperative state and trait anxiety and HRV parameters, the time when patients were filling in these questionnaires (first assessment) was used for analysis. The mean of one hour of recording (twelve consecutive 5-min intervals) was computed and correlated with the respective questionnaire data. Due to the fact that because of organizational reasons not all patients were monitored while filling in their first questionnaires, only data of about half of the patient sample are available for this analysis.

Patient characteristics and variable means were compared with the independent or dependent samples *t*-test, the non-parametric Mann-Whitney or the Wilcoxon rank-sum test, or the X^2 test, as appropriate.

An alpha level of .05 was applied for all statistical tests. Additionally, effect sizes were calculated to inform about the magnitude of the effect and to indicate the practical relevance of the results. Data are mostly presented as mean (*M*) $\pm$ standard deviation (*SD*).

With respect to sample size calculation, 34 patients (17 per group) were estimated for 80% power and $\alpha = .05$, when defining a significant interaction between time (pre- versus postoperative) and intervention (CEA versus CAS) in the HRV time domain parameter SDNN as the primary outcome and presuming an effect of medium size (ANOVA for repeated measures: within-between interaction; $f = 0.25$).

Due to differing HRV-recording periods and lengths, exclusion of HRV-data due to severe arrhythmia, missing questionnaire data, and the fact that not all patients filled in all questionnaires or agreed to the ECG-recording, the number of patients varies from analysis to analysis and will be explicitly indicated each time. See Figure 11 for an overview of the number of patients per group for HRV-data (analysis of variance for repeated measures – pre-post – and correlation analysis) and questionnaire data.

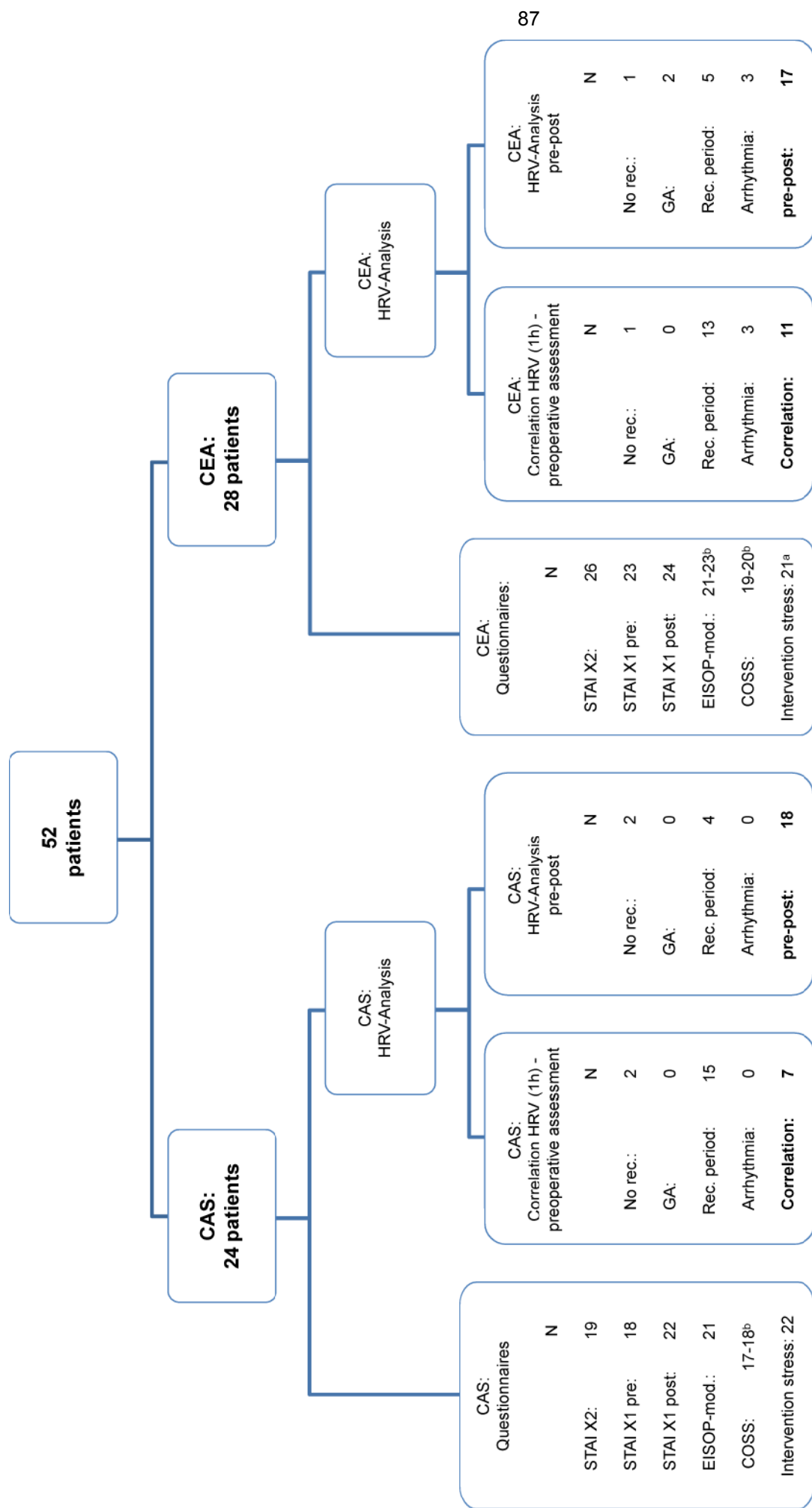


Figure 11. Sample size (N) separately for both treatment groups (CEA – CAS) and different analyses. For HRV-Analyses the reasons for missing data are specified. GA = general anesthesia; No rec. = no recording available; Rec. period = no suitable recording period available for a certain analysis; Intervention stress = Perceived medical intervention stress; Arrhythmia = exclusion of the whole recording due to severe arrhythmia. ^aoriginally 23 patients, but the two patients who received general anesthesia were excluded from this analysis; ^bdepending on the respective subscale.

3 Results

3.1 Sample Characteristics

Altogether 52 patients (CEA: $n = 28$; CAS: $n = 24$) with a mean age of 69 ± 10 years took part in the study. The two treatment groups were comparable with regard to gender distribution, age, BMI, marital status, living situation, education, employment status, smoking behavior, and physical activity (χ^2 test). See Table 6 and Table B 1 for patient characteristics.

Table 6. Sample characteristics.

	Whole sample				CEA			CAS		
	$N = 52$				$n = 28$			$n = 24$		
	MD	Count	M	SD	Count	M	SD	Count	M	SD
Gender F/M	0	22/30			13/15			9/15		
Age (yrs) at study entry	0		69	10	69	10		69	10	
BMI	3		28	5	29	6		27	3	

Note. MD = missing data; N = number; M = mean; BMI = body mass index.

Altogether 28 surgeries (CEA) with a mean duration of 119 ± 40 minutes (range: 59 – 214) and 24 minimally invasive interventions (CAS) with a mean duration of 67 ± 15 minutes (range: 40 – 94 minutes) were performed. All patients presented with a stenosis-degree of more than 80%. The carotid plaque was successfully removed in all surgeries, and no patients suffered from neurological deficits postprocedurally. One patient developed a neck hematoma shortly after surgery and received revision surgery on the same day. Concerning CAS, recanalization was achieved in all patients and stenting was performed in all but one patient, who had to undergo CEA afterwards.

See Table 7 for some aspects of the patients' medical history and risk factors.

Table 7. Patients' medical history and risk factors.

Patient characteristics	Total MD	Total Count	CEA Count	CAS Count
At least one prior surgical episode	1	47	25	22
Hospitalized before	1	49	26	23
Hypertension	0	38	20	18
Diabetes mellitus	0	27	15	12
History of myocardial infarction	0	6	5	1
Coronary heart disease	0	14	7	7
Previous endarterectomy	0	2	2	0
Previous carotid artery stenting	0	3	2	1

Note. MD = missing data; Total = whole patient sample ($N = 52$; $n = 28$ for CEA; $n = 24$ for CAS).

The two patient groups didn't differ (X^2 test) with respect to the occurrence of prior surgical episodes or prior hospitalization, prior carotid artery stenting or endarterectomy, and medical risk factors such as hypertension, diabetes mellitus, coronary heart disease, and history of myocardial infarction.

Table 8 gives an overview of the patients' self-rated general, preoperative, and postoperative well-being and subjective health status. The whole sample rated their well-being and their health status as about average and as significantly better shortly after the procedure than shortly before (paired samples t -test). The two patient samples differed only with regard to general well-being (independent samples t -test).

Table 8. Patients' subjective well-being and health status for the whole sample and separately for both patient subsamples.

	Whole sample <i>N</i> = 52				CEA <i>n</i> = 28			CAS <i>n</i> = 24		
	MD	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>
General well-being	2	50	2.92	0.73	27	2.70 ^a	0.78	23	3.17 ^a	0.58
Well-being pre	2	50	3.36**	0.78	27	3.30	0.82	23	3.43*	0.73
Well-being post	6	46	2.89**	0.85	23	2.83	0.89	23	2.96*	0.83
General health status	2	50	3.16	0.74	27	3.00	0.73	23	3.35	0.71
Health status pre	2	50	3.36**	0.72	27	3.30	0.78	23	3.43**	0.66
Health status post	6	46	2.98**	0.68	23	2.96	0.71	23	3.00**	0.67

Note. MD = missing data; *N* = number; *M* = mean; *SD* = standard deviation; **p* (two-tailed) < .05, ***p* (two-tailed) < .01: indicates significant differences (paired samples *t*-test) between the pre- and postoperative time (*N* = 44 for the whole sample; *n* = 22 for the CEA and CAS subsamples). ^a *p* (two-tailed) < .05: indicates significant differences (independent samples *t*-test) between the two groups.

3.2 HRV and CEA/CAS

3.2.1 Time Domain Parameters of HRV

- H1.1: There is a significant interaction of intervention (CEA versus CAS) and time (pre- versus postoperative) in time domain indices of HRV: SDNN, pNN50, and rMSSD are expected to be decreased after CEA and increased after CAS.

To analyze the interaction of time (pre- versus postoperative) and intervention (CEA versus CAS) in HRV parameters, analysis of variance for repeated measures with the time domain parameters SDNN, pNN50, and rMSSD as dependent variables, treatment group (CEA versus CAS) as the independent variable, and the means of three preoperative (three 5-min intervals starting 15, 10, and 5 minutes before the start of the respective medical procedure) and three postoperative time intervals (three 5-min intervals starting 295, 300, and 305 minutes after the end of the respective medical

procedure) as repeated measures was conducted. In case of significant effects, post hoc tests (Tukey's HSD for unequal n) were performed.

The course of all time domain parameters of HRV over time, ranging from the pre-, to the intra-, and to the postoperative period of time will be shown separately for both treatment groups. For this display, nine time intervals of the mean of three 5-min intervals each were computed [15min_pre_OP = mean of three 5-min intervals starting 15 minutes before the start of the intervention; Start_OP_plus_5min_intra = mean of three 5-min intervals starting five minutes after the start of the intervention; Stop_OP_minus_15min_intra = mean of three 5-min intervals stopping right before the end of the intervention; 5min_post_OP = mean of three 5-min intervals starting five minutes after the end of the intervention; 1h_post_OP = mean of three 5-min intervals starting one hour after the end of the intervention (plus 55, 60, and 65 minutes); 2h_post_OP = mean of three 5-min intervals starting two hours after the end of the intervention (plus 115, 120, and 125 minutes); 3h_post_OP = mean of three 5-min intervals starting three hours after the end of the intervention (plus 175, 180, and 185 minutes); 4h_post_OP = mean of three 5-min intervals starting four hours after the end of the intervention (plus 235, 240, and 245 minutes); 5h_post_OP = mean of three 5-min intervals starting five hours after the end of the intervention (plus 295, 300, and 305 minutes)].

See Figure 30 for a graphical display of the effect sizes (partial η^2) of all HRV parameters for the time $\times$ intervention interaction. Descriptive statistics of all HRV parameters as well as additional tables and figures for all HRV analyses are presented in APPENDIX B: HRV-ANALYSIS.

3.2.1.1 SDNN

See Figure 12 for the course of SDNN over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

Because of the positively skewed distribution the absolute values of SDNN were log transformed (log SDNN) to approach normally distributed data (see Table B 3 and Table B 4).

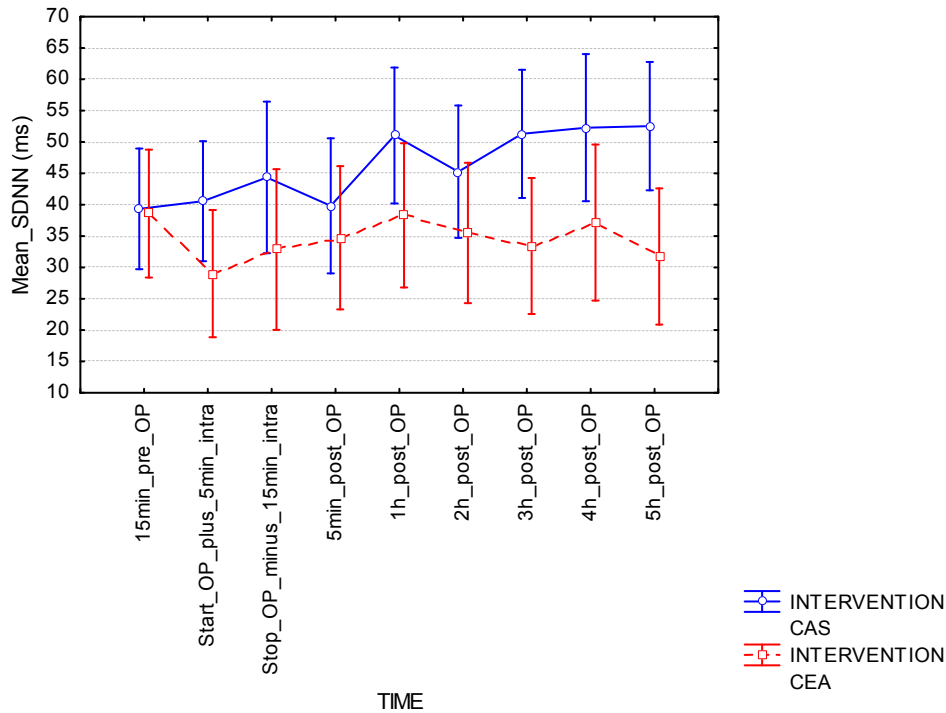


Figure 12. Graph of the course of SDNN over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.1.

There was a significant interaction effect between time and intervention, $F(1, 33) = 12.39$, p (two-tailed) $< .01$, partial $\eta^2 = .27$, indicating that the HRV parameter SDNN differed from the pre- to the postoperative period depending on the type of medical intervention (see Figure 13 and Table B 5). Tukey's HSD for unequal n post hoc test revealed significant differences for the CAS treatment group between the pre- and postoperative time, p (two-tailed) $= .05$, and significant differences between the CAS and CEA treatment groups at the postoperative time, p (two-tailed) $= .05$ (Table B 6). There were no significant main effects of the type of intervention, $F(1, 33) = 3.43$, ns , or of the pre- and postoperative time, $F(1, 33) = 0.27$, ns . Thus, the experimental hypothesis of a significant interaction of intervention (CAS – CEA) and time (preoperative – postoperative) is accepted.

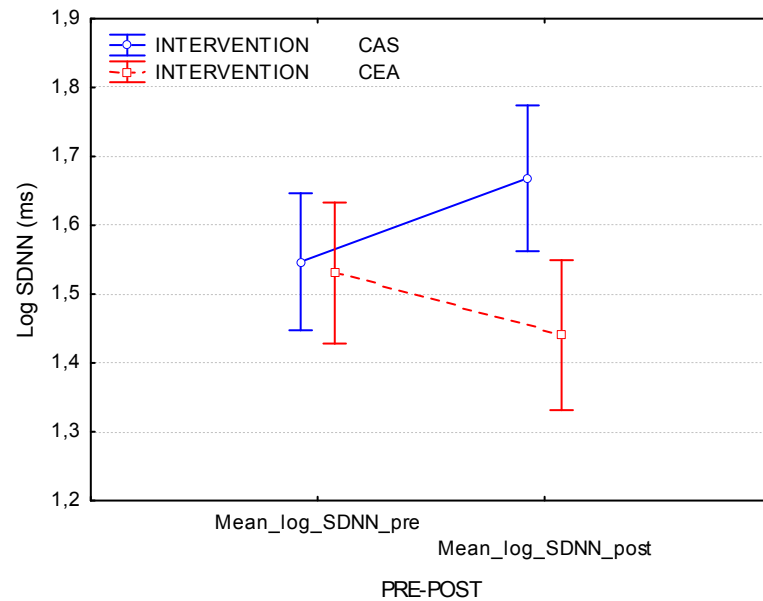


Figure 13. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 12.39$, p (two-tailed) $< .01$ for log SDNN. Vertical bars denote .95 confidence intervals.

3.2.1.2 PNN50

See Figure 14 for the course of pNN50 over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

Because of the positively skewed distribution the absolute values of pNN50 were log transformed (log pNN50) to approach normally distributed data (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 1.70$, ns (see Figure 15 and Table B 7). There were no significant main effects of the type of intervention, $F(1, 33) = 0.66$, ns , or of the pre- and postoperative time, $F(1, 33) = 0.77$, ns . Thus, the null-hypothesis cannot be rejected.

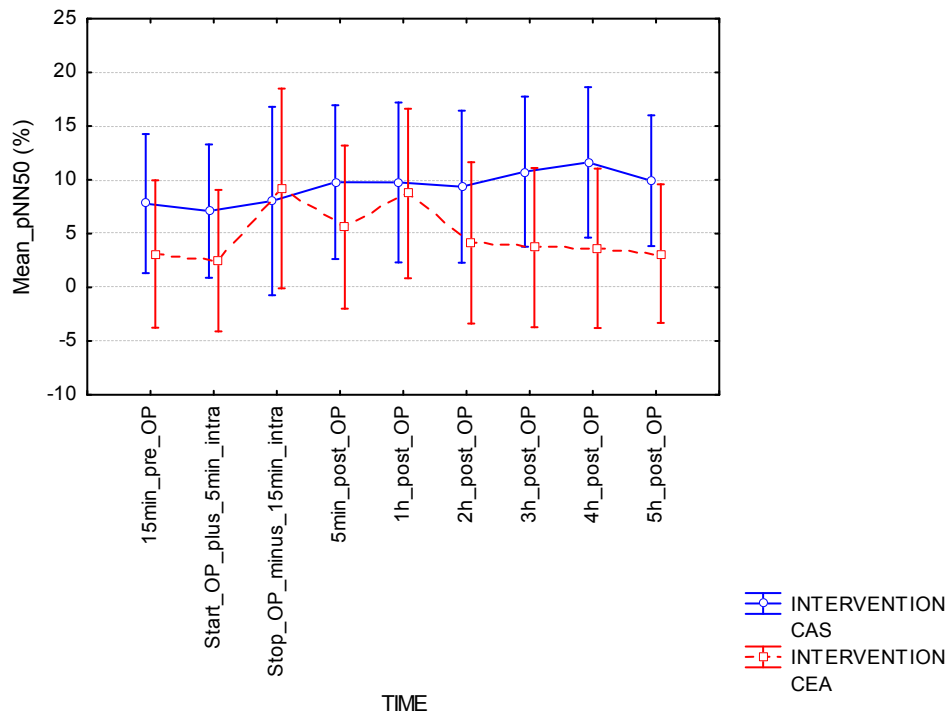


Figure 14. Graph of the course of pNN50 over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.1.

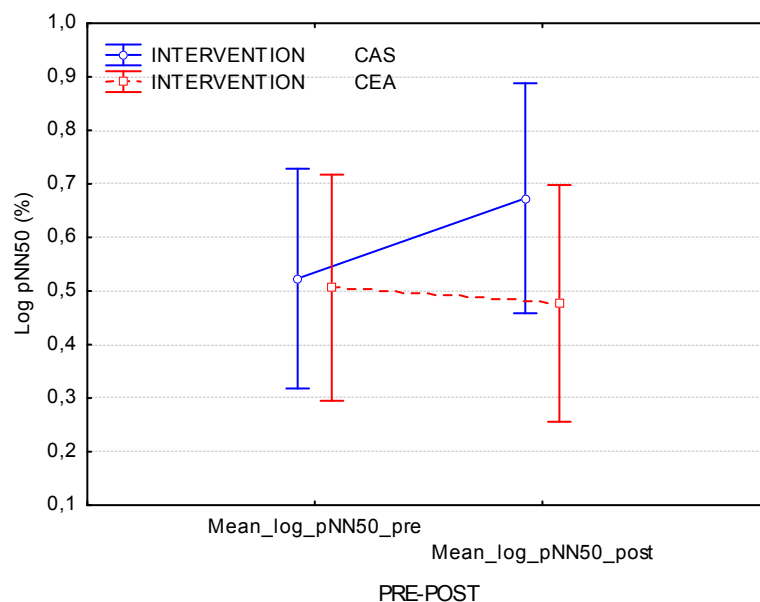


Figure 15. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 1.70$, ns , for log pNN50. Vertical bars denote .95 confidence intervals.

3.2.1.3 RMSSD

See Figure 16 for the course of rMSSD over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

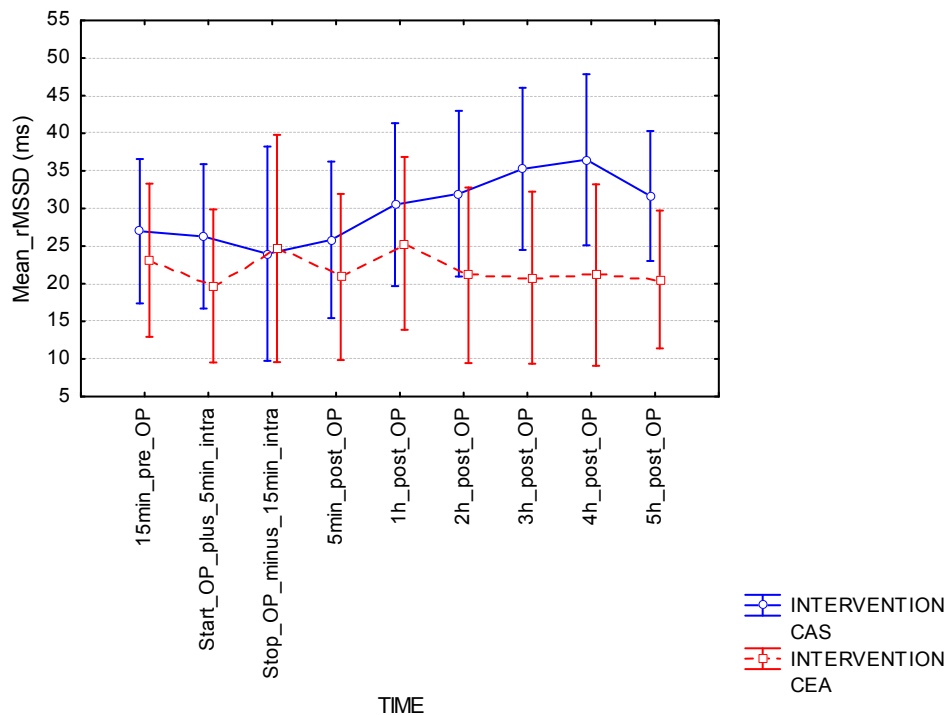


Figure 16. Graph of the course of rMSSD over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.1.

