Surgery and Rehabilitation

Research Article ISSN: 2514-5959

Comparing cardiovascular load by heart rate variability (HRV) including pNNxx parameters with ratings of perceived medical intervention load (PMIL) in patients undergoing carotid endarterectomy or carotid artery stenting

Catherina Jahn and Michael Trimmel*

Institute for Environmental Health, Center for Public Health, Medical University of Vienna, Vienna, Austria

Abstract

Objective: The aim was to compare subjectively experienced load with cardiovascular load in patients undergoing a medical intervention by either carotid endarterectomy (CEA) or carotid artery stenting (CAS). Heart rate variability (HRV), including parameters of the pNNxx family, and perceived medical intervention load (PMIL) were investigated and compared in a prospective study.

Methods: In a sample of 52 patients (CEA: n = 28; CAS: n = 24) aged 69 ± 10 years, electrocardiogram was recorded throughout the perioperative period and questionnaires on pre- and postoperative state (STAI X1) and trait anxiety (STAI X2) as well as the PMIL were filled in. Preoperative (15 minutes before surgery) HRV parameter values of time and frequency domain were compared to postoperative values (15 minutes lasting epoch 5 hours after surgery).

Results: A 2 (Time: pre vs. post) × 2 (Intervention: CEA vs. CAS) repeated measures ANOVA revealed increased HRV after CAS compared to CEA, with the most pronounced effect size for SDNN. Effect sizes for the pNNxx family around 25ms namely pNN20, pNN25, and pNN30 were also pronounced and greater than the effect size for the traditional pNN50. In both groups state anxiety was preoperatively (M = 40.03 ± 11.00) higher than postoperatively (M = 32.74 ± 7.36) but no group differences were observed for anxiety or for the subjective measure of the PMIL.

Conclusion: Cardiovascular load as indicated by HRV is less for CAS compared to CEA whereas subjective measures displayed no differences. In addition, HRV assessed by pNNxx (with xx 20 – 30 ms) beside global parameters like SDNN and Total Power seems to be in particular sensitive for load.

Introduction

Patients suffering from high-grade stenosis of the carotid artery have an increased risk of cerebrovascular accidents as a consequence of thromboembolism. Especially symptomatic stenoses with more than 50% degree of occlusion that have already caused transient ischemic attacks substantially raise the risk of severe strokes, and may result in permanent disabilities or death [1,2]. Patients can be treated with medication to reduce inflammation and to stabilize the plaque or they can undergo prophylactic interventions for stroke prevention, which permanently remove the plaque and restore vascularization. These prophylactic interventions can be either surgical therapies such as carotid endarterectomy (CEA) or eversion carotid endarterectomy (ECEA) or carotid artery stenting (CAS), a minimally invasive intervention. CEA has shown to be the best medical treatment and has been the gold standard for treating carotid artery disease for decades. It has recently been challenged by minimally invasive, endovascular techniques that show some advantages, such as less invasiveness, shorter duration of the procedure, and a shorter hospital stay. Large randomized controlled trials indicate comparable effectiveness and suggest that the right treatment for each patient should be decided on individually [2-6].

Besides the medical effectiveness of treatments, the patients' cardiovascular and psychological loads deserve closer attention. The physiological stress response caused by medical procedures comprises hemodynamic, metabolic, inflammatory, and immunologic changes mediated by the hypothalamic-pituitary-adrenal (HPA) axis through the activation of the autonomic nervous system, ANS [7]. Intraoperative stress responses can have detrimental effects on patients' well-being, postoperative recovery, and clinical outcomes. Thus, the perioperative monitoring of physiological parameters provides valuable insight into a medical procedure's load. For this purpose, analysis of heart rate variability (HRV) is particularly suitable as it allows a non-invasive, continuous recording throughout the perioperative period and the drawing of conclusions on cardiovascular load.