Because of the positively skewed distribution the absolute values of rMSSD were log transformed (log rMSSD) to approach normally distributed data (see Table B 3 and Table B 4).

There was a significant interaction effect between time and intervention, $F(1, 33) = 7.78$, p (two-tailed) $< .01$, partial $\eta^2 = .19$, indicating that the rMSSD parameter of HRV differed from the pre- to the postoperative period depending on the type of medical intervention (see Figure 17 and Table B 8). Tukey's HSD for unequal n post hoc test, however, revealed no significant differences (see Table B 9). There were no significant main effects of the type of intervention, $F(1, 33) = 0.38$, ns , or of the pre- and postoperative time, $F(1, 33) = 0.13$, ns . Thus, the experimental hypothesis of a significant interaction of intervention (CAS – CEA) and time (preoperative – postoperative) is accepted.

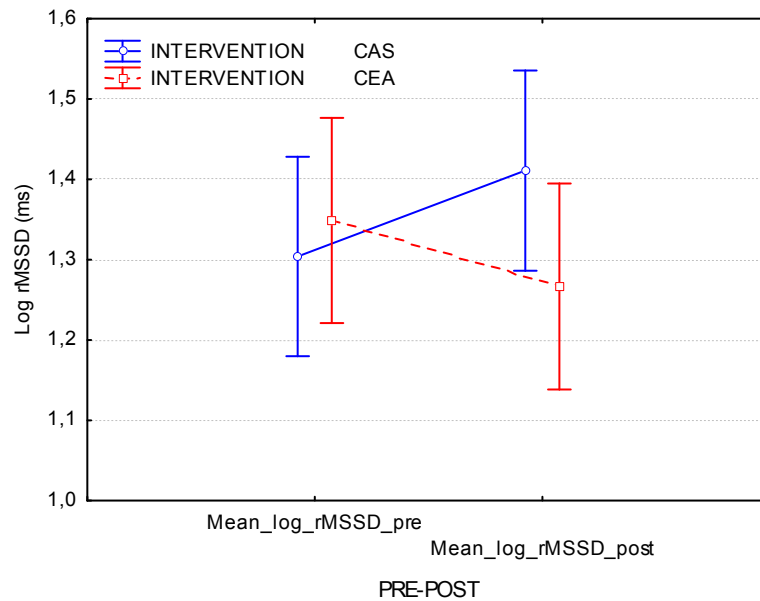


Figure 17. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 7.78$, p (two-tailed) $< .01$, for log rMSSD. Vertical bars denote .95 confidence intervals.

3.2.2 Frequency Domain Parameters of HRV

- H1.2: There is a significant interaction of intervention (CEA versus CAS) and time (pre- versus postoperative) in frequency domain indices of HRV: LF, LF (nu), and the LF/HF ratio are expected to be increased and HF, HF (nu), and TP to be decreased after CEA, whereas HF, HF (nu), and TP are expected to be increased and the LF/HF ratio, LF, and LF (nu) to be decreased after CAS.

To analyze the interaction of time (pre- versus postoperative) and intervention (CEA versus CAS) in HRV parameters, analysis of variance for repeated measures with the frequency domain parameters LF, LF (nu), HF, HF (nu), LF/HF ratio, and TP as dependent variables, treatment group (CEA versus CAS) as the independent variable, and the means of three preoperative (three 5-min intervals starting 15, 10, and 5 minutes before the start of the respective medical procedure) and three postoperative time intervals (three 5-min intervals starting 295, 300, and 305 minutes after the end of the respective medical procedure) as repeated measures was conducted. In case of significant effects, post hoc tests (Tukey's HSD for unequal n) were performed.

The course of all time domain parameters of HRV over time, ranging from the pre-, to the intra-, and to the postoperative period of time will be shown separately for both treatment groups. For this display, nine time intervals of the mean of three 5-min intervals each were computed [15min_pre_OP = mean of three 5-min intervals starting

15 minutes before the start of the intervention; Start_OP_plus_5min_intra = mean of three 5-min intervals starting five minutes after the start of the intervention; Stop_OP_minus_15min_intra = mean of three 5-min intervals stopping right before the end of the intervention; 5min_post_OP = mean of three 5-min intervals starting five minutes after the end of the intervention; 1h_post_OP = mean of three 5-min intervals starting one hour after the end of the intervention (plus 55, 60, and 65 minutes); 2h_post_OP = mean of three 5-min intervals starting two hours after the end of the intervention (plus 115, 120, and 125 minutes); 3h_post_OP = mean of three 5-min intervals starting three hours after the end of the intervention (plus 175, 180, and 185 minutes); 4h_post_OP = mean of three 5-min intervals starting four hours after the end of the intervention (plus 235, 240, and 245 minutes); 5h_post_OP = mean of three 5-min intervals starting five hours after the end of the intervention (plus 295, 300, and 305 minutes)].

See Figure 30 for a graphical display of the effect sizes (partial η^2) of all HRV parameters for the time $\times$ intervention interaction. Descriptive statistics of all HRV parameters as well as additional tables and figures for all HRV analyses are presented in APPENDIX B: HRV-ANALYSIS.

3.2.2.1 LF

See Figure 18 for the course of LF over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

Because of the positively skewed distribution the absolute values of LF were log transformed (log LF) to approach normally distributed data (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 3.86$, *ns* (see Figure 19 and Table B 10). There were no significant main effects of the type of intervention, $F(1, 33) = 2.93$, *ns*, or of the pre- and postoperative time, $F(1, 33) = 0.00$, *ns*. Thus, the null-hypothesis cannot be rejected.

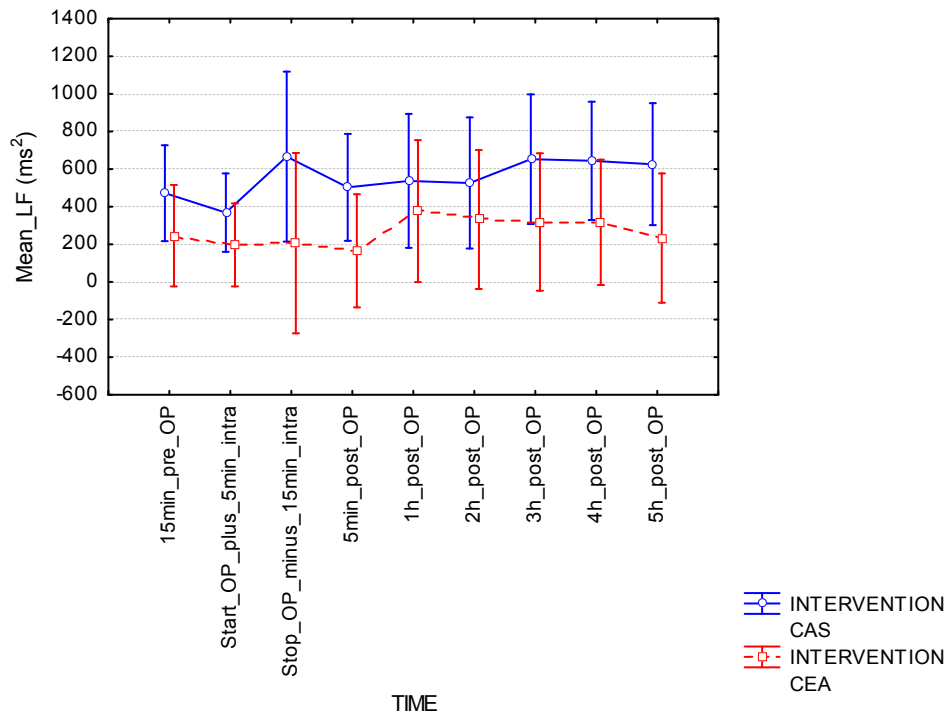


Figure 18. Graph of the course of LF over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

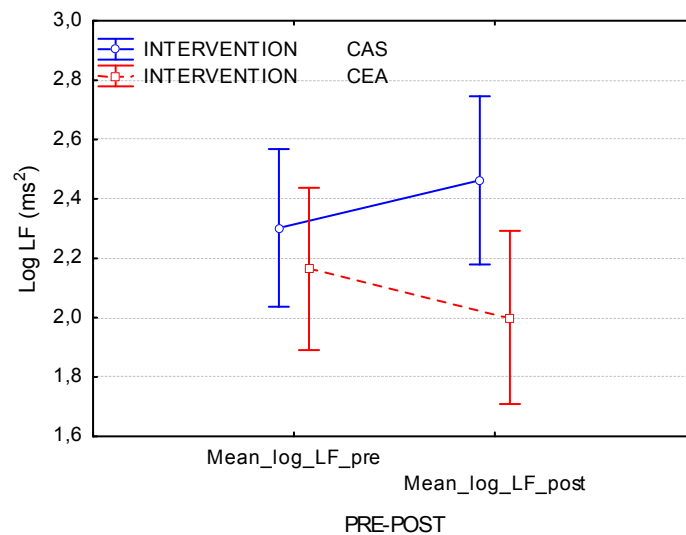


Figure 19. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 3.86$, ns , for log LF. Vertical bars denote .95 confidence intervals.

3.2.2.2 LF (nu)

See Figure 20 for the course of LF (nu) over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

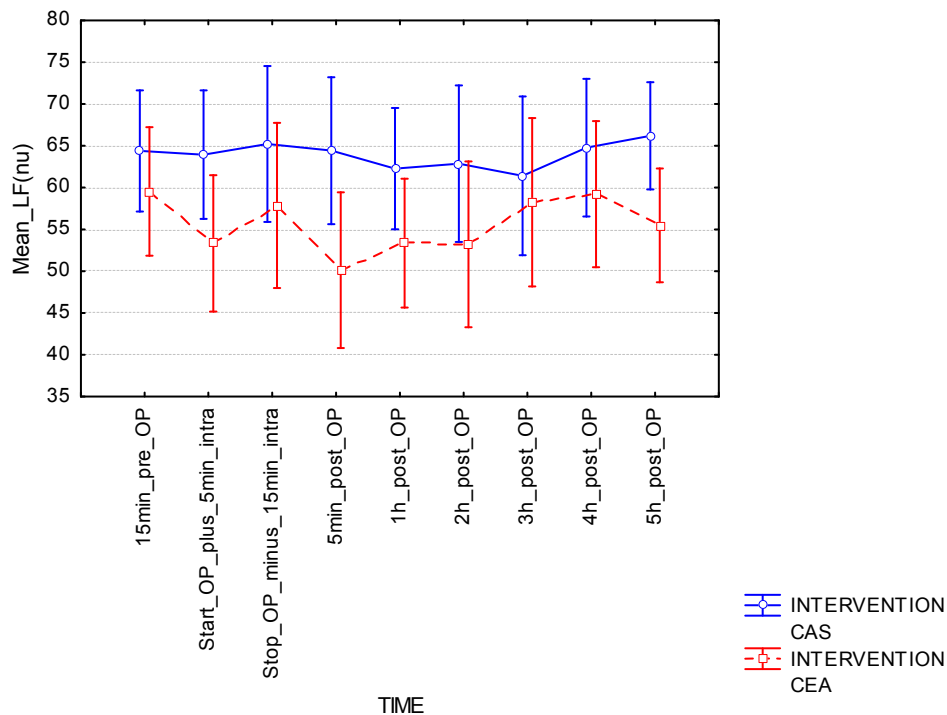


Figure 20. Graph of the course of LF (nu) over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

As LF (nu) was normally distributed, no log transformation was necessary (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 2.35$, *ns* (see Figure 21 and Table B 11). There were no significant main effects of the type of intervention, $F(1, 33) = 3.72$, *ns*, or of the pre- and postoperative time, $F(1, 33) = 0.46$, *ns*. Thus, the null-hypothesis cannot be rejected.

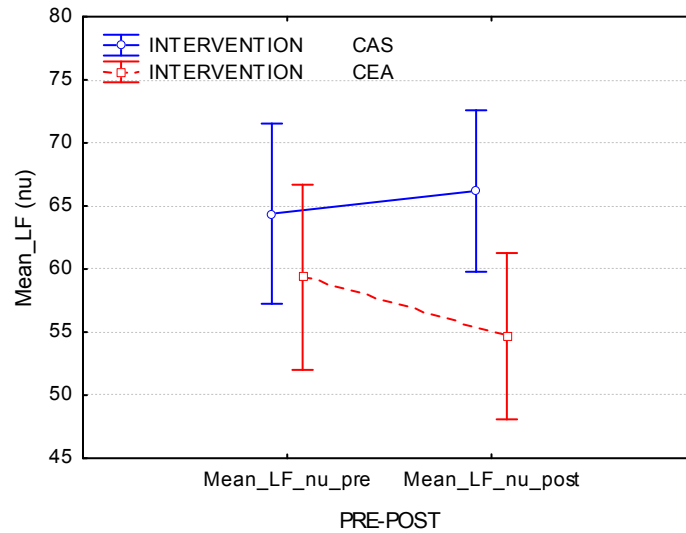


Figure 21. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 2.35$, *ns*, for LF (nu). Vertical bars denote .95 confidence intervals.

3.2.2.3 HF

See Figure 22 for the course of HF over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

Because of the positively skewed distribution the absolute values of HF were log transformed (log HF) to approach normally distributed data (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 0.88$, *ns* (see Figure 23 and Table B 12). There were no significant main effects of the type of intervention, $F(1, 33) = 0.18$, *ns*, or of the pre- and postoperative time, $F(1, 33) = 0.06$, *ns*. Thus, the null-hypothesis cannot be rejected.

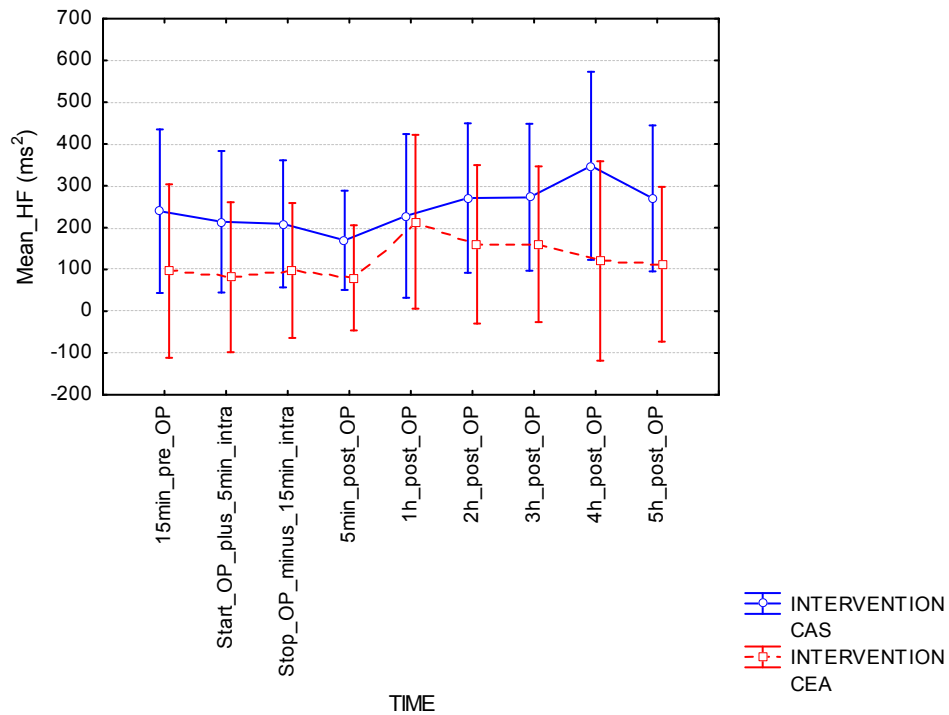


Figure 22. Graph of the course of HF over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

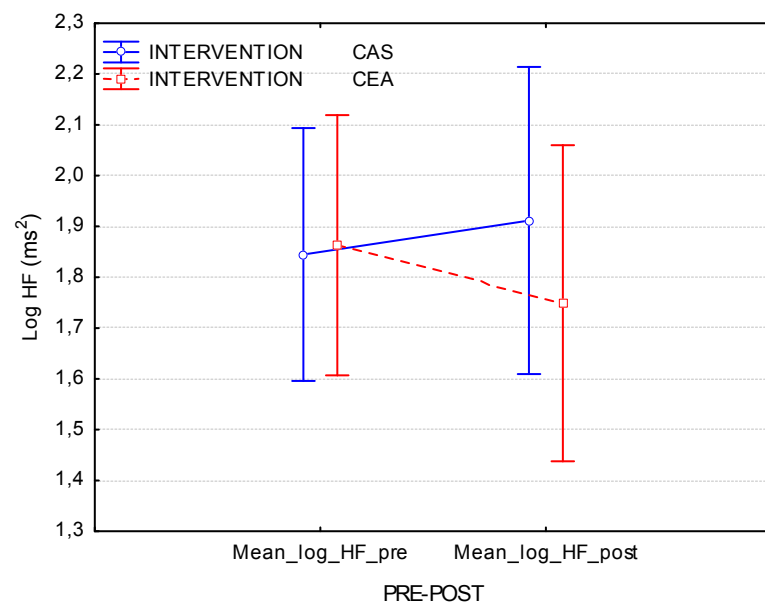


Figure 23. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 0.88$, ns , for log HF. Vertical bars denote .95 confidence intervals.

3.2.2.4 HF (nu)

See Figure 24 for the course of HF (nu) over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

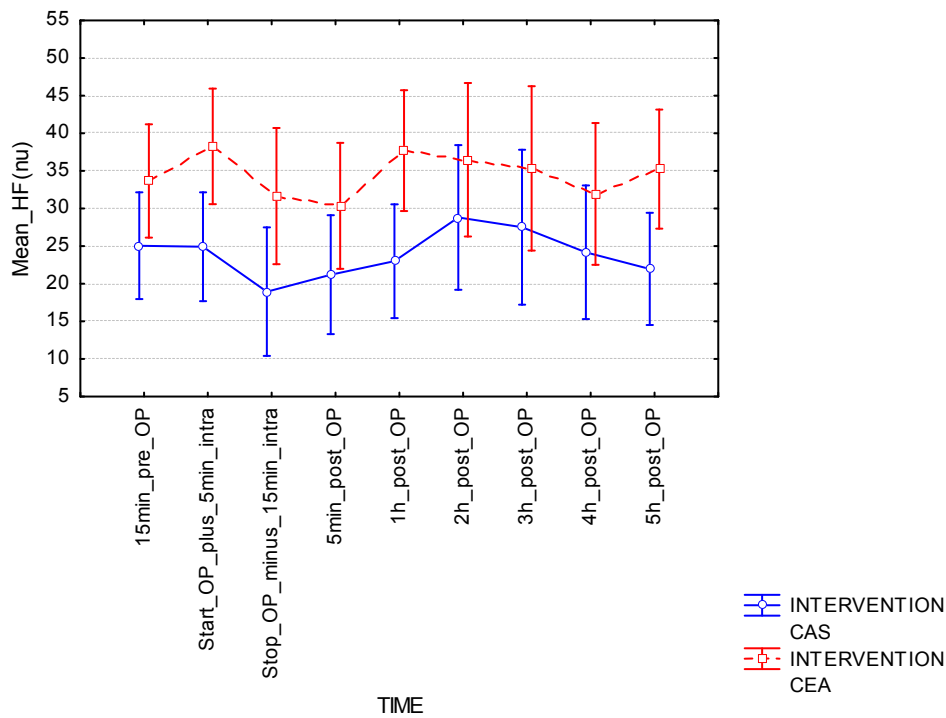


Figure 24. Graph of the course of HF (nu) over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

Because of the positively skewed distribution the absolute values of HF (nu) were log transformed [$\log \text{HF (nu)}$] to approach normally distributed data (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 1.98$, *ns* (see Figure 25 and Table B 13). There was, however, a significant main effect of the type of intervention, $F(1, 33) = 4.95$, $p(\text{two-tailed}) < .05$, partial $\eta^2 = .13$. Tukey's HSD for unequal n post hoc test revealed significant differences between the treatment groups, $p(\text{two-tailed}) < .05$, with higher values for the CEA group (see Table B 14). There was no significant main effect of the pre- and postoperative time, $F(1, 33) = 0.42$, *ns*. Thus, the null-hypothesis cannot be rejected.

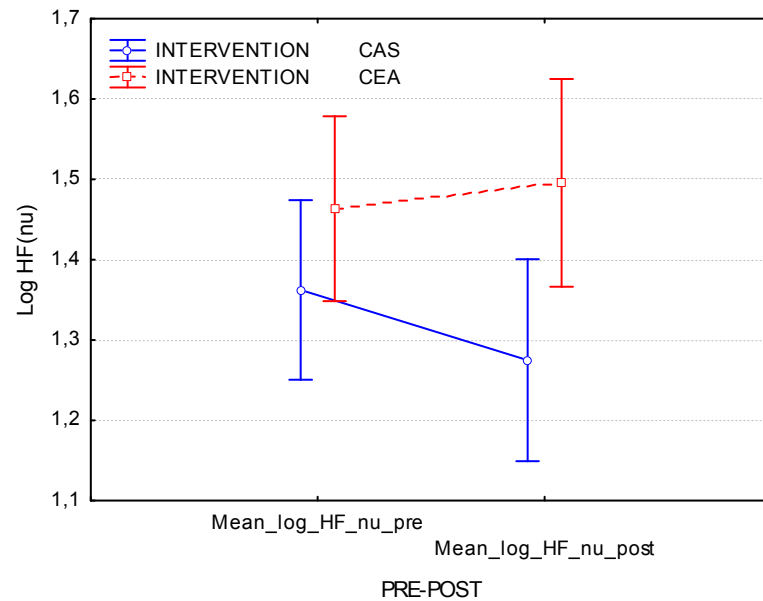


Figure 25. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 1.98$, *ns*, for log HF (nu). Vertical bars denote .95 confidence intervals.

3.2.2.5 LF/HF ratio

See Figure 26 for the course of log LF/HF ratio over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

Because of the positively skewed distribution the absolute values of the LF/HF ratio were log transformed (log LF/HF ratio) to approach normally distributed data (see Table B 3 and Table B 4).

There was no significant interaction effect between time and intervention, $F(1, 33) = 2.24$, *ns* (see Figure 27 and Table B 15). There was, however, a significant main effect of the type of intervention, $F(1, 33) = 4.45$, p (two-tailed) $< .05$, partial $\eta^2 = .12$. Tukey's HSD for unequal n post hoc test revealed significant differences between the treatment groups, p (two-tailed) $< .05$, with higher values for the CAS group (see Table B 16). There was no significant main effect of the pre- and postoperative time, $F(1, 33) = 0.19$, *ns*. Thus, the null-hypothesis cannot be rejected.

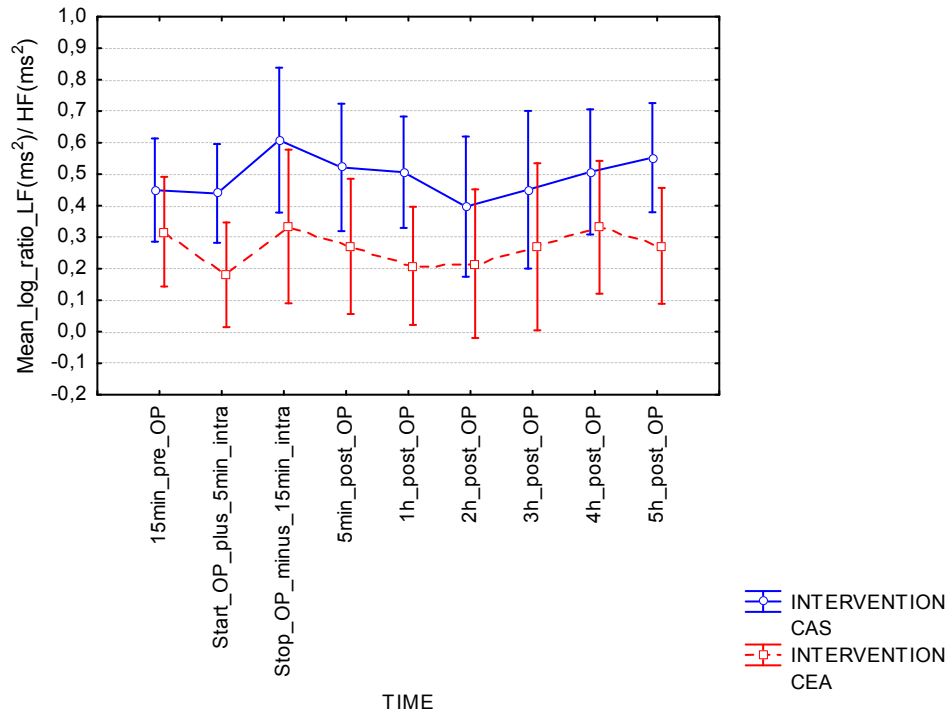


Figure 26. Graph of the course of log_ratio_LF/HF over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

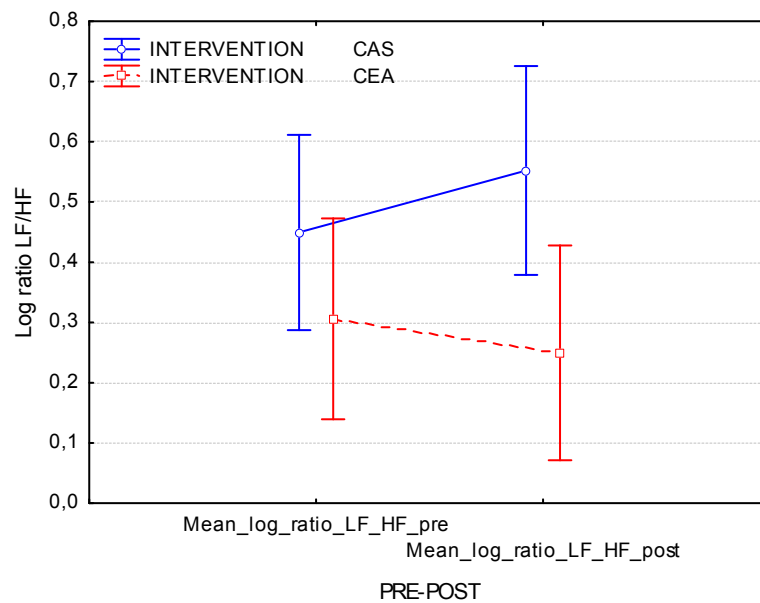


Figure 27. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 2.24$, *ns*, for log LF/HF ratio. Vertical bars denote .95 confidence intervals.

3.2.2.6 TP

See Figure 28 for the course of TP over time separately for both treatment groups. The nine chosen time intervals represent the means of in each case three 5-min intervals, ranging from the preoperative, to the intraoperative, and finally to the postoperative period of time.

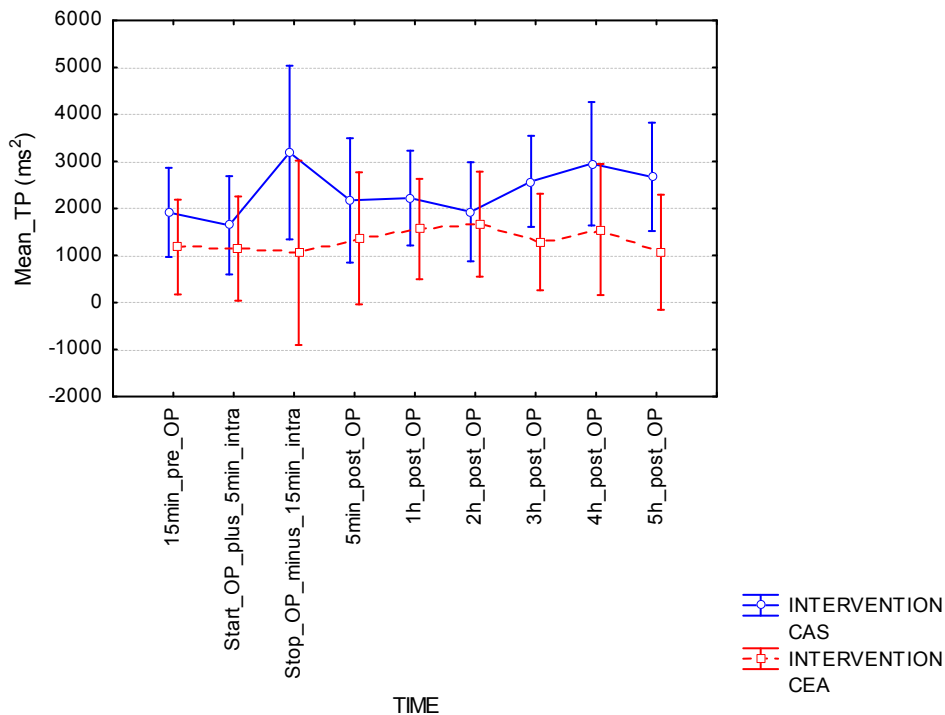


Figure 28. Graph of the course of TP over time separately for both treatment groups (CAS and CEA). Vertical bars denote .95 confidence intervals. For a description of the chosen time intervals see section 3.2.2.

Because of the positively skewed distribution the absolute values of TP were log transformed (log TP) to approach normally distributed data (see Table B 3 and Table B 4).

There was a significant interaction effect between time and intervention, $F(1, 33) = 5.87$, p (two-tailed) $< .05$, partial $\eta^2 = .15$, indicating that the TP parameter of HRV differed from the pre- to the postoperative period depending on the type of medical intervention (see Figure 29 and Table B 17). Tukey's HSD for unequal n post hoc test revealed significant differences only between the CEA and CAS treatment groups at the postoperative time, p (two-tailed) $< .05$ (see Table B 18). There was, moreover, a significant main effect of the type of intervention, $F(1, 33) = 4.29$, p (two-tailed) $< .05$, partial $\eta^2 = .11$. Tukey's HSD for unequal n post hoc test revealed significant differences between the treatment groups, $p < .05$, with higher values for the CAS

group (see Table B 19). There was, however, no significant main effect of the pre- and postoperative time, $F(1, 33) = 0.42$, *ns*. Thus, the null-hypothesis cannot be rejected.

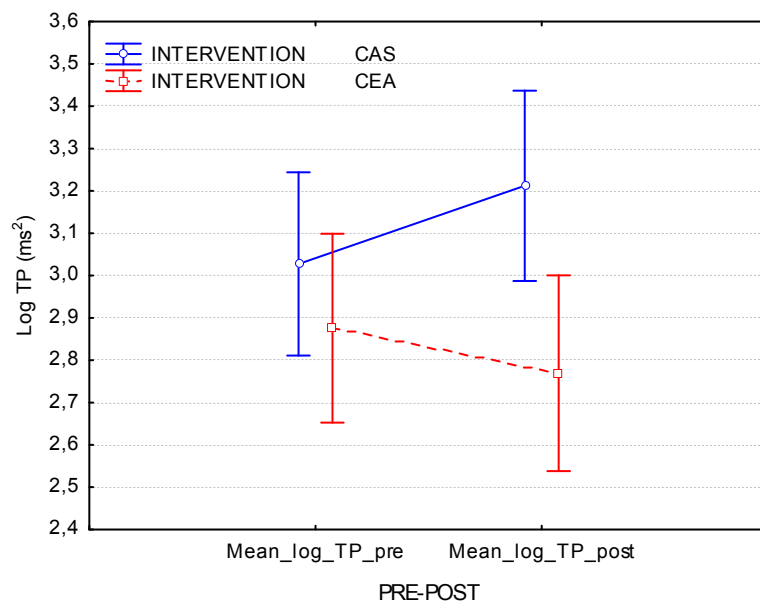


Figure 29. Interaction graph of the interaction between intervention (CAS – CEA) and time [preoperative (1) – postoperative (2)], $F(1, 33) = 5.87$, p (two-tailed) $< .05$, for log TP. Vertical bars denote .95 confidence intervals.

In Figure 30 the effect sizes (partial η^2) of all HRV parameters for the time $\times$ intervention interaction are graphically displayed. The interaction was significant for the parameters log SDNN, log rMSSD, and log TP.

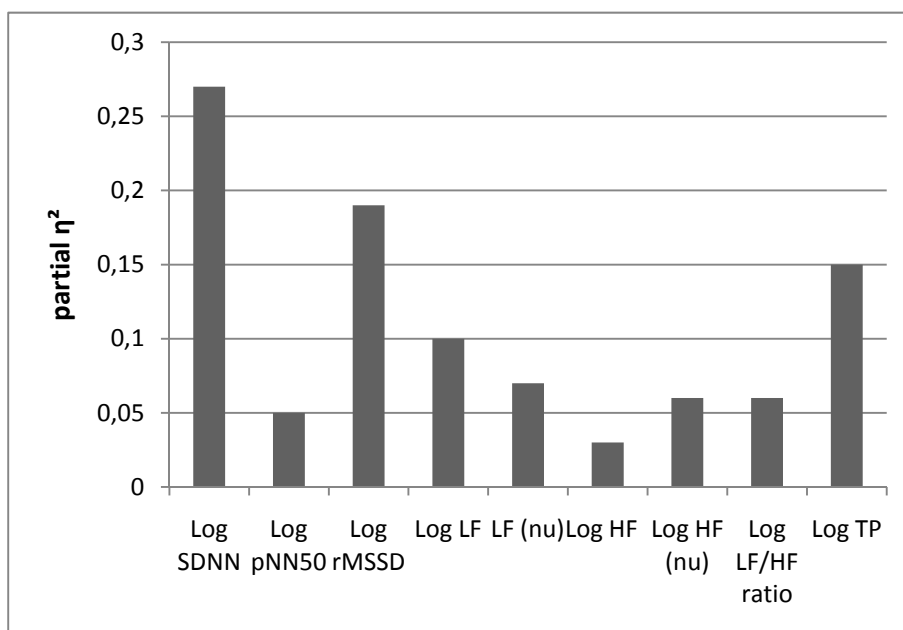


Figure 30. Effect sizes (partial η^2) for the time $\times$ intervention interaction for all HRV parameters.

3.2.3 Correlations between HRV and Anxiety

Although the K-S test indicated normally distributed data, data of HRV-parameters were skewed (see Table B 20), and Spearman's correlation coefficient was used to test the hypothesized associations between trait anxiety, preoperative state anxiety, and the HRV parameter values of the hour while patients were filling in the preoperative questionnaires. See Table 9 for descriptive statistics of trait anxiety, preoperative state anxiety, and the HRV-parameters for this subsample.

Table 9. Descriptive statistics (number [*N*], mean [*M*], standard deviation [*SD*], median [*Mdn*], and *range*) of preoperative state anxiety, trait anxiety, and the 1-hour means of all HRV-parameters of the subsample.

	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>Range</i>
Trait anxiety	17	35.82	11.27	32.00	39.00
Preoperative state anxiety	16	40.19	11.81	38.50	42.00
Mean_1h_SDNN	18	36.38	15.99	34.55	59.78
Mean_1h_rMSSD	18	21.63	9.96	20.21	36.37
Mean_1h_pNN50	18	4.54	5.09	2.85	19.72
Mean_1h_LF	18	293.24	323.21	218.47	1244.74
Mean_1h_HF	18	108.39	98.07	69.28	284.07
Mean_1h_log_ratio_LF_HF	18	0.44	0.29	0.48	1.06
Mean_1h_total_power	18	1328.47	1248.48	1027.35	4657.87
Mean_1h_LF_nu	18	61.65	11.60	63.10	44.87
Mean_1h_HF_nu	18	26.59	12.44	25.09	45.41

- H1.3: Trait anxiety, as measured by the STAI X2, correlates negatively with time domain parameters of HRV (SDNN, pNN50, and rMSSD), HF, HF (nu), and TP, and positively with LF, LF (nu), and the LF/HF ratio.

There were no significant negative relationships between a patient's trait anxiety and SDNN, $r_s = -.24$, *ns*, $n = 17$, rMSSD, $r_s = -.40$, *ns*, $n = 17$, pNN50, $r_s = -.43$, *ns*, $n = 17$, HF, $r_s = -.29$, *ns*, $n = 17$, HF (nu), $r_s = -.37$, *ns*, $n = 17$, and TP, $r_s = -.24$, *ns*, $n = 17$. Thus, the null hypothesis cannot be rejected.

There were no significant positive relationships between a patient's trait anxiety and LF, $r_s = -.22$, *ns*, $n = 17$, LF (nu), $r_s = .21$, *ns*, $n = 17$, and the log LF/HF ratio, $r_s = .24$, *ns*, $n = 17$. Thus, the null hypothesis cannot be rejected.

- H1.4: Preoperative state anxiety, as measured by the STAI X1, correlates negatively with time domain parameters of HRV (SDNN, pNN50, and rMSSD), HF, HF (nu), and TP, and positively with LF, LF (nu), and the LF/HF ratio.

There were no significant negative relationships between a patient's preoperative state anxiety and SDNN, $r_s = -.17$, *ns*, $n = 16$, rMSSD, $r_s = -.47$, *ns*, $n = 16$, HF, $r_s = -.22$, *ns*, $n = 16$, HF (nu), $r_s = -.47$, *ns*, $n = 16$, and TP, $r_s = .00$, *ns*, $n = 16$, but a significant negative relationship between preoperative state anxiety and pNN50, $r_s = -.52$, p (two-tailed) $< .05$, $n = 16$. Thus, the null hypothesis cannot be rejected with the exception of pNN50.

There were no significant positive relationships between a patient's preoperative state anxiety and LF, $r_s = -.03$, *ns*, $n = 16$, and the log LF/HF ratio, $r_s = .41$, *ns*, $n = 16$, but a significant positive relationship between preoperative state anxiety and LF (nu), $r_s = .55$, p (two-tailed) $< .05$, $n = 16$. Thus, the null hypothesis cannot be rejected with the exception of LF (nu).

3.3 Perceived Medical Intervention Stress

- H1.5: Patients undergoing CEA have significantly higher values in the perceived stress associated with the medical interventions, as measured by the perceived medical intervention stress questionnaire, than patients undergoing CAS.

Due to the non-normal distribution of perceived medical intervention stress, $D(43) = 0.18$, $p < .01$, the Mann-Whitney test was used to test for differences in the reported stress according to the type of intervention. See Table 10 (p. 110) for descriptive statistics of perceived medical intervention stress, trait anxiety, and postoperative state anxiety. In APPENDIX A: QUESTIONNAIRES you additionally find descriptive statistics for the whole scale as well as for each item.

There was no significant difference in the reported stress between patients undergoing CEA ($Mdn = 1.70$) and patients undergoing CAS ($Mdn = 1.67$), $U = 223.5$, *ns*, $r = -.03$, $n = 43$ (see Figure 31). Thus, the null-hypothesis cannot be rejected.

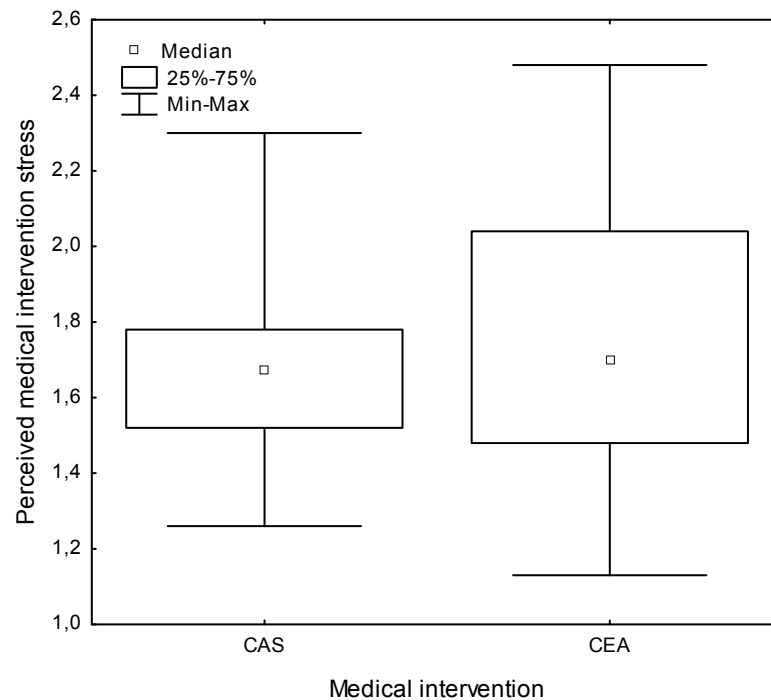


Figure 31. Boxplots of the perceived medical intervention stress associated with the medical interventions (CAS and CEA).

When looking at the 23 items in detail, the two groups differed only with respect to four items (the original, not reversely poled items are reported): item 9 (“I experienced the communication with the medical staff as calming.”), CAS ($Mdn = 3.0$) < CEA ($Mdn = 4.0$), $U = 149.0$, p (two-tailed) < .05, $n = 43$, item 10 (“I experienced the operating room as alarming.”), CAS ($Mdn = 1.0$) < CEA ($Mdn = 2.0$), $U = 137.0$, p (two-tailed) < .05, $n = 43$, item 14 (“I was able to relax during the procedure.”), CAS ($Mdn = 2.0$) < CEA ($Mdn = 3.0$), $U = 156.5$, p (two-tailed) < .05, $n = 43$, and item 15 (“I trusted the medical staff”), CAS ($Mdn = 4.0$) = CEA ($Mdn = 4.0$), $U = 164.0$, p (two-tailed) < .05, $n = 43$.

To account for a possible association between the intervention’s duration and the perceived medical intervention stress, correlation analysis was conducted. There was no relationship between a patient’s perception of the stress associated with the medical intervention and the duration of the intervention, $r_s = -.11$, ns , $n = 39$, thus ruling out procedure duration as an important confounding factor.

Additionally, gender differences in the patients’ perception of the stress associated with the medical interventions were analyzed by using the Mann-Whitney test. There was no significant difference in the reported stress associated with the medical interventions between male ($Mdn = 1.61$) and female ($Mdn = 1.70$) patients, $U = 179$, ns , $n = 43$.

3.4 State and Trait Anxiety

The means and standard deviations of all psychological variables are presented in Table 10 for the whole sample of patients and separately for the two subgroups (CEA and CAS). The two subgroups didn't differ in any of these variables.

Table 10. Descriptive statistics (number [*N*], mean [*M*], and standard deviation [*SD*]) of all psychological variables for the whole patient sample and separately for patients undergoing CEA or CAS.

	Whole sample			CEA			CAS		
	<i>N</i> = 52			<i>n</i> = 28			<i>n</i> = 24		
	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>
Trait anxiety	45	37.51	10.67	26	35.27	9.49	19	40.58	11.67
State anxiety pre	41	40.39	11.53	23	39.30	12.01	18	41.78	11.07
State anxiety post	46	33.22	8.44	24	32.33	9.81	22	34.18	6.73
Perceived medical intervention stress	43	1.73	0.33	21	1.76	0.40	22	1.70	0.26
Overall social support	42	3.17	0.83	21	3.41	0.41	21	2.92	1.06
Support from social network	44	3.24	0.94	23	3.45	0.56	21	3.02	1.20
Support from hospital staff	43	3.02	1.02	22	3.25	0.86	21	2.79	1.14
Rumination	36	1.88	0.57	19	1.79	0.60	17	1.98	0.54
Optimism and trust	36	3.50	0.41	19	3.53	0.46	17	3.46	0.34
Downward comparison	37	2.82	0.89	19	3.07	0.85	18	2.56	0.86
Recourse to personal resources	36	2.63	0.64	19	2.81	0.57	17	2.44	0.68

	Whole sample			CEA			CAS		
	<i>N</i> = 52			<i>n</i> = 28			<i>n</i> = 24		
	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>
Belief	38	2.18	1.02	20	2.20	0.98	18	2.17	1.08
Distraction	36	2.51	0.66	19	2.64	0.51	17	2.35	0.78
Seeking social support	36	2.27	0.74	19	2.20	0.73	17	2.35	0.77
Information seeking	36	2.61	0.73	19	2.63	0.77	17	2.58	0.71

Due to the normal distribution of preoperative state anxiety, $D(41) = 0.13$, $p > .05$, postoperative state anxiety, $D(46) = 0.13$, $p > .05$, and trait anxiety, $D(45) = 0.12$, $p > .05$, parametric tests were used for all hypotheses concerning anxiety. See Table 10 (p. 110) for descriptive statistics of preoperative state anxiety, postoperative state anxiety, and trait anxiety.

- H1.6: State anxiety levels, as measured by the STAI X1, are preoperatively significantly higher than postoperatively.

The t -test for dependent samples was used to test for differences in anxiety levels. STAI X1 scores were significantly higher preoperatively ($M = 40.03$) than postoperatively ($M = 32.74$), $t(37) = 4.33$, $p < .001$ (one-tailed), $r = .58$, $n = 38$ (see Figure 32). Thus, the experimental hypothesis is accepted.