Correspondence to: Michael Trimmel, Institute for Environmental Health, Center for Public Health, Medical University of Vienna, Vienna, Austria, Tel. +4314016034901, E-mail: michael.trimmel@meduniwien.ac.at

Key words: *carotid artery stenting (CAS); carotid endarterectomy (CEA); heart rate variability (HRV); stress; load; perceived medical intervention load*

Received: September 12, 2017; **Accepted:** October 02, 2017; **Published:** October 04, 2017

HRV refers to the continuous variation in the time between two consecutive heart beats/ R-waves (RR interval). Besides the automaticity due to pacemakers, the heart's electrical and contractile activity is substantially modulated by the ANS, thus allowing the organism to quickly and effectively adapt to changing internal or external demands. HRV analysis of the ECG quantifies these cyclical fluctuations in ANS control of the heart's sinus node and provides insight into autonomic tone. Time domain methods refer to indices derived from direct measurements of inter-beat intervals – e.g. standard deviation of all normal sinus RR intervals (SDNN) – and from comparisons of adjacent cycle lengths (RR intervals) – e.g. proportion of adjacent normal sinus RR intervals of more than 50 ms (pNN50). As there is no rational for a 50 ms interval, other intervals were suggested (pNNxx) and proven for their sensitivity to cardiovascular load [8]. In 24-hour recordings it was furthermore shown that pNN10 – pNN40 are negatively correlated with anxiety [9], stress and depression [10], and pNN100 – pNN200 positively correlated with relaxation and good mood [10].

Frequency domain methods in HRV refer to the analysis of the power spectral density, which decomposes the periodic oscillations in heart rate (HR) into their component frequencies. In short-term recordings, very low (VLF: < 0.04 Hz), low (LF: 0.04 – 0.14 Hz), and high (HF: 0.15 – 0.4 Hz) frequency parameters can be differentiated. The total power (TP) of HRV is the total variance corresponding to all frequency bands. HF in absolute (ms^2) and normalized units (nu) primarily reflects vagal activity and respiratory sinus arrhythmia [11-13]. LF and LF (nu) are assumed to reflect fluctuations of both ANS branches as well as baroreceptor and chemoreceptor activity. The LF/HF ratio was suggested as an index of sympathovagal balance; however, there are also controverse opinions [12,14-16]. A recent investigation indicated some sensitivity of the LF/HF ratio to short term activation [17] but seems to be less associated with affect and activation in 24-hour recordings [10].

Considering the heated debate over and the great amount of research on outcome and effectiveness of CEA and CAS from a medical perspective, this study aimed at comparing the load caused by both interventions from a psychophysiological point of view by analyzing HRV and asking for patients' subjective perception. Most studies measuring HRV in the context of CEA or CAS concentrated on their influence on the carotid baroreflex function and therewith postoperative hemodynamic instability [18-22]. Sigaudo-Roussel, *et al.* [21] focused on deterioration in carotid baroreflex during and after CEA under general anesthesia (GA) and demonstrated a temporary sympathetic predominance (LF nu > HF nu) and reduced TP until six weeks afterwards. Investigating both CEA and CAS, Yakhou, *et al.* [22] demonstrated parasympathetic predominance (increased HF nu, decreased LF/HF ratio) 8 and 24 hours after CAS and no change after CEA in 20 patients. Starting from similar baseline-values in the two groups, they interpreted the changes as activation of the baroreflex after CAS. However, they analyzed within-group and not between-group effects. Also addressing the influence of both CEA and CAS on HRV, Demirci, *et al.* [18] demonstrated sympathetic predominance after CEA (decreased HF nu, increased LF nu and LF/HF ratio, and vice versa after CAS) and parasympathetic predominance after CAS in a sample of 22 patients, when comparing HRV parameters on the day before the procedure to those one, two, and three days afterwards. However, CEA was performed under GA and CAS under local anesthesia (LA); therefore effects of GA can't be differentiated from CEA vs. CAS.

The present study aimed at directly comparing load assessed by HRV and subjective ratings in patients undergoing CEA and CAS, both performed under LA, with a sufficient sample size based on power analysis. We expected a Time × Intervention interaction in terms of increased HRV and parasympathetic activity after CAS compared to CEA. As the HRV parameter selection varies considerably between studies and different parameters have on the one hand shown to correlate substantially, but on the other hand have their unique contribution [8,10,13], the present study simultaneously considered a number of parameters. In this regard, several pNN thresholds (pNNxx) below the commonly used 50 ms threshold were examined, as they have been suggested to better discriminate between normal and various pathological conditions and to provide valuable information on the very short-term control of sinus rhythm dynamics [8,10,23,24]. As evidence is still poor whether pNN50 and pNN thresholds below 50 ms can be regarded as equivalent or not [23-25] and in how far they reflect vagal activity, the association between the pNNxx parameters and HF power was examined. Consequently, effect sizes were compared with regard to the Time × Intervention interaction in order to get a picture of the parameters' effect sizes.