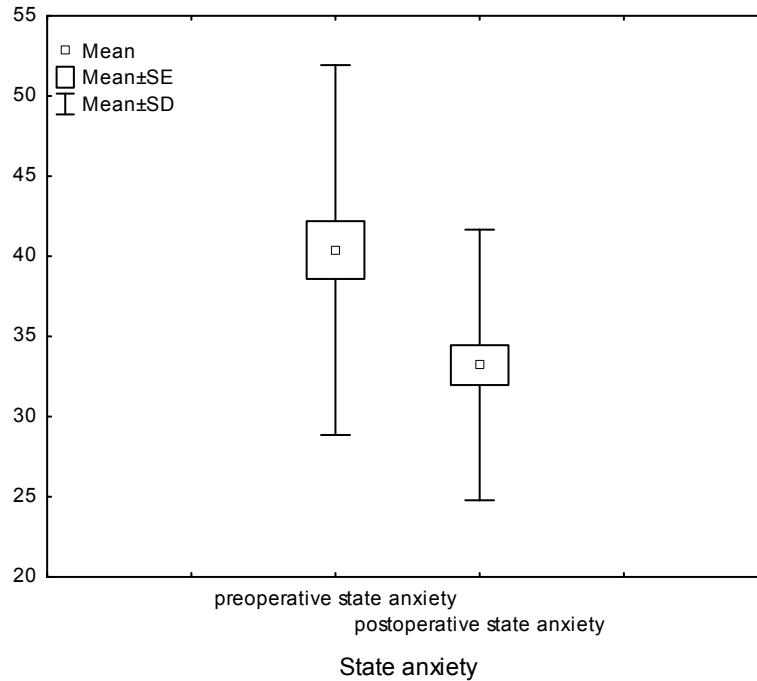


Figure 32. Boxplots of preoperative and postoperative state anxiety.

The *t*-test for independent samples was used to test for differences in anxiety levels according to gender. Women did neither significantly differ from men in their preoperative state anxiety levels (female: $M = 39.28$, $n = 18$; male: $M = 41.26$, $n = 23$), $t(39) = -.54$, *ns*, $r = .09$, nor in their postoperative state anxiety levels (female: $M = 35.2$, $n = 20$; male: $M = 31.69$, $n = 26$), $t(44) = 1.41$, *ns*, $r = .21$.

3.4.1 *Interrelations between Anxiety, Perceived Medical Intervention Stress, Social Support, and Coping*

- Due to the non-normal distribution of perceived medical intervention stress, $D(43) = 0.18$, $p < .01$, Spearman's correlation coefficient was used to test the associations between the perceived medical intervention stress and trait and postoperative state anxiety. See Table 10 (p. 110) for descriptive statistics of perceived medical intervention stress, trait anxiety, and postoperative state anxiety. In APPENDIX A: QUESTIONNAIRES you additionally find descriptive statistics for the whole scale as well as for each item.

There was a positive relationship between a patient's perception of the stress associated with the medical interventions and trait anxiety, $r_s = .36$, p (one-tailed) $< .05$, $n = 39$ (see Figure 33), and postoperative state anxiety, $r_s = .55$, p (one-tailed) $< .001$, $n = 42$ (see Figure 34).

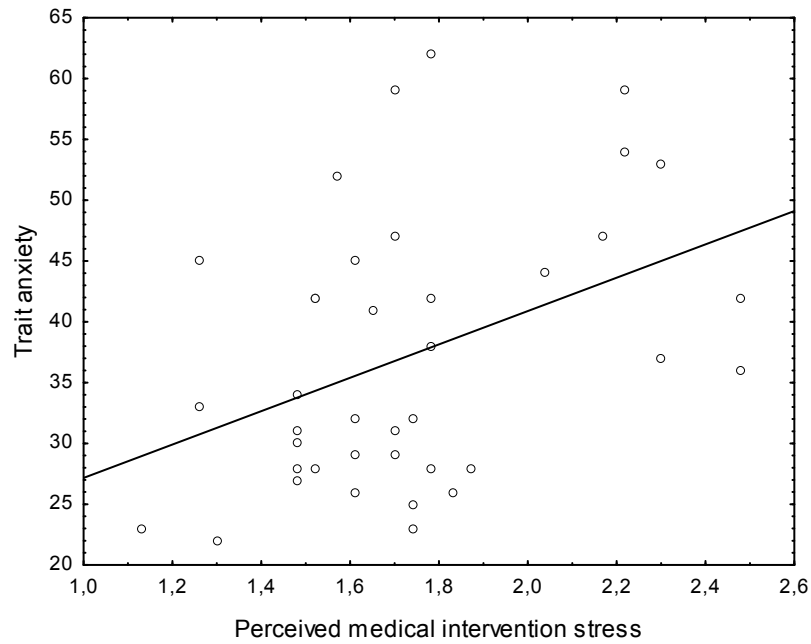


Figure 33. Scatterplot of trait anxiety against perceived medical intervention stress with a linear regression line.

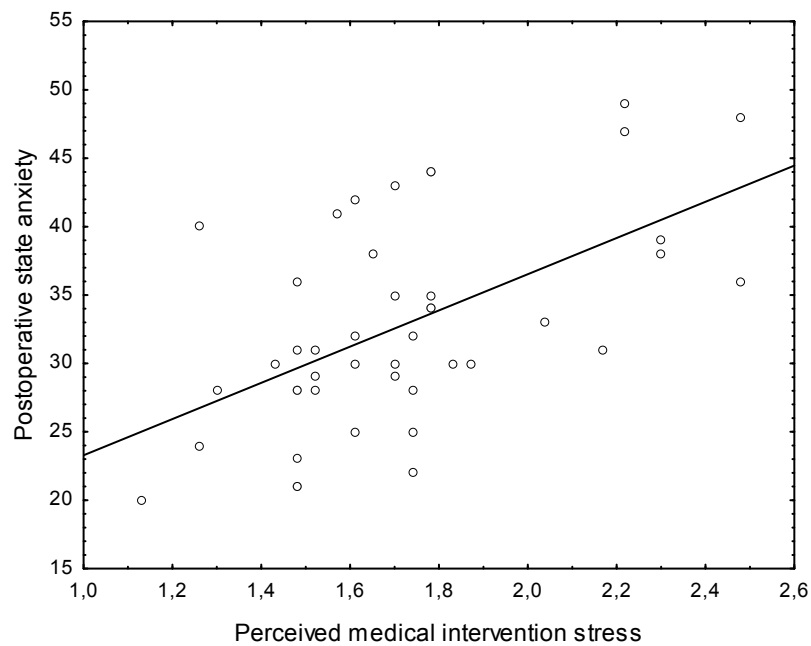


Figure 34. Scatterplot of postoperative state anxiety against perceived medical intervention stress with a linear regression line.

- Due to the normal distribution of preoperative state anxiety, $D(41) = 0.13$, $p > .05$, postoperative state anxiety, $D(46) = 0.13$, $p > .05$, and trait anxiety, $D(45) = 0.12$, $p > .05$, Pearson's correlation coefficient was used to test the association between trait anxiety and pre- and postoperative state anxiety. There was a positive relationship between a patient's trait anxiety and preoperative state anxiety, $r = .69$,

p (one-tailed) $< .001$, $n = 40$ (see Figure 35), and between trait anxiety and postoperative state anxiety, $r = .51$, p (one-tailed) $< .001$, $n = 43$ (see Figure 36).

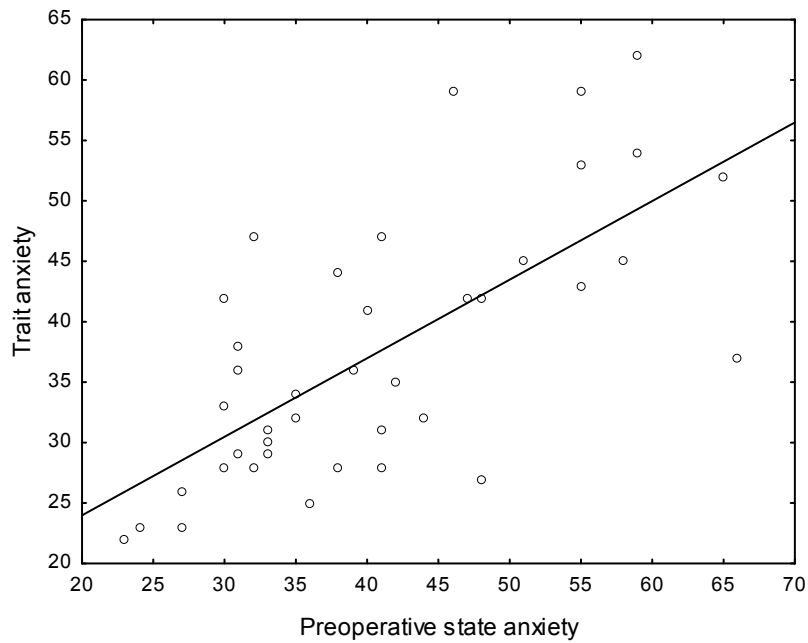


Figure 35. Scatterplot of trait anxiety against preoperative state anxiety with a linear regression line.

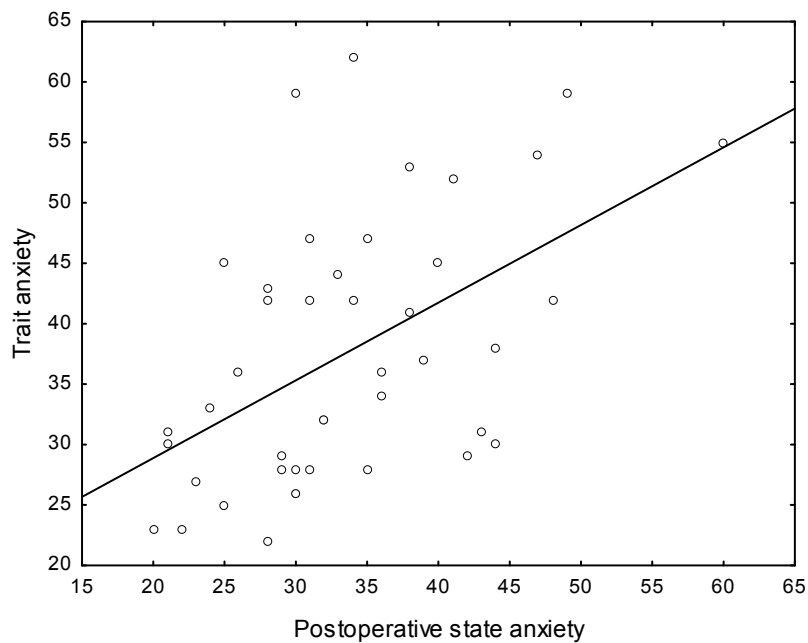


Figure 36. Scatterplot of trait anxiety against postoperative state anxiety with a linear regression line.

- Due to the non-normal distribution of overall social support, $D(42) = 0.25$, $p < .001$, social support from the social network, $D(44) = 0.21$, $p < .001$, and social support from the hospital staff, $D(43) = 0.19$, $p < .01$, Spearman's correlation coefficient

was used to test the associations between social support and preoperative and postoperative state anxiety. See Table 10 (p. 110) for descriptive statistics of all three social support scales, preoperative state anxiety, and postoperative state anxiety.

There was no significant relationship between a patient's overall social support and preoperative state anxiety, $r_s = -.27$, ns , $n = 35$ (see Figure 37). When social support was split according to the source of support, there was no significant relationship with social support from the social network, $r_s = -.19$, ns , $n = 37$, but a significantly negative relationship with social support from the hospital staff, $r_s = -.30$, p (one-tailed) $< .05$, $n = 35$.

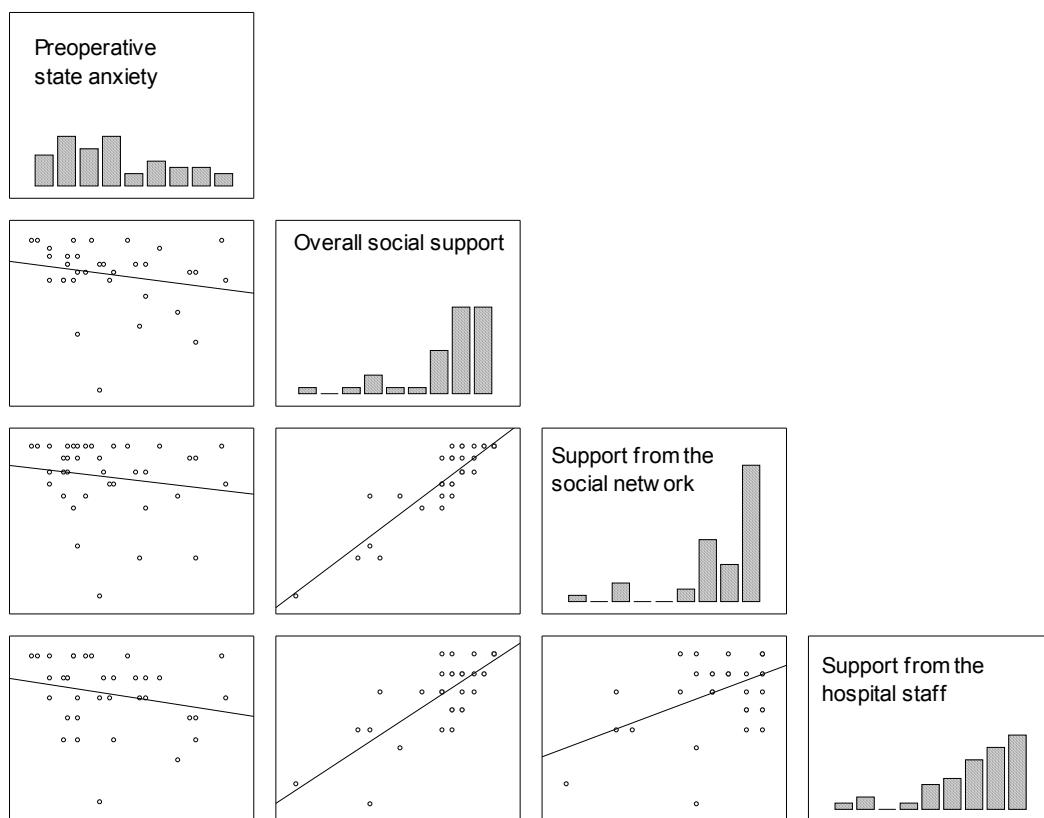


Figure 37. Matrix scatterplot of preoperative state anxiety, overall social support, social support from the social network, and social support from the hospital staff.

There was no significant relationship between a patient's overall social support and postoperative state anxiety, $r_s = -.26$, ns , $n = 38$ (see Figure 38). When social support was split according to the source of support, there was no significant relationship with social support from the social network, $r_s = -.01$, ns , $n = 40$, but a significantly negative relationship with social support from the hospital staff, $r_s = -.49$, p (one-tailed) $< .01$, $n = 39$.

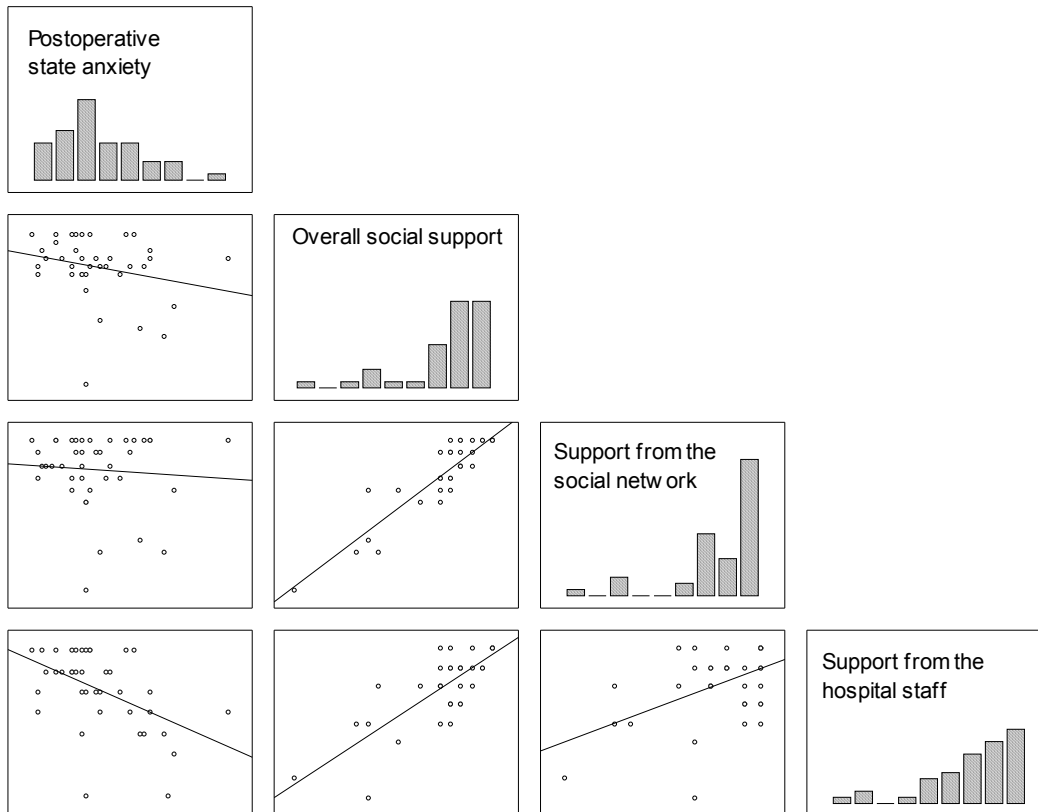


Figure 38. Matrix scatterplot of postoperative state anxiety, overall social support, social support from the social network, and social support from the hospital staff.

Additionally, gender differences in the patients' perceived social support were analyzed by using the Mann-Whitney test. There were no significant differences between male and female patients in overall social support, $U = 183.0$, ns , $n = 42$, social support from the social network, $U = 182.5$, ns , $n = 44$, and social support from the hospital staff, $U = 223.0$, ns , $n = 43$.

- Due to the non-normal distribution of three out of eight coping scales [recourse to personal resources, $D(36) = 0.18$, $p < .05$, belief, $D(38) = 0.26$, $p < .001$, and seeking social support, $D(36) = 0.15$, $p < .05$], the non-parametric Spearman correlation coefficient was used for testing all associations concerning coping. See Table 10 (p. 110) for descriptive statistics of all coping scales and preoperative state anxiety.

Negative relationships between the coping strategy optimism and trust and preoperative state anxiety, $r_s = -.45$, $p < .01$, $n = 32$, between recourse to personal resources and preoperative state anxiety, $r_s = -.59$, $p < .001$, $n = 32$, and between distraction and preoperative state anxiety, $r_s = -.35$, $p < .05$, $n = 32$, were found. Positive relationships between the coping strategy rumination and preoperative state anxiety, $r_s = .36$, $p < .05$, $n = 32$, and between seeking social support and preoperative

state anxiety, $r_s = .37$, $p < .05$, $n = 32$, were found. No significant relationships between the coping strategy information seeking and preoperative state anxiety, $r_s = -.01$, ns , $n = 32$, between belief and preoperative state anxiety, $r_s = -.15$, ns , $n = 33$, and between downward comparison and preoperative state anxiety, $r_s = -.26$, ns , $n = 33$, were found. (See Figure 39, Figure 40, and Figure 41)

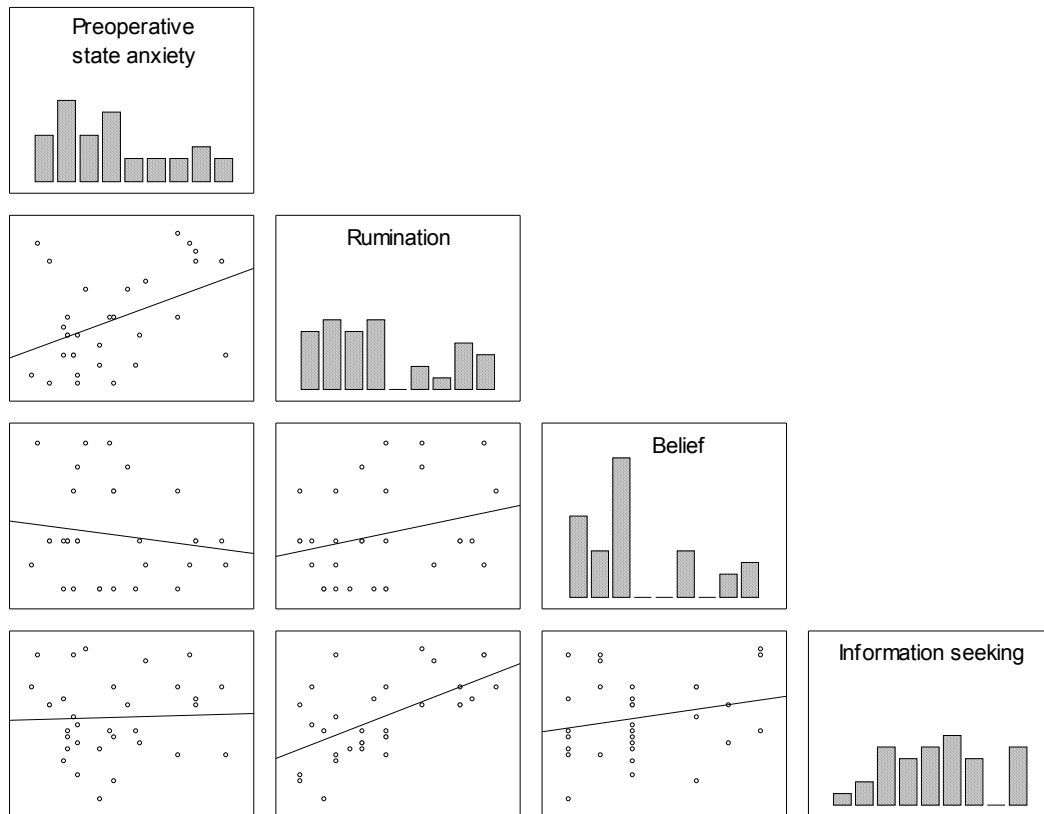


Figure 39. Matrix scatterplot of preoperative state anxiety and the coping strategies information seeking, rumination, and belief.

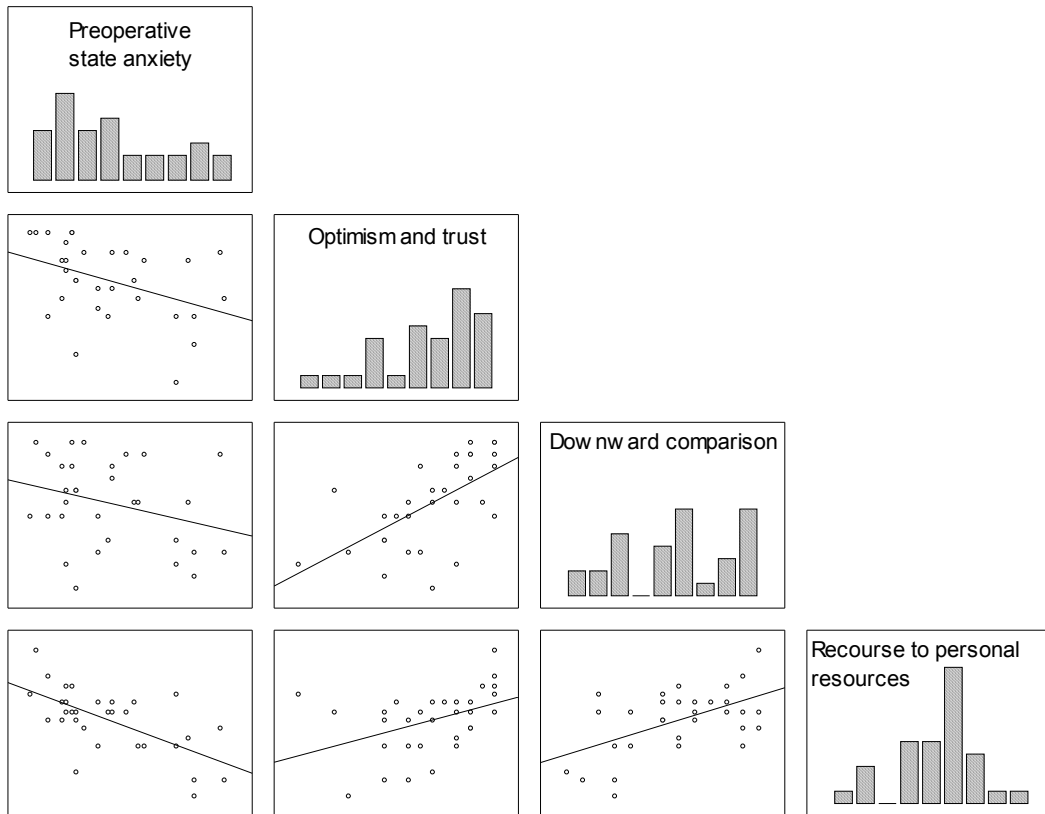


Figure 40. Matrix scatterplot of preoperative state anxiety and the coping strategies optimism and trust, downward comparison, and recourse to personal resources.

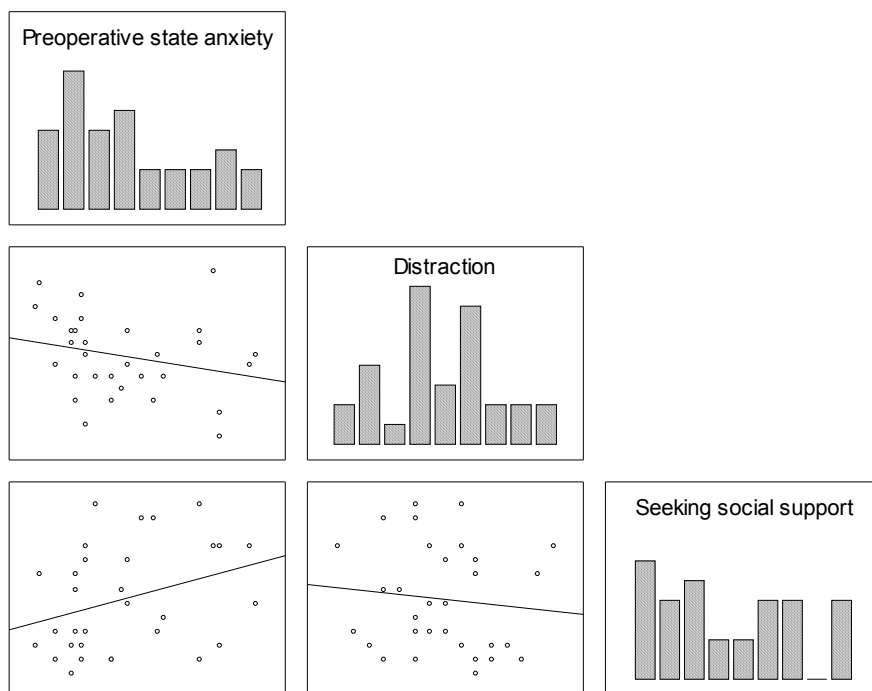


Figure 41. Matrix scatterplot of preoperative state anxiety and the coping strategies distraction and seeking social support.

The Mann-Whitney test was used to test for differences in the use of specific coping strategies according to gender. There were no significant differences in either of the coping strategies between male and female patients: rumination, $U = 130.0$, *ns*, $n = 36$, optimism and trust, $U = 146.0$, *ns*, $n = 36$, downward comparison, $U = 163.5$, *ns*, $n = 37$, recourse to personal resources, $U = 142.5$, *ns*, $n = 36$, belief, $U = 173.0$, *ns*, $n = 38$, distraction, $U = 129.0$, *ns*, $n = 36$, seeking social support, $U = 129.5$, *ns*, $n = 36$, and information seeking, $U = 142.5$, *ns*, $n = 36$.

4 Discussion

4.1 *HRV in the Perioperative Course of CEA and CAS*

In order to investigate the stress response and the impact of the interventions on patients' HRV, HRV was monitored pre-, intra- and postoperatively and analyzed with regard to changes over time from the pre- to the postoperative period, differences between the two treatment groups, and possible interactions of time and type of treatment as the main hypotheses (see sections 3.2.1 and 3.2.2).

In line with the hypotheses, analysis of variance for repeated measures reveals significant interaction effects of time (pre – post) and intervention (CEA – CAS) for SDNN, rMSSD, and TP: While all patients show rather similar SDNN values preoperatively, patients undergoing CAS show an increase and patients undergoing CEA a decrease postoperatively (the post hoc test reveals significant differences for the CAS treatment group between the pre- and postoperative time, and significant differences between the CAS and CEA treatment groups at the postoperative time). While patients undergoing CAS show smaller rMSSD values preoperatively compared to patients undergoing CEA, the former treatment group shows an increase, whereas the latter group shows a decrease postoperatively (post hoc tests, however, reveal no significant differences). While patients undergoing CAS show slightly higher TP values preoperatively compared to patients undergoing CEA, the former treatment group shows an increase, whereas the latter group shows a decrease postoperatively (the post hoc test reveals significant differences only between the CEA and CAS treatment groups at the postoperative time).

Contrary to the hypotheses, no interaction effects are found for pNN50, LF, LF (nu), HF, HF (nu), and the LF/HF ratio.

Significant main effects of treatment are found for TP, the LF/HF ratio, and HF (nu): TP and LF/HF ratio values of patients undergoing CAS are constantly higher at the pre- as well as postoperative time compared to patients undergoing CEA, whereas

HF (nu) values of patients undergoing CEA are constantly higher at the pre- as well as postoperative time compared to patients undergoing CAS.

Taken together, the results demonstrate that HRV parameters are affected differently by the medical interventions and have differing specificity and sensitivity. As hypothesized, CAS brings about generally increased HRV in the postoperative period. Descriptive statistics show that practically all parameters with the exception of HF (nu) increase slightly or even considerably from the pre- to the postoperative time period (with the only significant effect for SDNN). Whether also a shift to parasympathetic predominance occurs cannot easily be answered. On the one hand, the increases in rMSSD and pNN50 indicate short-term changes in HRV that reflect predominantly vagally mediated alterations in autonomic tone. Both parameters have been shown to be highly correlated with the HF component, which also increases in the present sample. The significantly increased SDNN parameter and TP indicate generally increased HRV. The simultaneous increases in LF, LF (nu), and the LF/HF ratio, on the other hand, are difficult to interpret. The LF component of HRV, as previously described, is modulated by sympathetic as well as parasympathetic activity and is subject to many more influences. In this regard, the contribution of baroreceptors to the oscillations in the LF band might play an important role. Consistent with the hypotheses, CEA seems to result in decreased HRV, as shown by a (not significant) postoperative decrease in all investigated parameters with the exception of HF and HF (nu). It is, again, difficult to find reasons for the diminished HRV observed in patients after CEA. Possibly, primarily vagal withdrawal as well as high levels of sympathetic input contribute to a decrease in HRV. Concerning main effects of treatment, patients undergoing CAS show higher TP pre- and postoperatively, thus indicating generally more HRV compared to the CEA group. The constantly higher HF (nu) and lower LF/HF ratio values in patients undergoing CEA, however, indicate more variability in the high frequency range and thus generally high vagal activity in the CEA treatment group.

With regard to CAS, the findings of Yakhou et al. (2006) could not fully be replicated, as the HF component of HRV in the present sample slightly increased, but the LF/HF ratio did not decrease, but rather slightly increase. Concerning CEA, these authors found no changes in HRV parameters.

The results concerning CEA are in line with the findings of Sigaucho-Roussel et al. (2002) who observed a significant reduction in HRV when comparing preoperative values with those six weeks later in patients after CEA. Moreover, just as in the present sample, they observed significantly higher LF (nu) compared to HF (nu) values

preoperatively and two days after the surgery, pointing to a sympathetic predominance. These markedly higher LF (nu) values compared to HF (nu) values can be found in both patient groups in the pre- and postoperative time period. One can speculate that the preoperative values reflect stress before surgery, whereas the postoperative values reflect the impact of the surgery. Demirci et al. (2006) also observed distinct influences of CEA and CAS on cardiac autonomic balance. Their findings of increased nLF, decreased nHF, and increased LF/HF ratio – all pointing to a shift towards sympathetic predominance – after CEA cannot be replicated in this sample (nLF and nHF: LF and HF were normalized to TP, thus they can't be compared one-to-one to the normalized units). The opposite effect for CAS in terms of a decrease of nLF, an increase in nHF, and a decrease of the LF/HF ratio – all pointing to a shift towards parasympathetic predominance – can also not be found in the present sample. One has to bear in mind, though, that Demirci et al. (2006) compared the values of HRV parameters one day before the treatment to those one, two, and three days afterwards, whereas the present study compares the values immediately before the treatment with those five hours afterwards. The different time frames could possibly yield differing results.

As pointed out before, only some parameters demonstrate significant changes from the pre- to the postoperative period, whereas others do not. Apart from TP, only time domain parameters display significant changes, whereas frequency domain parameters in the low and high frequency range don't change significantly.

4.2 *Correlations between HRV and Anxiety*

To investigate whether HRV can be used as a sensitive indicator for state and trait anxiety, correlations between different HRV parameters and subjective ratings were analyzed (see section 3.2.3). For this analysis, the preoperative HRV-recordings of the time when patients were filling in the respective questionnaires were evaluated (mean of 1h).

Although the hypothesis of a negative relationship between patients' trait anxiety and parameters of HRV that are indicative of high variability and high parasympathetic activity [SDNN, rMSSD, pNN50, HF, HF (nu), and TP] can't be accepted, the correlation coefficients all show small to medium effects in the hypothesized direction, though never reaching statistical significance. The same applies to the hypothesized positive relationship between patients' trait anxiety and parameters of HRV that are indicative of increased sympathetic activity [LF, LF (nu), and LF/HF ratio], with small but not statistically significant positive correlation coefficients for LF (nu) and the LF/HF ratio, but, interestingly, a small but not statistically significant negative correlation

coefficient for LF. The contrary results concerning LF and LF (nu) underline the differing informative value of both parameters.

Similarly, the hypothesis of a negative relationship between preoperative state anxiety and parameters of HRV that are indicative of high variability and high parasympathetic activity is not accepted with the exception of pNN50. Although again, all correlation coefficients show small to medium effects in the hypothesized direction, only pNN50 reaches statistical significance and thus proves to be an especially sensitive indicator of state anxiety. The hypothesis of a positive relationship between patients' preoperative state anxiety and parameters of HRV that are indicative of increased sympathetic activity is not accepted with the exception of LF (nu). Whereas the LF/HF ratio shows a medium effect in the hypothesized direction without reaching statistical significance, LF shows no relationship with state anxiety at all, so it once again produces contrary results to LF (nu). The LF component of HRV expressed in normalized units thus seems to be an especially sensitive indicator of state anxiety. Taken together, the more preoperative state anxiety a patient reports, the lower pNN50 and the higher LF (nu) values he has.

Taken together, the results support the assumption of associations between HRV and anxiety, although only a few findings reach statistical significance. The few significant findings could be, amongst other factors, due to the small sample size in this analysis. The findings nevertheless show the pattern of decreased variability, reduced vagal component of HRV, and at the same time increased sympathetic activity in case of anxiety. Friedman (2007; 1998) also found such a pattern of reduced HRV and reduced vagal tone in patients suffering from anxiety disorders in several studies. The findings are, moreover, consistent with those of Watkins et al. (1998) who reported significantly reduced vagal control of the heart (as measured by RSA) in individuals scoring high in trait anxiety. Jönsson (2007), on the other hand, did not find any correlation between trait anxiety and RSA in a sample of healthy individuals. In opposition to the present findings, he observed a significantly positive correlation between state anxiety and HF power. One has to consider, though, that his subjects were tested for a very short period in a laboratory situation without any external stressors and can thus not easily be compared with patients suffering from state anxiety due to impending surgery. Like Jönsson (2007), Dishman et al. (2000) reported no significant association between trait anxiety and any HRV parameter, but an inverse relationship between perceived emotional stress during the past week and HF (nu) in a sample of healthy adults.

The results, moreover, underline the importance of considering different HRV parameters as indicators of stress or negative affect. In the present sample, the normalized units of LF and HF [LF (nu) and HF (nu)], pNN50, and rMSSD seem to be especially sensitive. Additionally, the differing results with regard to LF in absolute and in normalized units are of interest. These findings are, for example, in line with those of Lucini et al. (2005) who reported significantly higher LF (nu), LF/HF ratio, and smaller HF (nu) values in highly stressed individuals compared to a control group and significant correlations of the parameters expressed in normalized units with subjective ratings of stress. Likewise, Dishman et al. (2007) found a significant correlation only between perceived stress and HF expressed in normalized units. Generally, HRV parameters seem to be more sensitive for state than for trait anxiety.

4.3 *Psychological Variables in the Perioperative Course of CEA and CAS*

The investigations of physiological stress reactions and the impact of CEA and CAS on HRV were supplemented by a focus on the patients' subjectively perceived stress associated with the medical procedures, the course of anxiety in the perioperative period, the resource social support, and coping strategies in the preoperative period.

4.3.1 *Perceived Medical Intervention Stress and Anxiety*

Concerning the experience of the intraoperative situation (see section 3.3), the two patient groups experience the medical interventions as similarly stressful. Out of 23 items, there are significant differences only with regard to four items: the CAS patient group experiences the communication with the medical staff as less calming, they experience the operating room as less alarming, they are less able to relax during the procedure, and they express a little bit less trust in the medical staff. The difference in the perception of the operating room can be explained by the fact that the intervention room, which is used for CAS, might seem less frightening than the "real" operating room. The other differences could be due to the fact that an anesthesiologist monitors the patient throughout the CEA procedure, even when only LA is administered. As this doctor sits right beside the patient, it might enhance communication and increase trust in the medical staff. The reassuring effect of someone attending especially to the patient throughout the procedure was also reported by McCarthy et al. (2004).

These empirical findings contradict the hypothesis of a more stressful experience of CEA compared to CAS. They could at least partly be explained by the increased use of sedatives during the surgical procedure. Therefore the differences in the perception of the longer and more invasive surgery might be blurred, while patients of the CAS

group experience the whole procedure more clearly and consciously. The duration of the medical intervention was considered as a possibly confounding factor, but correlation analysis reveals no significant relationship between the duration of the intervention and its stress. Additionally, no effect of gender on the intervention's stress is found. The impact of sedatives on a patient's perception of the intervention can, however, not be evaluated in the context of the present study.

It is moreover worth mentioning that both procedures are experienced as stressful only to a small extent, meaning that patients are able to deal with them very well and don't regard them as very frightening or stressful procedures. Patients are satisfied with many aspects related to the intraoperative experience, like their level of information and education concerning many aspects, communication, trust in the medical staff, feelings of security, aspects of the operating room and medical equipment, and experience of pain. An optimistic and trustful attitude towards the doctors and the medical treatment was also observed by Jordan (1992) in his investigation of patients after PTCA. He speculated that the high satisfaction with and trust towards the doctors in spite of only little direct communication was facilitated by the patients' transference ability (transference of deep trust towards important persons to doctors in the hospital situation), idealization of the doctors, temporary regression, ability to relax and to withdraw in a narcissistic way, narcissistic interpretation of affect- and self-control ("heroism"), identification with the doctors due to the conscious witnessing of the procedure, and, possibly, processes of denial. Taken together, these and other factors contribute to the finding that patients do rather effectively cope with the surgery and do not necessarily regard it as a negative or stressful experience. The patients' rather positive perceptions of both medical interventions are furthermore consistent with the findings of McCarthy et al. (2004), Quigley et al. (2000), and Barnason and Rasmussen (2002). Moreover, the need for information (also intraoperatively), a factor Jordan (1992) identified as important, seems to have been satisfied in the present investigation.

One has to consider, though, that the patients rated their intraoperative experience retrospectively and thus might see the medical interventions and rate their experience differently afterwards. Intraoperative ratings could, however, also raise difficulties as they are even more prone to factors of influence, such as the impact of sedatives or social desirability when answering the questions directly to a doctor.

The positive relationship between trait anxiety and the reported stress associated with the medical intervention is also of interest. It could be caused by a focus on threatening aspects of the intraoperative situation by highly anxious patients. This

finding is once again of practical relevance, as a screening for trait anxiety in the preoperative period might help in identifying those individuals high in anxiety, who could then profit a lot from brief interventions aiming at a reduction in anxiety and stress and the development of effective coping strategies for the perioperative period.

Moreover, the reported stress associated with the medical intervention correlates positively with state anxiety in the postoperative period. No statement concerning causality can be made, so either patients who have had a stressful experience might still feel uneasy and anxious shortly after the procedure, or those patients generally high in trait and state anxiety experience the procedure as more frightening.

As mentioned before, a reduction in anxiety is not only of importance with regard to the patients' well-being, but also with regard to a possible reduction in sedatives needed in the perioperative period and with regard to effects on health and recovery.

Consistent with the patients' satisfaction regarding the intraoperative experience, the whole sample rates their current well-being and health status as better shortly after the procedure than before (see section 3.1).

4.3.2 *State and Trait Anxiety*

With regard to anxiety, the patients of the present study are preoperatively characterized by rather high state anxiety levels, which significantly decrease shortly after the medical intervention or surgery (see section 3.4). These results are in line with many empirical findings which all indicated heightened anxiety before and a quick reduction in anxiety after surgery (de Groot, et al., 1996; Duits, et al., 1998; Gauter-Fleckenstein, et al., 2007; Karanci & Dirik, 2003; Krohne, 1992; Krohne, de Bruin, et al., 2000; Krohne, et al., 2003; Krohne, et al., 2005; Slangen, et al., 1993). The high preoperative state anxiety levels mainly reflect negative feelings of uneasiness, strain, and fear, and unspecific or specific worries related, for instance, to anesthesia, the procedure itself, its outcome, and the subsequent recovery. Moreover, the patients' situation is characterized by significantly reduced behavioral control and predictability of important situational factors (e.g. exact time or outcome of the procedure), which again contribute to increased anxiety. The fast decline in anxiety presumably reflects the relief that the surgery is over and successfully completed and – due to the very few incidences of perioperative complications or side-effects – the patients' good state of health after surgery. As the patients normally recover quickly and stay in hospital only for a couple of days, they can look ahead rather optimistically and free of anxiety.

Furthermore, as also reported in the literature (e.g. Kain, et al., 2000; Krohne, de Bruin, et al., 2000; Krohne, et al., 2005), the degrees of preoperative as well as

postoperative state anxiety are associated with the degree of trait anxiety, in the sense that the more trait anxiety a patient reports before surgery, the more state anxiety he or she experiences shortly before and shortly after surgery. Thus, a person who habitually experiences lots of anxiety is also prone to react anxiously in stressful situations, such as the perioperative period, whereas habitually low anxious people usually show low levels of state anxiety.

The often reported findings of higher anxiety levels in women compared to men (e.g. Duits, et al., 1998; Jordan, 1992; Karanci & Dirik, 2003; Krohne, et al., 2005; Krohne & Slangen, 2005) cannot be replicated in the present patient sample (see section 3.4). On the contrary, male and female patients are very similar with regard to preoperative and postoperative state anxiety levels. In general, no gender differences are found in any psychological variable in the present patient sample.

These findings are of practical importance, as trait and/or state anxiety questionnaires might be useful for screening for patients who are likely to or already do demonstrate high levels of anxiety. If those individuals are identified at an early stage (e.g. shortly after admittance to the hospital), psychological interventions (e.g. counseling or relaxation techniques) could aim at preventing or reducing distress and anxiety (see for example Krohne, et al., 2005). This, in turn, could prevent detrimental effects of anxiety on the patient's physical health, subjective well-being, perioperative adaptation, and recovery from any kind of medical intervention or treatment (Broadbent, et al., 2003; de Groot, et al., 1996; Kain, et al., 2000; Krohne & Slangen, 2005; Linn, Linn, & Klimas, 1988; Maranets & Kain, 1999; Pearson, et al., 2005).

4.3.3 *Social Support and Anxiety*

Regarding social support, negative associations between perceived social support – according to the source of support – and preoperative and postoperative state anxiety are found (see section 3.4.1). When looking at the source of support, no associations exist between social support from the network and state anxiety, but negative associations exist for support provided by the hospital staff (above all doctors, nurses, and caregivers). Thus, the more support patients perceive from the hospital staff, the less anxiety they experience pre- and postoperatively. In the present sample, no gender differences are found with regard to perceived social support, although other researchers have identified differences in the perceived availability of support between men and women (Krohne, et al., 2003; Krohne & Slangen, 2005).

Karanci and Dirik (2003) also found no association between perceived social support and preoperative anxiety, possibly because they did not consider support

provided by the hospital staff. These findings emphasize the importance of taking into account different sources (e.g. social network versus experts) and types of support (such as emotional, informational, and instrumental), as they might all contribute to different outcomes, like subjective well-being, in a distinct way. The EISOP (Krohne, et al., 2003; Krohne & Slangen, 2005) is an example for such a questionnaire that distinguishes various types and sources of support and, moreover, focuses on the specificity of the perioperative situation.

Again, these findings are of practical relevance, as a supportive attitude on the part of the hospital staff might help in preventing or reducing high levels of anxiety and stress and the associated detrimental effects on health and well-being in the perioperative period. High levels of support have shown to be associated, for example, with less postoperative pain, a better perioperative health status, better wound healing, and a shorter postoperative stay in hospital (Krohne, et al., 2003; Krohne & Slangen, 2005). Special attention should be paid to those patients not married or currently in a relationship, as they probably have less support from the social network available and could thus profit a lot from support on the part of the hospital staff. Consistent with the assumption of a stress-buffering role of social support, both informational (e.g. concerning the hospital routine) as well as emotional (e.g. comforting) support are perceived as helpful and are related to less anxiety and stress – in this patient sample as well as in the literature (e.g. Krohne & Slangen, 2005).