Perceived medical intervention load (PMIL) and anxiety (pre- and postoperative state and trait anxiety) were expected to reflect different load in CEA versus CAS. Aspects of the subjective experience of patients undergoing CEA or CAS under LA have so far scarcely been investigated but research indicated that the majority of patients is satisfied with the surgical procedure independent of the type of anesthesia administered [26,27].

Thus, this prospective study aimed at comparing CEA and CAS with respect to their load as reflected by HRV including pNNxx statistics and by the subjective experience as dependent variables, with an additional focus on effect sizes of HRV parameters.

Methods

Study design

The study was designed as a prospective, quasi-experimental field study with two treatment groups (CEA versus CAS) and repeated measurements (pre versus post comparison).

Participants

The study was conducted in cooperation with the Hanusch Hospital in Vienna, Austria. All persons diagnosed with a high-grade stenosis of the carotid artery, scheduled for either CEA or CAS, and competent to personally sign informed consent were eligible for the study. The sample comprised 52 patients (CEA: $n = 28$; CAS: $n = 24$). The local Ethics Committee (Medical University of Vienna) approved the study protocol and written informed consent was obtained from all patients. Patients were assigned to the treatments based on personal (e.g. age) and medical characteristics (e.g. comorbid risk factors, characteristics of the stenosis and blood vessels) and on patients' preference. The groups were comparable regarding aspects of their medical history, risk factors, and sociodemographic characteristics (Table 1).

Instruments and data management

ECG recording and HRV analysis: A continuous ECG was recorded with a portable Holter monitor (Medilog® AR12, EVO Scientific Biosignal Recorder by TOM Medical Entwicklungs GmbH), using a modified Lead I recording. ECG data were analyzed by the Medilog Darwin analysis program (Schiller GmbH). The conversion of analog to digital data was performed at a sampling rate of 4096 Hz. HRV was measured and calculated according to the standards suggested by the Task Force [13]. After template analysis, the QRS complex and arrhythmia classification was visually inspected and

Table 1. Sample characteristics and results of Chi-Square (χ^2) Tests for the comparison CEA versus CAS.

Patient characteristics	Total MD	Total count	CEA count	CAS count	χ^2
Gender: F/M	0	22/ 30	13/ 15	9/ 15	0.42§
At least one prior surgical episode	1	47	25	22	0.71§
Hospitalized before	1	49	26	23	1.84§
Hypertension	0	38	20	18	0.08§
Diabetes mellitus	0	27	15	12	0.07§
History of myocardial infarction	0	6	5	1	2.37§
Coronary heart disease	0	14	7	7	0.11§
Previous endarterectomy (CEA)	0	2	2	0	1.78§
Previous carotid artery stenting (CAS)	0	3	2	1	0.21§
Single, divorced, widowed, separated/ married, in relationship	1	19/ 32	10/ 18	9/ 14	0.06§
Living alone/ with company (children, partner etc.)	1	15/ 36	9/ 19	6/ 17	0.22§
Highest Education: No graduation/ secondary general school/ apprenticeship/ examination for the master craftsman's certificate/ grammar school with general qualification for university entrance/ academy or university	1	3/ 20/ 7/ 12/ 4/ 5	3/ 10/ 3/ 6/ 3/ 3	0/ 10/ 4/ 6/ 1/ 2	3.89§
Employed/ unemployed/ retired	2	5/ 3/ 42	4/ 1/ 22	1/ 2/ 20	1.92§
Currently smoking/ never smoked/ stopped smoking	1	12/ 16/ 23	5/ 11/ 12	7/ 5/ 11	2.16§
Frequency of doing sports: Daily/ several times per week/ per month/ per year/ not at all	2	5/ 13/ 6/ 8/ 18	3/ 9/ 5/ 3/ 7	2/ 4/ 1/ 5/ 11	5.90§
The heaviest physical activity during the last two weeks for at least two minutes: Very heavy/ heavy/ middle/ easy/ very easy	5	7/ 2/ 10/ 20/ 8	5/ 1/ 7/ 8 / 6	2/ 1/ 3/ 12/ 2	4.75§

Note: § *ns* (p > .05); MD = missing data; Total = whole patient sample (N = 52; CEA: n = 28; CAS: n = 24).

complexes identified as noise, ectopic beats, or other arrhythmias were excluded from 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. Total power (ms^2), spectral power of HF and LF, and the time domain parameters SDNN (ms) and the pNNxx statistics were calculated. PNNxx (pNN05, pNN10, pNN20, pNN25, pNN30, pNN40, and pNN50) were assessed by estimating the percentage of successive RR interval differences whose absolute values exceed xx ms, respectively.