4.3.4 *Coping Strategies and Anxiety*

Concerning coping styles in the preoperative period (see section 3.4.1), information seeking (e.g. efforts to inform oneself of the medical treatment, weighing pros and cons of treatment possibilities) and belief (e.g. trust in god) are not associated with state anxiety in the preoperative period, although this vigilant coping style and hold in religion/belief have shown to be related to anxiety (see for example Krohne, et al., 2005). Krohne, de Bruin, et al. (2000), however, also found no relationship between the search for information and different components (somatic, autonomic, and cognitive) of state anxiety. Additionally, the strategy downward comparison (e.g. thinking of the fact that others are worse off) is not related to preoperative state anxiety. Avoidant coping such as distraction (e.g. not thinking about the surgery, distraction by reading or watching TV) is negatively related to state anxiety. Likewise, the employment of strategies such as recourse to personal resources (e.g. staying calm, humor) and optimism and trust (e.g. trust in doctors, thinking positive, feeling safe) are negatively associated with anxiety. Rumination, however, (e.g. worrying about the treatment, possible side-effects, the anesthesia, recovery) is positively associated with anxiety. In

line with the findings of Krohne, de Bruin, et al. (2000), seeking social support (e.g. seeking support from friends, talking about one's burdens) is also positively associated with anxiety. It can be hypothesized that very anxious patients turn to social support in order to deal with their stress and anxiety. In line with the above mentioned finding that only support from the hospital staff is associated with reduced anxiety, merely support from family and friends or talking about one's worries concerning surgery, anesthesia et cetera with other patients does not effectively reduce anxiety. The feeling of being supported by the hospital staff, however, seems to have an anxiety-reducing effect. Moreover, the findings point out that an optimistic and trustful attitude, the recollection of one's strengths such as humor, as well as the belief that others are worse off and that one has already managed or been through worse situations in life, are all negatively associated with anxiety in the preoperative period. Similarly, distracting oneself and not thinking about the surgery and anesthesia are negatively associated with anxiety, whereas worrying about everything and seeking information are positively related to anxiety. The findings concerning coping in the preoperative period are consistent with those of Krohne et al. (1992; Krohne, de-Bruin, et al., 2000; Krohne, et al., 2005), who also found rumination to be associated with high anxiety and cognitive or threat avoidance, recourse to personal resources, and optimism and trust to be associated with low anxiety levels. Besides, the two groups of patients did not differ in their coping styles, and no gender differences were found in this sample, although Krohne, de Bruin, et al. (2000) and Slangen et al. (1993), for example, observed differences in the use of coping strategies between men and women.

From a practical point of view, the findings suggest that interventions for patients awaiting surgery should focus on their strengths and resources and help them to establish a positive, trusting, and self-confident attitude. As the patients find themselves in a situation of restricted behavioral control, they have limited instrumental influence, but have the possibility to change their situational appraisal and their emotions and can thus influence the level of stress they experience. A supportive attitude on the part of the medical staff can further enhance the patients' feelings of comfort, safety, and confidence and thus reduce anxiety. It seems adverse, however, to give patients too much detailed information and therewith maybe initiate worries and further information seeking. The use of a coping inventory like the COSS (Krohne, de-Bruin, et al., 2000), which focuses on the actual coping strategies employed in the presurgical situation, can be helpful in identifying patients' actual ways of coping. As a consequence, interventions in the preoperative period could focus on the encouragement of strategies that have proven to be related to reduced anxiety and at the same time a reduction in coping attempts that have shown to be related to

increased levels of anxiety. Nonetheless, all interventions should consider the individual patient's preference for certain ways of coping as well as the respective situational circumstances (e.g. type of surgery/treatment, severity of the disease, or probable postoperative outcome).

4.4 *Limitations of the Present Study and Future Perspectives*

There are some constraints of the present study that should be addressed. One limitation concerns the non-random allocation of patients to the two treatment groups. Randomization, however, wouldn't have been feasible, as the best treatment for each individual patient can only be guaranteed by individually deciding on the best alternative for each patient based on characteristics of the disease, the patient's anatomy, risk factors, and the patient's preference, amongst other factors. Moreover, this grouping goes along with high ecological validity as it mirrors the real clinical practice. Likewise, patients were practically not preselected, but all patients not simultaneously suffering from a life-threatening disease came into consideration for participating in the study. Furthermore, concomitant medications might have had an influence on HRV values in both groups. Practically all patients suffered from medical conditions necessitating drugs, such as hypertension or diabetes. Due to the multiple administration of drugs, their individual impact could not be evaluated and considered as confounding factors in the statistical analyses. Thus, once again, the study did not influence clinical practice and all patients were maintained on their normal and – after surgery – revised schedule of medication. Another point of criticism concerns subjective ratings in general. As widely known, they can be subject to various biases and the problem of social desirability raises the question of whether all items were answered honestly. Despite their disadvantages, questionnaires nevertheless provide a valuable source of information that cannot easily or economically be gathered otherwise.

As high HRV, specifically high vagal and low sympathetic activity, is important with regard to possible associations between HRV and morbidity (e.g. hypertension or CHD) and mortality, any medical intervention should positively affect ANS modulation of HR. The findings of the present study show an interaction between the type of intervention and changes in the HRV parameters over time (from the pre- to the postoperative period), in the form of increased HRV after CAS and decreased HRV after CEA. However, inferences have to be drawn with caution as, firstly, only a small time span was analyzed (shortly before the intervention until five hours after the end of the intervention) and thus conclusions can only refer to short-term effects of the treatments. Secondly, the present study did not control for a possible influence of

medication on HRV parameters. Patients were maintained on their normal or revised schedule of medication and the HRV-recording periods for analysis were chosen amongst others in consideration of the administration and effective period of drugs. Thus, whereas the present study gives an overview of short-term physiological changes in HRV parameters in response to CEA and CAS, many interesting questions still remain unanswered.

Future research could, for example, address possible long-term effects of the two procedures and investigate not only the pre-, intra-, and early postoperative period, but also carry out follow-up investigations, which were, unfortunately, not possible in the present study. It would also be interesting to pay more attention to the intraoperative situation and to give a detailed picture of the changes in HRV parameters occurring at different stages of the procedures. For this analysis, however, the impact of any pre- or intraoperatively administered medication should be accurately evaluated. Future research could also simultaneously assess blood pressure, baroreceptor activity, and HRV, in order to be able to describe the physiological alterations during and after the procedures more thorough or even identify the causes of changes. With regard to the subjective experience of stress and anxiety, it would be interesting to try to replicate the finding of practically no difference in the perception of CEA and CAS. One could, for example, take external factors such as the administration of sedatives and the attention a patient receives from the medical staff during the procedure into account, in order to identify mediators of the perceived stress associated with the procedures. This, in turn, might assist in increasing patients' compliance during the intraoperative situation, increasing their subjective well-being, and decreasing state anxiety, all important factors concerning perioperative adaptation and postoperative recovery.

4.5 Conclusion

Despite all the still pending questions, the present investigation nevertheless sheds light on distinct patterns of change in parameters of heart rate variability (HRV) in response to the two alternative procedures for achieving revascularization in patients with carotid artery stenosis. A clear effect of intervention on physiological parameters is confirmed: increased HRV in the early postoperative period after carotid artery stenting (CAS) and decreased HRV after carotid endarterectomy (CEA) are observed. From the subjective point of view, the medical interventions are perceived as rather equally stressful and patients show signs of relief in terms of significantly reduced anxiety afterwards. When looking at the relation between physiological and psychological variables, a notable pattern of reduced HRV, decreased vagal, and increased sympathetic modulation of the heart in anxiety is identified. State anxiety is positively

associated with trait anxiety and negatively with social support. The coping strategies optimism/trust, recourse to personal resources, and distraction are negatively, rumination and seeking social support positively, and information seeking, belief, and downwards comparison are not related to preoperative state anxiety.

ABSTRACT

Against the background of a psychophysiological stress model, physiological and subjective stress responses of patients with high-grade carotid artery stenosis undergoing either carotid endarterectomy (CEA), a surgery under local anesthesia, or carotid artery stenting (CAS), a minimally-invasive intervention, for revascularization were investigated. In a sample of 52 patients (two comparable groups: CEA: $n = 28$; CAS: $n = 24$) aged 69 ± 10 years, heart rate was recorded throughout the perioperative period and psychological questionnaires (STAI X1, STAI X2, COSS, EISOP-modified, Perceived Medical Intervention Stress) were filled-in. Time- and frequency domain parameters of heart rate variability (HRV), illustrating the autonomic nervous system's modulation of heart rate, were then calculated. In both treatment groups HRV values shortly before the interventions were compared with those 5h afterwards. As hypothesized, a 2×2 repeated measures ANOVA revealed intervention $\times$ time interactions: HRV increased after CAS and decreased after CEA (significant for the HRV parameters SDNN, rMSSD, and TP; not significant for pNN50, HF, HF (nu), LF, LF (nu), and LF/HF ratio). HRV parameters showed the expected pattern of reduced HRV and vagal activity in high anxiety (pNN50 correlated significantly negatively and LF (nu) positively with preoperative state anxiety). Contrary to the hypothesis, no difference in the perceived stress associated with the medical interventions was found, but the intervention's stress was related to trait and postoperative state anxiety. State anxiety was higher in the preoperative than in the postoperative period and was positively associated with trait anxiety and negatively with social support. The coping strategies optimism/trust, recourse to personal resources, and distraction were negatively, rumination and seeking social support positively, and information seeking, belief, and downwards comparison were not related to preoperative state anxiety.

ZUSAMMENFASSUNG

Vor dem Hintergrund eines psychophysiologischen Stressmodells wurden subjektive und physiologische Stressreaktionen von Patienten mit hochgradigen Karotisstenosen, die sich unter Lokalanästhesie einem chirurgischen (TEA: Thrombendarteriektomie) oder minimal-invasiven Kathetereingriff (Stent-PTA: stentgeschützte perkutane transluminare Angioplastie) zur Revaskularisation unterzogen, untersucht. In einer anfallenden Stichprobe von 52 Patienten (zwei vergleichbare Gruppen: TEA: $n = 28$; Stent-PTA: $n = 24$) mit einem Alter von 69 ± 10 Jahren wurden psychologische Fragebögen (STAI X1, STAI X2, COSS, EISOP-modified, Perceived Medical Intervention Stress) vorgegeben sowie die Herzrate prä-, intra- und postoperativ aufgezeichnet. Verschiedene Parameter (Time und Frequency Domain) der Herzratenvariabilität (HRV) wurden berechnet, die Aufschluss über die Modulation der Herzrate durch das autonome Nervensystem geben. Für beide Behandlungsgruppen wurden HRV-Werte unmittelbar vor den Eingriffen mit jenen 5h nachher verglichen. Hypothesenkonform ergab eine 2×2 ANOVA mit Messwiederholung Eingriffsart $\times$ Zeit Interaktionen: es zeigte sich ein Anstieg der HRV nach der Stent-PTA und eine Verringerung nach der TEA (signifikant für die HRV Parameter SDNN, rMSSD und TP; nicht signifikant für pNN50, HF, HF (nu), LF, LF (nu) und LF/HF ratio) gefunden. HRV-Parameter zeigten das erwartete Muster von reduzierter HRV und parasympathischer Aktivität bei hoher präoperativer Angst (pNN50 korrelierte signifikant negativ und LF (nu) signifikant positiv mit präoperativer Zustandsangst). Entgegen der Hypothese zeigte sich kein Unterschied in der subjektiven Belastung zwischen den Eingriffsarten. Der Belastungsgrad hing mit habitueller Ängstlichkeit und postoperativer Zustandsangst zusammen. Die Zustandsangst sank wie erwartet nach den Eingriffen ab und zeigte positive Zusammenhänge mit habitueller Ängstlichkeit und negative mit sozialer Unterstützung. Die Coping-Strategien Optimismus/Vertrauen, Rückgriff auf persönliche Ressourcen und Ablenkung hingen negativ, Rumination und Suche nach sozialer Unterstützung positiv und Informationssuche, Glaube/Religion und Abwärtsvergleich nicht mit präoperativer Zustandsangst zusammen.

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APPENDIX A: QUESTIONNAIRES

1 Perceived Social Support (EISOP-modified)

A shortened and modified version of the German Emotional and Informational Support Scales – Operations (EISOP), which were developed by Krohne et al. (Krohne, et al., 2003; Krohne & Slangen, 2005), was used for assessing the patients' perceived available social support (see section 2.3.2).

Instruction: Bitte schätzen Sie Ihre Beziehungen in der momentanen Krankenhaussituation zum medizinischen Personal (Ärzte, Schwestern und Pfleger) und Ihren Angehörigen, Freunden oder Bekannten ein. Wie sehr treffen die folgenden Aussagen aktuell auf Sie zu?

☐ gar nicht ☐ etwas ☐ mittelmäßig ☐ ziemlich ☐ sehr

See Table A 1 for a list of all EISOP-modified items, Cronbach's alpha for each scale, and means and standard deviations for each scale and each item of the scales.

Table A 1. EISOP-modified items, Cronbach's alpha, means and standard deviations for each scale and each item of the scales.

EISOP-Scales	Item number	Item	α	N	Mean	SD
Overall perceived social support			.80	5	15.83	4.14
	01	In meinem Familien- oder Bekanntenkreis gibt es Menschen, die mich wieder aufrichten, wenn ich mir wegen des Eingriffs Sorgen mache, die mir Mut machen, wenn es mir schlecht geht und die sich um mich kümmern und mir helfen, solange ich im Krankenhaus bin.		42	3.24	1.17
	02	Ich habe Angehörige, Freunde oder Bekannte, die mich so mögen, wie ich bin und in deren Nähe ich mich wohl fühle.		42	3.48	0.92
	03	Wenn ich mehr über den Eingriffsverlauf, mögliche Komplikationen oder		42	3.07	1.20

EISOP-Scales	Item number	Item	α	N	Mean	SD
		Nebenwirkungen wissen möchte oder Fragen zum Krankenhausaufenthalt und -alltag (z.B. Telefon, Mahlzeiten) habe, gibt es hier in der Klinik Fachleute, die meine Fragen beantworten.				
	04	Wenn ich wegen des Eingriffs bedrückt bin, gibt es hier Ärzte, Schwestern oder Pfleger, die mir zuhören, mich aufmuntern, für mich da sind und denen ich meine Sorgen mitteilen kann.		42	3.10	1.01
	05	Ich habe Angehörige, Freunde oder Bekannte, an die ich mich mit Fragen zum Eingriff, zu möglichen Nebenwirkungen oder Komplikationen, zu Nachsorgemöglichkeiten (z.B. Kur) und zum Alltag im Krankenhaus (Telefon, Mahlzeiten etc.) wenden kann.		42	2.95	1.23
Social support from the social network			.82	3	9.73	2.82
	01			44	3.25	1.14
	02			44	3.48	0.90
	05			44	3.00	1.22
Social support from the hospital staff			.69	2	6.05	2.04
	03			43	3.02	1.23
	04			43	3.02	1.10

Note. α = Cronbach's alpha; N = number; SD = standard deviation.

EISOP-modified: Internal structure:

Principal-component analysis (PCA) was performed on the altogether 42 patients who completed the questionnaire. One factor with an eigenvalue greater than 1 (factor 1: 2.86), explaining 57.2% of the total variance, was identified. It constituted a global perceived social support scale, comprising both emotional and informational support from the social network and from the hospital staff. See Table A 2 for the correlation matrix, Figure A 1 for the scree plot, and Table A 3 for the component matrix.

Table A 2. Correlation matrix (Pearson's correlation coefficient) of all EISOP-modified items.

	Emotional support from the social network 01	Emotional support from the social network 02	Informational support from the hospital staff	Emotional support from the hospital staff	Informational support from the social network
Emotional support from the social network 01	1.00				
Emotional support from the social network 02	.62	1.00			
Informational support from the hospital staff	.29	.35	1.00		
Emotional support from the hospital staff	.44	.43	.48	1.00	
Informational support from the social network	.66	.56	.25	.52	1.00

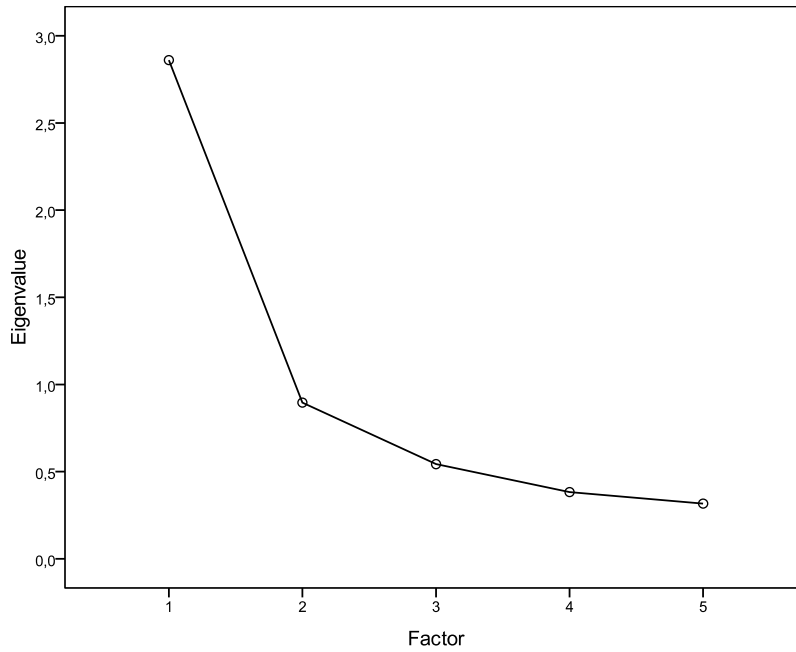


Figure A 1. Scree plot of the eigenvalues of the five EISOP-modified items.

Table A 3. Component matrix of all EISOP-modified items after Principal component analysis.

	Component 1
Emotional support from the social network 01	.818
Informational support from the social network	.814
Emotional support from the social network 02	.797
Emotional support from the hospital staff	.749
Informational support from the hospital staff	.576

In order to differentiate the source of support, a second PCA was performed with the instruction to extract two factors. As the factors were believed to be related, subsequent oblique rotation (oblimin with Kaiser normalization) was performed. After rotation, two factors with eigenvalues greater than 1 (factor 1: 2.65 and factor 2: 1.85) were identified. One factor comprised all three items relating to support from the social network, whereas the second factor comprised the two items relating to support from the hospital staff. See Table A 4 for the pattern matrix after PCA with oblique rotation.

Table A 4. Pattern matrix after Principal component analysis with oblique rotation.

	Component 1	Component 2
Emotional support from the social network 01	.902	-.048
Informational support from the social network	.879	-.023
Emotional support from the social network 02	.783	.083
Informational support from the hospital staff	-.105	.972
Emotional support from the hospital staff	.332	.626

2 Coping (COSS)

The Coping with Surgical Stress (COSS) questionnaire, which was developed by Krohne et al. (Krohne, de-Bruin, et al., 2000; Krohne, et al., 2005), was used for assessing the patients' preoperative coping strategies in the present study (see section 2.3.2).

Instruction: Sie liegen seit kurzem hier im Krankenhaus, um bald operiert zu werden. Es gibt nun verschiedene Möglichkeiten, wie Menschen mit einer solchen Situation umgehen. Uns geht es darum, etwas darüber zu erfahren, was Menschen in dieser Situation denken, tun oder fühlen. Auf den nächsten Seiten sind verschiedene mögliche Gefühle, Gedanken und Verhaltensweisen aufgeführt. Wir bitten Sie nun, für jede Aussage anzugeben, ob diese für Sie persönlich jetzt, in der augenblicklichen Kliniksituation, zutrifft. Kreuzen Sie bitte an, ob die jeweilige Aussage im Augenblick *überhaupt nicht*, *ein wenig*, *ziemlich* oder *sehr* für Sie zutrifft.

See Table A 5 for a list of all COSS items, Cronbach's alpha for each scale, and means and standard deviations for the scales as well as each item per scale, and Table A 6 for the correlation matrix of all COSS scales.

Table A 5. COSS items, Cronbach's alpha, means and standard deviations for each scale and each item of the scales.

COSS-Scales	Item number	Item	α	N	Mean	SD
Information seeking			.89	9	23.47	6.60
	COSS_03	Ich befrage die Ärzte bei der Visite genau, wie es um mich steht		36	3.11	0.95
	COSS_09	Ich informiere mich über alle Vor- und Nachteile einer Operation		36	2.69	0.95
	COSS_13	Ich informiere mich über die längerfristigen Erfolgsaussichten meiner Operation		36	2.67	1.07
	COSS_22	Ich versuche zu erfahren, was bei der Operation/Narkose mit mir gemacht wird		36	2.81	1.12
	COSS_27	Ich informiere mich über den Ablauf der Operation		36	2.81	0.98
	COSS_35	Ich befrage die Ärzte über mein voraussichtliches Befinden nach der Operation		36	2.67	1.01
	COSS_40	Ich befrage die Ärzte zu den Risiken der Operation		36	2.69	1.04
	COSS_46	Ich informiere mich über den Alltag im Krankenhaus		36	2.14	0.96
	COSS_49	Ich informiere mich bei Patienten, die einen ähnlichen Eingriff hinter sich haben		36	1.89	0.92
Rumination			.84	9	16.92	5.15

COSS-Scales	Item number	Item	α	N	Mean	SD
	COSS_01	Ich stelle mir vor, was alles schief laufen könnte		36	1.78	0.76
	COSS_06	Ich spiele mögliche Komplikationen oder Folgen der Operation gedanklich durch		36	1.89	0.82
	COSS_11	Ich stelle mir vor, wie mein Leben aussieht, wenn die Operation nicht gut verläuft		36	1.94	0.92
	COSS_17	Ich mache mir Gedanken, ob die Ärzte mir auch nichts verschweigen		36	1.36	0.64
	COSS_19	Ich denke viel über den Eingriff nach		36	2.39	0.87
	COSS_25	Ich stelle mir den Ablauf der Operation in allen Einzelheiten vor		36	2.14	0.96
	COSS_34	Ich denke über die unangenehmen Dinge nach, die Bekannte im Krankenhaus schon erlebt haben		36	1.92	0.91
	COSS_38	Ich überlege mir, was wohl während der Narkose mit mir passiert		36	1.94	1.01
	COSS_48	Ich sehe die Zeit vor der Narkose vor meinen Augen ablaufen		36	1.56	0.88
Optimism and trust			.76	10	34.97	4.05
	COSS_02	Ich sage mir, dass ich mich in guten Händen befinde		36	3.61	0.69

COSS-Scales	Item number	Item	α	N	Mean	SD
	COSS_07	Ich denke daran, dass ich im Krankenhaus gut aufgehoben bin		36	3.61	0.65
	COSS_15	Ich sage mir, dass ich den Ärzten und dem Pflegepersonal vertrauen kann		36	3.67	0.68
	COSS_24	Ich sage mir, dass es nach der Operation stetig bergauf geht		36	3.14	1.02
	COSS_30	Ich denke, die Ärzte wissen, was sie tun müssen		36	3.83	0.45
	COSS_32	Ich denke an die Hilfe, die ich hier im Krankenhaus erhalte		36	3.47	0.81
	COSS_36	Ich versuche, das Positive an der Operation zu sehen		36	3.50	0.66
	COSS_41	Ich versuche, der Situation eine positive Bedeutung zu geben		36	3.08	0.77
	COSS_45	Ich denke mir, dass alles gut gehen wird		36	3.47	0.65
	COSS_51	Ich denke daran, dass so ein Eingriff hier zur Routine gehört		36	3.58	0.73
Downward_comparison			.89	4	11.27	3.54
	COSS_05	Ich denke daran, dass es Menschen gibt, denen es noch schlechter geht als mir		37	2.95	1.08
	COSS_21	Ich sage mir, dass es mir schon schlechter ging als jetzt		37	2.51	1.02

COSS-Scales	Item number	Item	α	N	Mean	SD
	COSS_23	Ich sage mir, dass andere ein ähnliches Schicksal erleiden müssen und damit fertig werden		37	2.62	1.11
	COSS_37	Ich sage mir, dass es noch schlimmere Schicksale gibt		37	3.19	0.88
Recourse to personal resources			.75	6	15.81	3.85
	COSS_08	Ich nehme die Situation mit Humor		36	2.42	1.03
	COSS_12	Ich bleibe ruhig und gelassen		36	2.83	1.08
	COSS_29	Ich sage mir, dass ich schon schlimmere Situationen durchgestanden habe		36	2.75	0.91
	COSS_44	Ich sage mir, dass ich im Vergleich zu anderen schneller wieder fit sein werde		36	2.81	0.89
	COSS_47	Ich sage mir, andere würden viel schlechter mit dieser Situation fertig werden		36	2.42	0.94
	COSS_50	Ich denke daran, dass ich besser als viele andere mit der Situation umgehen kann		36	2.58	0.91
Belief			.92	2	4.37	2.03
	COSS_04	Ich suche Halt in meinem Glauben		38	2.11	1.06
	COSS_18	Ich vertraue auf Gott		38	2.26	1.06
Distraction			.64	5	12.53	3.30

COSS-Scales	Item number	Item	α	<i>N</i>	<i>Mean</i>	<i>SD</i>
	COSS_20	Ich unterhalte mich mit meinen Mitpatienten oder meinem Besuch über andere Themen		36	2.50	1.03
	COSS_28	Ich denke so wenig wie möglich über das Operiertwerden nach		36	2.39	1.05
	COSS_31	Ich versuche, meine Gedanken auf etwas anderes als die Operation zu konzentrieren		36	2.44	0.97
	COSS_39	Ich lenke mich mit anderen Dingen ab, z.B. Zeitschriften, Bücher, Fernsehen, Rätseln		36	2.39	1.20
	COSS_42	Ich denke an angenehme Dinge		36	2.81	0.86
Seeking social support			.78	5	11.36	3.72
	COSS_10	Ich suche Zuspruch bei Personen, die mir nahestehen		36	2.64	1.18
	COSS_14	Ich versuche, durch das Gespräch mit anderen Menschen Mut zu gewinnen		36	2.08	1.00
	COSS_26	Ich suche Unterstützung bei Freunden		36	2.22	1.07
	COSS_33	Ich rede mit anderen darüber, wie es mir geht		36	2.19	0.82
	COSS_43	Ich spreche Ärzten und dem Pflegepersonal gegenüber das an, was mich belastet		36	2.22	0.99
Excluded item						
	COSS_16	Ich schlafe viel		39	2.18	0.79

Note. α = Cronbach's alpha; *N* = number; *SD* = standard deviation.

Table A 6. Correlation matrix (Spearman's rank order correlation) of all COSS scales.

	Rumi- nation	Opti- mism and trust	Downward compar- ison	Re- course to personal re- sources	Be- lief	Dis- traction	Seek- ing social support	Inform- ation seeking
Rumination	1.00							
Optimism and trust	-.14	1.00						
Downward comparison	.01	.51	1.00					
Recourse to personal resources	-.44	.47	.30	1.00				
Belief	.38	.16	.27	-.09	1.00			
Distraction	-.05	.24	.40	.37	-.09	1.00		
Seeking social support	.47	.03	.12	-.21	.43	-.19	1.00	
Information seeking	.64	.30	.39	-.18	.32	.22	.39	1.00

Note. Significant correlations are marked in bold.

3 Perceived Medical Intervention Stress

The self-developed questionnaire Perceived Medical Intervention Stress (see section 2.3.2) was used for assessing the patients' subjective experience of the intraoperative situation.

Instruction: Die folgenden Fragen beziehen sich auf Ihre Erfahrungen, Eindrücke und Ihr Befinden während des Eingriffs in der aktuellen Krankenhaussituation. Kreuzen Sie bitte an, ob die jeweilige Aussage *überhaupt nicht*, *ein wenig*, *ziemlich* oder *sehr* für Sie zutrifft.

See Table A 7 for a list of all items, means and standard deviations of each item and mean, standard deviation, and Cronbach's alpha for the scale perceived medical intervention stress.

Table A 7. Means and standard deviations of each item and mean, standard deviation, and Cronbach's alpha for the scale perceived procedure stress.

Scale	Item number	Item	α	<i>N</i>	Mean	SD
Perceived medical intervention stress			.81	23	39.77	7.70
	01	Ich hatte ausreichend Zeit, mich für den Eingriff zu entscheiden (reversely poled)		43	1.53	0.70
	02	Ich fühlte mich vor dem Eingriff ausreichend aufgeklärt (reversely poled)		43	1.35	0.53
	03	Ich empfand die Wartezeit vor dem Eingriff als belastend		43	2.05	0.72
	04	Ich empfand die Vorbereitung am Untersuchungstisch als belastend		43	1.56	0.73
	05	Ich empfand die körperliche Nähe der medizinischen Geräte als beunruhigend		43	1.63	0.79
	06	Ich fühlte mich ausreichend informiert über das Vorgehen während des Eingriffs (reversely poled)		43	1.40	0.62
	07	Ich fühlte mich während des Eingriffs sicher und geborgen (reversely poled)		43	1.84	0.81
	08	Der Eingriff wurde von mir als bedrohlich wahrgenommen		43	1.42	0.79

Scale	Item number	Item	α	N	Mean	SD
	09	Ich erlebte die Kommunikation mit dem medizinischen Personal als beruhigend (reversely poled)		43	1.67	0.78
	10	Ich empfand den OP/ Interventionsraum als beunruhigend		43	1.93	0.99
	11	Ich empfand den gesamten Eingriff als belastend		43	1.95	0.79
	12	Ich empfand das medizinische Personal als kompetent (reversely poled)		43	1.14	0.41
	13	Ich hatte Schmerzen während des Eingriffs		43	1.65	0.78
	14	Ich konnte mich während des Eingriffs entspannen (reversely poled)		43	2.74	0.76
	15	Ich hatte Vertrauen in das medizinische Personal (reversely poled)		43	1.33	0.52
	16	Ich erlebte unangenehme Körperempfindungen		43	1.51	0.77
	17	Ich hatte Angst vor Komplikationen		43	1.84	0.84
	18	Ich empfand das lange Liegen auf dem OP-Tisch als unangenehm		43	2.09	0.84
	19	Ich empfand die Hintergrundgeräusche als unangenehm		43	1.44	0.59

Scale	Item number	Item	α	N	Mean	SD
	20	Ich hatte das Gefühl, keine Kontrolle zu besitzen		43	1.70	0.99
	21	Ich empfand die eingeschränkte Bewegungsfreiheit als unangenehm		43	2.16	0.87
	22	Ich empfand das Betreten und Verlassen des OP durch das Personal als unangenehm		43	1.16	0.37
	23	Durch Ablenkung konnte ich die Belastung durch den Eingriff reduzieren		43	2.67	0.97

Note. α = Cronbach's alpha; N = number; SD = standard deviation.

4 General Questionnaire

The General Questionnaire (see section 2.3.2) was used for assessing sociodemographic and possibly confounding variables.

Allgemeiner Fragebogen

Name _____

Nr _____ Datum _____ Zeit _____ Eingriff _____

1. Alter: _____ Jahre

2. Körpergröße: _____ cm

3. Gewicht: _____ kg

4. Geschlecht: ☐ männlich ☐ weiblich

5. Personenstand: ☐ ledig ☐ verheiratet ☐ in Partnerschaft ☐ verwitwet
☐ geschieden ☐ getrennt

6. Wie leben Sie aktuell? ☐ alleine ☐ in Partnerschaft/ Familie/ Gemeinschaft
7. Welche Schulausbildung haben Sie?
- ☐ keinen Abschluss ☐ Hauptschulabschluss ☐ Lehre ☐ Meisterprüfung
- ☐ Matura ☐ Akademie/ Fachhochschule ☐ Universitätsabschluss
8. Sind sie derzeit berufstätig? ☐ ja Wenn ja: Beruf: _____
- ☐ arbeitslos ☐ im Ruhestand ☐ Haushalt führend
9. Trinken Sie Kaffee? ☐ gar nicht ☐ weniger als 1x täglich ☐ 1-2 x täglich
- ☐ 3- 4 x täglich ☐ 5-7 x täglich ☐ mehr als 7 x tägl.
10. Trinken Sie schwarzen od. grünen Tee? ☐ gar nicht ☐ weniger als 1x täglich
- ☐ 1-2 x täglich ☐ 3- 4 x täglich ☐ 5-7 x täglich ☐ mehr als 7 x tägl.
11. Trinken Sie Energiedrinks? ☐ gar nicht ☐ weniger als 1x täglich
- ☐ 1-2 x täglich ☐ 3- 4 x täglich ☐ 5-7 x täglich ☐ mehr als 7 x tägl.
12. Rauchen Sie?
- ☐ ja, täglich Wie viele Zigaretten durchschnittlich pro Tag ? _____
- ☐ ja, gelegentlich Wie viele Zigaretten durchschnittlich pro Monat ? _____
- ☐ nein
- ☐ nein, aber ich habe früher geraucht
13. Wann haben Sie aufgehört zu rauchen? ☐ ich habe nie geraucht ☐ ich rauche
- ☐ diese Woche ☐ vor 1 Woche - 1 Monat ☐ vor 1 Monat - 1 Jahr
- ☐ vor 1 Jahr - 3 Jahren ☐ vor über 3 Jahren ☐ vor über 10 Jahren
14. Leiden Sie aktuell unter einer Erkrankung? ☐ nein
- ☐ Koronare Herzkrankheit ☐ Bluthochdruck ☐ Diabetes mellitus
- ☐ Sonstiges: _____
15. Nehmen Sie zurzeit irgendwelche Medikamente ein? ☐ nein
- ☐ ja: _____
-

16. Hatten Sie bereits einen stationären Krankenhausaufenthalt?

- ☐ nein, noch nie ☐ ja, ein Mal ☐ ja, mehr als ein Mal

17. Wurden Sie schon einmal operiert?

- ☐ nein, noch nie ☐ ja, ein Mal ☐ ja, mehr als ein Mal

18. Was war während der letzten zwei Wochen die schwerste körperliche Aktivität, die Sie für mindestens 2 Minuten ausüben konnten?

- ☐ sehr schwer (z.B. schnelles Laufen oder Radfahren)
☐ schwer (z.B. langsames Joggen)
☐ mittel (z.B. schnelles Gehen)
☐ leicht (z.B. Gehen mit mittlerer Geschwindigkeit)
☐ sehr leicht (z.B. langsames Gehen)

19. Wie oft sind Sie körperlich aktiv bzw. treiben Sie Sport?

- ☐ täglich ☐ mehrmals die Woche ☐ mehrmals monatlich
☐ ein paar Mal im Jahr ☐ gar nicht

20. Für wie körperlich aktiv halten Sie sich im Vergleich zu anderen Menschen ihren Alters und Geschlechts?

- ☐ viel aktiver ☐ etwas aktiver ☐ gleich aktiv ☐ weniger aktiv
☐ viel weniger aktiv

21. Wie würden Sie Ihren *Gesundheitszustand im Allgemeinen* beschreiben?

- ☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ weniger gut ☐ schlecht

22. Wie würden Sie Ihren *aktuellen Gesundheitszustand* beschreiben?

- ☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ weniger gut ☐ schlecht

23. Wie würden Sie Ihr *Wohlbefinden im Allgemeinen* beschreiben?

- ☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ weniger gut ☐ schlecht

24. Wie würden Sie Ihr *aktuelles Wohlbefinden* beschreiben?

- ☐ ausgezeichnet ☐ sehr gut ☐ gut ☐ weniger gut ☐ schlecht

25. Leiden Sie aktuell an Schmerzen?

Wenn ja, kreuzen Sie bitte die aktuelle Schmerzstärke an.

0 1 2 3 4 5 6 7 8 9 10

kein Schmerz

stärkster vorstellbarer Schmerz

APPENDIX B: HRV-ANALYSIS

1 Sample Characteristics

See Table B 1 for demographics and characteristics (marital status, living situation, highest education, employment, smoking behavior, and physical activity) of the patient sample.

Table B 1. Sample characteristics.

Patient characteristics	Total MD	Total count	CEA count	CAS count
Marital status:	1			
Single, divorced, widowed, separated		19	10	9
Married, in relationship		32	18	14
Living situation:	1			
Living alone		15	9	6
Living with company (children, partner etc.)		36	19	17
Highest Education:	1			
No graduation		3	3	0
Secondary general school		20	10	10
Apprenticeship		7	3	4
Examination for the master craftsman's certificate		12	6	6
Grammar school with general qualification for university entrance		4	3	1
Academy/ University		5	3	2
Employment:	2			

Patient characteristics	Total MD	Total count	CEA count	CAS count
Employed		5	4	1
Unemployed		3	1	2
Retired		42	22	20
Smoking behavior:	1			
Currently smoking		12	5	7
Never smoked		16	11	5
Stopped smoking		23	12	11
Frequency of doing sports:	2			
Daily		5	3	2
Several times per week		13	9	4
Several times per month		6	5	1
Several times per year		8	3	5
Not at all		18	7	11
The heaviest physical activity during the last two weeks for at least two minutes:	5			
Very heavy		7	5	2
Heavy		2	1	1
Middle		10	7	3
Easy		20	8	12
Very easy		8	6	2

Note. MD = missing data; Total = whole patient sample ($N = 52$; CEA: $n = 28$; CAS: $n = 24$).

2 HRV Results

See Table B 2 for descriptive statistics of the means of the three preoperative and three postoperative time intervals for each HRV-parameter for the whole patient sample and separately for both treatment groups (CAS and CEA).

Table B 2. Mean (*M*) and standard deviation (*SD*) of the pre- and postoperative means for all HRV parameters for the whole patient sample and separately for both treatment groups (CAS and CEA).

HRV- Parameter	Mean Interval	Whole sample: <i>N</i> = 35		CAS: <i>n</i> = 18		CEA: <i>n</i> = 17	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
SDNN	pre	38.57	19.62	39.34	21.76	37.75	17.70
	post	41.95	23.62	52.52 ^a	26.00	30.75 ^c	14.45
rMSSD	pre	25.45	19.57	26.98	26.22	23.83	8.85
	post	26.45	18.31	31.66	22.92	20.94	9.57
pNN50	pre	5.49	13.29	7.79	18.26	3.07	2.95
	post	6.59	12.78	9.92	17.01	3.07	3.71
LF	pre	358.93	528.17	471.72	684.92	239.51	254.76
	post	429.06	687.40	626.08	888.59	220.46 ^b	274.33
LF (nu)	pre	61.94	14.88	64.39	13.64	59.35	16.10
	post	60.60	14.39	66.19	11.67	54.68 ^b	14.93
HF	pre	169.73	402.42	239.21	555.21	96.17	73.57

		Whole sample:		CAS:		CEA:	
		<i>N</i> = 35		<i>n</i> = 18		<i>n</i> = 17	
HRV- Parameter	Mean Interval	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
	post	190.99	362.68	269.99	489.14	107.34	104.13
	pre	29.50	15.16	25.05	10.84	34.21	17.83
HF (nu)	post	28.98	17.09	21.96	11.69	36.41 ^b	19.01
	pre	0.38	0.34	0.45	0.26	0.31	0.40
Log LF/HF ratio	post	0.41	0.39	0.55	0.32	0.25 ^b	0.40
	pre	1535.74	1964.18	1915.70	2511.95	1133.42	1076.85
TP	post	1867.71	2483.47	2672.16	3110.59	1015.94 ^b	1151.88

Note. ^a $p < .05$ (two-tailed): significant difference between the pre- and postoperative period (nonparametric Wilcoxon matched pairs test); ^b $p < .05$ (two-tailed): significant difference between the two groups (Mann-Whitney *U* test). ^c $p < .01$ (two-tailed): significant difference between the two groups (Mann-Whitney *U* test). *M* = mean; *SD* = standard deviation; VLF = very low frequency; LF = low frequency; HF = high frequency; TP = total power; nu = normalized units; Mean_pre = mean of three preoperative 5-min intervals (Minus_15 = 5-min interval starting 15 minutes before the start of the intervention; Minus_10 = 5-min interval starting 10 minutes before the start of the intervention; Minus_05 = 5-min interval starting 5 minutes before the start of the intervention); Mean_post = mean of three postoperative 5-min intervals (Plus_295 = 5-min interval starting 295 minutes after the end of the intervention; Plus_300 = 5-min interval starting 300 minutes after the end of the intervention; Plus_305 = 5-min interval starting 305 minutes after the end of the intervention).

The normal distribution of variables was tested by the Kolmogorov-Smirnov test (K-S test) and by standardized values (z-scores) of skewness and kurtosis (absolute values greater than 2.58 were considered significant at $p < .01$). Prior to each statistical analysis, the parameters' distributions were tested and parameters that were not normally distributed in the respective sample were log transformed to reduce the skewness of their distribution. See Table B 3 for K-S *D*, the absolute values, standard

errors, and z-scores of skewness and kurtosis of the pre- and postoperative means of all HRV-parameters for the whole sample ($N = 35$) and Table B 4 for K-S D , the absolute values, standard errors, and z-scores of skewness and kurtosis for the transformed pre- and postoperative means of all HRV-parameters for the whole sample ($N = 35$).

Table B 3. K-S D , skewness, standard error (SE) of skewness, z-score of skewness, kurtosis, standard error (SE) of kurtosis, and z-score of kurtosis for the pre- and postoperative means of all HRV-parameters for the whole patient sample.

HRV-Parameter-Mean	K-S D	Skewness	SE skewness	z skewness	Kurtosis	SE kurtosis	z kurtosis
Mean_SDNN_pre	0.22	1.65	0.40	4.15**	3.54	0.78	4.55**
Mean_SDNN_post	0.14	1.14	0.40	2.85**	1.08	0.78	1.39
Mean_rMSSD_pre	0.23*	3.31	0.40	8.33**	14.42	0.78	18.54**
Mean_rMSSD_post	0.23*	1.96	0.40	4.92**	4.68	0.78	6.02**
Mean_pNN50_pre	0.34**	4.44	0.40	11.17**	21.09	0.78	27.12**
Mean_pNN50_post	0.32**	3.23	0.40	8.13**	11.21	0.78	14.42**
Mean_LF_pre	0.31**	2.82	0.40	7.08**	8.04	0.78	10.34**
Mean_LF_post	0.28**	3.05	0.40	7.66**	10.30	0.78	13.25**
Mean_HF_pre	0.35**	5.16	0.40	12.98**	28.44	0.78	36.57**
Mean_HF_post	0.34**	3.18	0.40	8.00**	9.78	0.78	12.58**
Mean_total_power_pre	0.30**	2.65	0.40	6.67**	7.24	0.78	9.30**
Mean_total_power_post	0.24*	3.09	0.40	7.77**	11.63	0.78	14.95**
Mean_log ratio_LF_HF_pre	0.12	-0.26	0.40	-0.64	-0.60	0.78	-0.77

HRV-Parameter-Mean	K-S <i>D</i>	Skewness	<i>SE</i> skewness	<i>z</i> skewness	Kurtosis	<i>SE</i> kurtosis	<i>z</i> kurtosis
Mean_log ratio_LF_HF_post	0.12	-0.45	0.40	-1.13	0.15	0.78	0.19
Mean_LF_nu_pre	0.15	-0.41	0.40	-1.02	-0.65	0.78	-0.84
Mean_LF_nu_post	0.12	-0.70	0.40	-1.75	1.07	0.78	1.38
Mean_HF_nu_pre	0.15	0.69	0.40	1.74	-0.41	0.78	-0.53
Mean_HF_nu_post	0.11	0.99	0.40	2.48	1.28	0.78	1.64

Note. * $p < .05$. ** $p < .01$. $N = 35$. K-S = Kolmogorov-Smirnov test.

Table B 4. K-S D , skewness, standard error (SE) of skewness, z-score of skewness, kurtosis, standard error (SE) of kurtosis, and z-score of kurtosis for the transformed pre- and postoperative means of the HRV-parameters for the whole patient sample.

HRV-Parameter-Mean	K-S <i>D</i>	Skewness	<i>SE</i> skewness	<i>z</i> skewness	Kurtosis	<i>SE</i> kurtosis	<i>z</i> kurtosis
Mean_log_SDNN_pre	0.14	0.03	0.40	0.07	0.80	0.78	1.03
Mean_log_SDNN_post	0.07	-0.16	0.40	-0.41	-0.24	0.78	-0.31
Mean_log_rMSSD_pre	0.12	0.35	0.40	0.87	1.32	0.78	1.70
Mean_log_rMSSD_post	0.12	0.16	0.40	0.41	0.29	0.78	0.37
Mean_log_pNN50_pre	0.13	1.37	0.40	3.43*	2.41	0.78	3.10*
Mean_log_pNN50_post	0.19	1.16	0.40	2.93*	0.78	0.78	1.01
Mean_log_LF_pre	0.09	-0.13	0.40	-0.34	0.30	0.78	0.39

HRV-Parameter-Mean	K-S <i>D</i>	Skewness	<i>SE</i> skewness	<i>z</i> skewness	Kurtosis	<i>SE.</i> kurtosis	<i>z</i> kurtosis
Mean_log_LF_post	0.05	-0.19	0.40	-0.48	0.06	0.78	0.07
Mean_log_HF_pre	0.11	0.52	0.40	1.32	1.55	0.78	2.00
Mean_log_HF_post	0.09	0.16	0.40	0.40	0.07	0.78	0.09
Mean_log_total_power_pre	0.10	0.05	0.40	0.14	0.49	0.78	0.63
Mean_log_total_power_post	0.08	-0.11	0.40	-0.27	-0.29	0.78	-0.37
Mean_log_ratio_LF_HF_pre	0.12	-0.26	0.40	-0.64	-0.60	0.78	-0.77
Mean_log_ratio_LF_HF_post	0.12	-0.45	0.40	-1.13	0.15	0.78	0.19
Mean_log_HF_nu_pre	0.10	-0.25	0.40	-0.64	-0.48	0.78	-0.62
Mean_log_HF_nu_post	0.14	-0.43	0.40	-1.09	-0.39	0.78	-0.51

Note. * $p < .05$. ** $p < .01$. $N = 35$. K-S = Kolmogorov-Smirnov test.

2.1 ANOVA Results

H1.1: There is a significant interaction of intervention (CEA versus CAS) and time (pre- and postoperative time) in time domain indices of HRV: SDNN, pNN50, and rMSSD are expected to be decreased after CEA and increased after CAS.

- SDNN (log SDNN):

Table B 5. Table of Repeated Measures Analysis of Variance with effect sizes for log SDNN.

Effect	SS	df	MS	F	p	partial η^2
Intercept	167.28	1	167.28	2204.25	.00	.99
Intervention	0.26	1	0.26	3.43	.07	.09
Error	2.50	33	0.08			
PRE-POST	0.00	1	0.00	0.27	.61	.01
PRE-POST*Intervention	0.20	1	0.20	12.39	.00	.27
Error	0.52	33	0.02			

Note. Significant effects are marked in bold. SS = sum of squares; *df* = degrees of freedom; MS = mean square; *F* = *F* ratio; *p* = probability; partial η^2 = partial eta-squared.

Table B 6. Probabilities for Tukey's HSD for unequal *n* post hoc tests for log SDNN.

Cell no.	Intervention	Pre-Post	{1}	{2}	{3}	{4}
			1.55	1.67	1.53	1.44
1	CAS	Mean_log_SDNN_pre		.03	1.00	.48
2	CAS	Mean_log_SDNN_post	.03		.25	.02
3	CEA	Mean_log_SDNN_pre	1.00	.25		.18
4	CEA	Mean_log_SDNN_post	.48	.02	.18	

Note. Significant effects are marked in bold. Pooled Mean square = .05; *df* = 46.13.

- pNN50 (log pNN50):

Table B 7. Table of Repeated Measures Analysis of Variance with effect sizes for log pNN50.

Effect	SS	df	MS	F	p	partial η^2
Intercept	20.76	1	20.76	69.03	.00	.68
Intervention	0.20	1	0.20	0.66	.42	.02
Error	9.93	33	0.30			
PRE-POST	0.06	1	0.06	0.77	.39	.02
PRE-POST*Intervention	0.14	1	0.14	1.70	.20	.05
Error	2.73	33	0.08			

Note. Significant effects are marked in bold. SS = sum of squares; df = degrees of freedom; MS = mean square; F = F ratio; p = probability; partial η^2 = partial eta-squared.

- rMSSD (log rMSSD):

Table B 8. Table of Repeated Measures Analysis of Variance with effect sizes for log rMSSD.

Effect	SS	df	MS	F	p	partial η^2
Intercept	124.19	1	124.19	1085.58	.00	.97
Intervention	0.04	1	0.04	0.38	.54	.01
Error	3.78	33	0.11			
PRE-POST	0.00	1	0.00	0.13	.72	.00
PRE-POST*Intervention	0.16	1	0.16	7.78	.01	.19
Error	0.66	33	0.02			

Note. Significant effects are marked in bold. SS = sum of squares; df = degrees of freedom; MS = mean square; F = F ratio; p = probability; partial η^2 = partial eta-squared.

Table B 9. Probabilities for Tukey's HSD for unequal n post hoc tests for log rMSSD.

Cell no.	Intervention	Pre-Post	{1}	{2}	{3}	{4}
			1.30	1.41	1.35	1.27
1	CAS	Mean_log_rMSSD_pre		.13	.96	.97
2	CAS	Mean_log_rMSSD_post	.13		.90	.38
3	CEA	Mean_log_rMSSD_pre	.96	.90		.34
4	CEA	Mean_log_rMSSD_post	.97	.38	.34	

Note. Significant effects are marked in bold. Pooled Mean square = .07; $df = 44.24$.

H1.2: There is a significant interaction of intervention (CEA versus CAS) and time (pre- and postoperative time) in frequency domain indices of HRV: LF, LF (nu), and LF/HF ratio are expected to be increased and HF, HF (nu), and TP to be decreased after CEA, whereas HF, HF (nu), and TP are expected to be increased and LF/HF ratio, LF, and LF (nu) to be decreased after CAS.

- LF (log LF):

Table B 10. Table of Repeated Measures Analysis of Variance with effect sizes for log LF.

Effect	SS	df	MS	F	p	partial η^2
Intercept	348.59	1	348.59	648.88	.00	.95
Intervention	1.57	1	1.57	2.93	.10	.08
Error	17.73	33	0.54			
PRE-POST	0.00	1	0.00	0.00	.98	.00
PRE-POST*Intervention	0.46	1	0.46	3.86	.06	.10
Error	3.92	33	0.12			

Note. Significant effects are marked in bold. SS = sum of squares; df = degrees of freedom; MS = mean square; F = F ratio; p = probability; partial η^2 = partial eta-squared.

- LF (nu):

Table B 11. Table of Repeated Measures Analysis of Variance with effect sizes for LF (nu).

Effect	SS	df	MS	F	p	partial η^2
Intercept	261580.25	1	261580.25	812.71	.00	.96
Intervention	1197.14	1	1197.14	3.72	.06	.10
Error	10621.42	33	321.86			
PRE-POST	36.01	1	36.01	0.46	.50	.01
PRE-POST*Intervention	182.84	1	182.84	2.35	.13	.07
Error	2568.04	33	77.82			

Note. Significant effects are marked in bold. SS = sum of squares; df = degrees of freedom; MS = mean square; F = F ratio; p = probability; partial η^2 = partial eta-squared.

- HF (log HF):

Table B 12. Table of Repeated Measures Analysis of Variance with effect sizes for log HF.

Effect	SS	df	MS	F	p	partial η^2
Intercept	237.33	1	237.33	469.97	.00	.93
Intervention	0.09	1	0.09	0.18	.67	.01
Error	16.66	33	0.50			
PRE-POST	0.01	1	0.01	0.06	.81	.00
PRE-POST*Intervention	0.14	1	0.14	0.88	.35	.03
Error	5.35	33	0.16			

Note. Significant effects are marked in bold. SS = sum of squares; df = degrees of freedom; MS = mean square; F = F ratio; p = probability; partial η^2 = partial eta-squared.

- HF (nu) [log HF (nu)]:

Table B 13. Table of Repeated Measures Analysis of Variance with effect sizes for log HF (nu).

Effect	SS	df	MS	F	p	partial η^2
Intercept	136.90	1	136.90	1496.54	.00	.98
Intervention	0.45	1	0.45	4.95	.03	.13
Error	3.02	33	0.09			
PRE-POST	0.01	1	0.01	0.42	.52	.01
PRE-POST*Intervention	0.06	1	0.06	1.98	.17	.06
Error	1.04	33	0.03			

Note. Significant effects are marked in bold. SS = sum of squares; *df* = degrees of freedom; MS = mean square; *F* = *F* ratio; *p* = probability; partial η^2 = partial eta-squared.

Table B 14. Probabilities for Tukey's HSD for unequal *n* post hoc tests for log HF (nu).

Cell no.	Intervention	{1}	{2}
		1.32	1.48
1	CAS		.04
2	CEA	.04	

Note. Significant effects are marked in bold.

Pooled Mean square = .09; df = 33.00.

- LF/HF ratio (log LF/HF ratio):

Table B 15. Table of Repeated Measures Analysis of Variance with effect sizes for log LF/HF ratio.

Effect	SS	df	MS	F	p	partial η^2
Intercept	10.60	1	10.60	54.28	.00	.62
Intervention	0.87	1	0.87	4.45	.04	.12
Error	6.44	33	0.20			
PRE-POST	0.01	1	0.01	0.19	.67	.01
PRE-POST*Intervention	0.11	1	0.11	2.24	.14	.06
Error	1.63	33	0.05			

Note. Significant effects are marked in bold. SS = sum of squares; *df* = degrees of freedom; *MS* = mean square; *F* = *F* ratio; *p* = probability; partial η^2 = partial eta-squared.

Table B 16. Probabilities for Tukey's HSD for unequal *n* post hoc tests for log LF/HF ratio.

Cell no.	Intervention	{1}	{2}
		0.50	0.28
1	CAS		.05
2	CEA	.05	

Note. Significant effects are marked in bold.

Pooled Mean square = .20; *df* = 33.00.

- TP (log TP)

Table B 17. Table of Repeated Measures Analysis of Variance with effect sizes for log TP.

Effect	SS	df	MS	F	p	partial η^2
Intercept	617.40	1	617.40	1712.27	.00	.98
Intervention	1.55	1	1.55	4.29	.05	.11
Error	11.90	33	0.36			
PRE-POST	0.03	1	0.03	0.42	.52	.01
PRE-POST*Intervention	0.37	1	0.37	5.87	.02	.15
Error	2.08	33	0.06			

Note. Significant effects are marked in bold. SS = sum of squares; *df* = degrees of freedom; MS = mean square; *F* = *F* ratio; *p* = probability; partial η^2 = partial eta-squared.

Table B 18. Probabilities for Tukey's HSD for unequal *n* post hoc tests for log TP.

Cell no.	Intervention	Pre-Post	{1}	{2}	{3}	{4}
			3.03	3.21	2.88	2.77
1	CAS	Mean_log_total_power_pre		.14	.77	.37
2	CAS	Mean_log_total_power_post	.14		.16	.04
3	CEA	Mean_log_total_power_pre	.77	.16		.61
4	CEA	Mean_log_total_power_post	.37	.04	.61	

Note. Significant effects are marked in bold. Pooled Mean square = .21; *df* = 44.20.

Table B 19. Probabilities for Tukey's HSD for unequal n post hoc tests for log TP.

Cell no.	Intervention	{1}	{2}
		3.12	0.82
1	CAS		.05
2	CEA	.05	

Note. Significant effects are marked in bold.

Pooled Mean square = .36; $df = 33.00$.

2.2 Results of the Correlation Analysis

With regard to the correlation between preoperative state and trait anxiety and parameters of HRV, the time when patients were filling in these questionnaires (first assessment) was used for analysis. The mean of one hour (1h) of recording (twelve consecutive 5-min intervals) was computed and correlated with the respective questionnaire data.

The normal distribution of variables was tested by the Kolmogorov-Smirnov test (K-S) and by standardized values (z-scores) of skewness and kurtosis (absolute values greater than 2.58 were considered significant at $p < .01$). See Table B 20 for K-S D , the absolute values, standard errors, and z-scores of skewness and kurtosis of the 1h-means of all HRV-parameters.

Table B 20. K-S D , skewness, standard error (SE) of skewness, z-score of skewness, kurtosis, standard error (SE) of kurtosis, and z-score of kurtosis for the 1h-means of all HRV-parameters.

HRV-Parameter-Mean	K-S D	Skewness	SE skewness	z skewness	Kurtosis	SE kurtosis	z kurtosis
Mean_1h_SDNN	0.11	0.58	0.54	1.09	0.00	1.04	0.00
Mean_1h_rMSSD	0.13	0.49	0.54	0.91	-0.25	1.04	-0.24
Mean_1h_pNN10	0.18	-0.13	0.54	-0.24	-1.37	1.04	-1.32
Mean_1h_pNN25	0.17	1.03	0.54	1.92	-0.03	1.04	-0.02
Mean_1h_pNN50	0.21	1.76	0.54	3.28**	3.75	1.04	3.62**
Mean_1h_LF	0.23	1.91	0.54	3.57**	3.97	1.04	3.82**
Mean_1h_HF	0.19	0.74	0.54	1.39	-0.93	1.04	-0.89
Mean_1h_log_ratio_LF_HF	0.13	-0.94	0.54	-1.75	0.44	1.04	0.43
Mean_1h_total_power	0.22	1.70	0.54	3.17**	2.74	1.04	2.64**
Mean_1h_LF_nu	0.13	-0.59	0.54	-1.09	0.31	1.04	0.30
Mean_1h_HF_nu	0.16	1.21	0.54	2.26	1.17	1.04	1.12

Note. * $p < .05$. ** $p < .01$. $N = 18$. K-S = Kolmogorov-Smirnov test.

APPENDIX C: PATIENT INFORMATION

In the following, the patient information leaflet is displayed.

Patienteninformationsblatt

Subjektives und objektives Stresserleben bei medizinischen Eingriffen

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Vielen Dank, dass Sie sich bereit erklärt haben, an der klinischen Studie teilzunehmen.

Der Zweck dieser klinischen Studie liegt in der Untersuchung des Stresserlebens von Patienten vor, während und nach einem medizinischen Eingriff.

Konkret interessiert uns, ob ein bevorstehender medizinischer Eingriff Stress oder Angst auslöst und so zu körperlichen und/ oder psychischen Veränderungen führt. Im Speziellen untersuchen wir mittels einer Langzeit-EKG-Aufzeichnung, ob es vor, während oder nach dem medizinischen Eingriff zu Veränderungen der Herzrate kommt und ob sich hier ein Zusammenhang mit dem subjektiven, psychischen Befinden zeigt.

Je nachdem, wann Sie im Krankenhaus aufgenommen werden, wird Ihnen entweder am Abend vor Ihrem medizinischen Eingriff oder in der Früh direkt vor dem Eingriff ein kleiner EKG-Rekorder mit drei Elektroden angelegt, der fortlaufend Ihre Herzrate aufzeichnet. Dieser wird Ihnen am Abend des Eingriffs oder am Morgen danach wieder abgenommen.

Während des Zeitraums der Aufnahme bitten wir Sie, den EKG-Rekorder von Kontakt mit Wasser fernzuhalten. Abgesehen davon können Sie allen Tätigkeiten normal nachgehen. Sollte sich wider Erwarten eine Elektrode lösen oder der EKG-Rekorder nicht mehr angenehm sitzen, sagen Sie bitte einer diensthabenden Schwester oder der Studienleiterin Bescheid. Bitte nehmen Sie den Rekorder nicht selbst ab und üben Sie keinen absichtlichen Zug auf die Elektroden aus.

Da wir uns nicht nur für das körperliche, objektive Befinden, sondern auch für Ihr subjektives, psychisches Befinden interessieren, möchten wir Sie bitten, ein paar Fragebögen auszufüllen. Die Fragebögen vor dem medizinischen Eingriff beinhalten allgemeine Fragen zu Ihrer Person, Fragen zu Ihrem generellen Wohlbefinden in der letzten Zeit, zu Ihrer allgemeinen Ängstlichkeit, zu Ihrer aktuellen Angst, zu der Art ihres Umganges mit der aktuellen Situation und zu Ihrer Einschätzung der sozialen Unterstützung im Krankenhaus. Weiters werden wir Sie bitten, direkt vor dem Eingriff kurze Angaben zu Ihrem momentanen Befinden und am Tag nach dem Eingriff Angaben zum Ihrem Wohlbefinden, eventuellen Schmerzen und Ihren persönlichen Erfahrungen während des Eingriffs zu machen.

Bitte bedenken Sie beim Ausfüllen der Fragebögen, dass es keine richtigen oder falschen Angaben gibt, sondern es nur darum geht, was Sie denken, fühlen oder tun. Kreuzen Sie also bitte immer jene Aussage oder Antwortmöglichkeit an, die am besten auf Sie persönlich zutrifft. Überlegen Sie bitte nicht zu lange und lassen Sie bitte möglichst keine Aussage aus.

Bei etwaigen Fragen können Sie sich jederzeit an die Studienleiterin wenden: Tel.: [REDACTED]

Vielen Dank für Ihre Mitarbeit! Catherina Tischler

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACTH = adrenocorticotrophic hormone

ANCOVA = analysis of covariance

ANS = autonomic nervous system

AR = autoregressive

AV-node = atrioventricular node

BAS = behavioral activation system

BIS = behavioral inhibition system

BMI = body mass index

BMT = best medical treatment

BRC = baroreflex control of the heart

CAD = coronary artery disease

CAS = carotid artery stenting

CCA = common carotid artery

CEA = carotid endarterectomy

CNS = central nervous system

COSS = Coping with Surgical Stress Scale

CRH = corticotropin-releasing hormone

CRP = C-reactive protein

CT = computed tomography

CVA = cerebrovascular accident

CVR = cardiovascular reactivity

DMS = dorsal motor nucleus

DVC = dorsal vagal complex

ECA = external carotid artery

ECEA = eversion carotid endarterectomy

ECG = electrocardiogram

EDA = electrodermal activity

EISOP = Emotional and Informational Support Scales – Operations

ENS = enteric nervous system

FFT = fast Fourier transform

GA = general anesthesia

GAS = general adaptation syndrome

H0 = null hypothesis

H1 = alternative hypothesis

HF (nu) = HF norm = $\{ \text{HF (ms}^2) / [\text{TP (ms}^2) - \text{VLF (ms}^2)] \} \times 100$

HF = high frequency

HPA axis = hypothalamic-pituitary-adrenocortical axis

HR = heart rate

HRV = heart rate variability

HTN = hypertension

ICA = internal carotid artery

Index α = average of the square root of the ratio between RR interval and systolic blood pressure spectral powers in the LF and HF regions; marker of the overall gain of the arterial pressure-heart period baroreflex

LA = local anesthesia

LF (nu) = LF norm = $\{ \text{LF (ms}^2) / [\text{TP (ms}^2) - \text{VLF (ms}^2)] \} \times 100$

LF = low frequency

LF/HF = ratio low frequency [ms^2]/ high frequency [ms^2]

M = mean

MD = missing data

MRI = magnetic resonance imaging

N = number

NA = nucleus ambiguus

NN50 count = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording

OR = orienting response

PCA = principal-component analysis

pNN50 = percentage of successive normal sinus RR intervals > 50 ms

PSNS = parasympathetic nervous system

PTA = percutaneous transluminal angioplasty

PTCA = percutaneous transluminal coronary angioplasty

PTSD = Post Traumatic Stress Disorder

RMSSD = root-mean-square of the successive normal sinus RR interval difference

RSA = respiratory sinus arrhythmia

SA node = sinoatrial node or sinus node

SAM system = sympathetic-adrenomedullary system

SAP = systolic arterial pressure

SBRs = spontaneous cardiac baroreflex sensitivity

SD = standard deviation

SDANN = standard deviation of the averaged normal sinus RR intervals for all 5-min segments

SDNN = standard deviation of all normal sinus RR intervals over 24 hours

SDNN index = mean of the standard deviations of the averaged normal sinus RR intervals for all 5-min segments

SDSD = standard deviation of differences between adjacent RR intervals

SE = standard error

SNS = sympathetic nervous system

STAI X1 = State-Trait Anxiety Inventory, subscale X1 (state anxiety)

STAI X2 = State-Trait Anxiety Inventory, subscale X2 (trait anxiety)

TIA = transient ischemic attack

TP = total power

ULF = ultra low frequency

VLF = very low frequency

VVC = ventral vagal complex

CURRICULUM VITAE

Zu meiner Person:

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Schul- und Universitätsausbildung:

1990 – 1994	Volksschule Steinlechnergasse, 1130 Wien
1994 – 2002	Neusprachliches Gymnasium St. Ursula, 1230 Wien; Matura mit ausgezeichnetem Erfolg
2002 – 2010	Studium der Psychologie an der Universität Wien
WS 2005/SS 2006	Erasmus-Auslandsaufenthalt in Berlin (Freie Universität)
Seit WS 2009	Universitätslehrgang Psychotherapeutisches Propädeutikum

Arbeitspraxis:

Seit 2002 unterstützende Tätigkeiten in der psychologisch-psychotherapeutischen
Praxis von Mag. Maria Tischler

April 2005 – Juni 2005: Praktikum im Ausmaß von 60 Stunden in ESRA (Zentrum für
psychosoziale, sozialtherapeutische und soziokulturelle Integration; Ambulanz
für Spätfolgen und Erkrankungen des Holocaust- und Migrations-Syndroms)

September 2005: Einwöchiges Praktikum in der Ambulanz für spezielle Psychosomatik
in der Kardiologie im Hanusch-Krankenhaus, 1140 Wien

Oktober 2005 – Jänner 2006: Praktikum im Ausmaß von 320 Stunden an der Medizinischen Klinik mit Schwerpunkt Psychosomatik der Charité (Campus Berlin Mitte)

Februar 2006 – April 2006: Vollzeit-Praktikum in der psychiatrischen Tagesklinik der Klinik für Psychiatrie und Psychotherapie der Charité (Campus Berlin Mitte)

September 2007 – November 2007: Praktikum am Zentrum für Public Health, Institut für Umwelthygiene

Dezember 2007 – März 2009: Anstellung als Projektmitarbeiterin im Rahmen des EU-Projektes ICE (Ideal Cabin Environment) an der Medizinischen Universität Wien, Zentrum für Public Health, Institut für Umwelthygiene

Oktober 2008 – Jänner 2009: Studienassistentin an der Universität Wien, Fakultät für Psychologie, Institut für Wirtschaftspsychologie, Bildungspsychologie und Evaluation

Seit Oktober 2009 Anstellung als Projektmitarbeiterin im Rahmen des EU-Projektes (Seventh Framework Programme) iSPACE (innovative Systems for Personalised Aircraft Cabin Environment) an der Medizinischen Universität Wien, Zentrum für Public Health, Institut für Umwelthygiene

Besondere Kenntnisse:

Sprachen:

Sehr gutes Englisch (2 Cambridge Zertifikate: FCE, CAE; mehrere Sprachaufenthalte in Amerika, Kanada, England und Irland)

Gutes Französisch (mehrere Sprachaufenthalte in Frankreich)

Grundkenntnisse in Italienisch

EDV-Kenntnisse (u.a. MS Office, SPSS, STATISTICA)

Ausbildungskurse „Progressive Muskelentspannung nach Jacobson“ (im Jahr 2005) und „Autogenes Training – Grundstufe“ (im Jahr 2009) bei Mag. Boris Zalokar, Institut für Psychosomatik und Gesundheitsbildung – Dr. Ambros KEG

Biofeedback-Fortbildungen der BFE (Biofeedback Foundation of Europe) in den Jahren 2004, 2005 und 2008