Self-report measurements: Patients answered questions regarding their sociodemographic characteristics and medical history (Table 1).

The patients' *state and trait anxiety* were assessed by the German version [28] of the State-Trait Anxiety Inventory (STAI) [29]. The X1 scale (state anxiety; 20 items) asks for a person's momentary feelings, whereas the X2 scale (trait anxiety; 20 items) asks for general anxiety. Cronbach's α = .93 for trait anxiety (M = 37.51, SD = 10.67, n = 45), α = .94 for preoperative state (M = 40.39, SD = 11.53, n = 41), and α = .91 for postoperative state anxiety (M = 33.22, SD = 8.44, n = 46) in the investigated sample.

The patients' *perceived medical intervention load* (PMIL) of CEA and CAS was assessed by a self-developed questionnaire based on observations of the intraoperative situation and discussions with patients and doctors in the pre-experimental period. Patients indicated their degree of agreement on 23 statements focusing on the specific characteristics and stressful elements of the interventions on a 4-point labeled rating scale (1 = *not at all*; 2 = *a little*; 3 = *fairly*; 4 = *very much*) with an average score ranging from 1 to 4 (higher scores indicate greater load). Cronbach's α = .81 (M = 39.77, SD = 7.70, n = 43) in the investigated sample. See Table 2 for items and descriptive statistics.

Procedure

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.

The preoperative assessment, lasting about 30 minutes, took place on the night before or in the morning of surgery at the ward, depending 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 the sociodemographic questionnaire, the STAI X1, and the STAI X2.

The postoperative assessment, lasting about 20 minutes, took place on the evening of surgery or the day after, depending on the patient's constitution and on organizational reasons. Patients were asked to fill in the STAI X1 and the questionnaire on the subjective experience of the intraoperative situation (PMIL). Afterwards the Holter monitor was removed.

Intraoperative information relevant for the study (e.g. procedure length, medication, complications) was obtained from the medical protocols.

Medical treatment: Patients stayed for about three to six days in hospital when there were no complications. All patients were operated on before noon and monitored in a post-anesthesia care unit for a few hours before returning to the ward.

Concerning CEA, the procedure 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. by *midazolam*) before surgery. Supplemental doses of sedatives or pain medication (*fentanyl*, *metamizol*, or *piritramid*) were administered intraoperatively if necessary. During surgery, HR, DBP, SBP, oxygen saturation, and temperature were monitored and the patient's status was continuously evaluated with regard to the occurrence of any neurological changes. A prophylactic *shunt* was placed in all surgeries. In two patients, who were excluded from all analyses, GA became necessary and was induced by the administration of *propofol*, *fentanyl*, and *sevorane*.

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 interventions were performed with cerebral protection devices. Predilatation was conducted when necessary. Patients were sedated preoperatively only by request at the ward.

All patients were maintained on their normal and postoperatively revised schedule of medication. Concerning CAS, treatment with *acetylsalicylic acid* (Thrombo ASS®) was started immediately after diagnosis and patients received *clopidogrel* (Plavix®) for three months and low-molecular-weight *heparin* (Lovenox®) for three days postprocedurally. Concerning CEA, patients received analgetics (e.g. *piritramid*: Dipidolor®) and low-molecular-weight *heparin* (Lovenox®) in the early postsurgical period.

Table 2. Means (*M*), standard deviations (*SD*), and results of Mann-Whitney-Test (*U*) of each item and the mean of the scale "perceived medical intervention load" (PMIL) for the whole sample (*N* = 43) and separately for patients undergoing CEA (*n* = 21) or CAS (*n* = 22).

Item no.	Item	Whole sample		CEA		CAS		*U*-test
		M	*SD*	*M*	*SD*	*M*	*SD*	*U*
01	I had enough time to decide in favor of the procedure (rv)	1.53	0.70	1.67	0.86	1.41	0.50	202.0
02	I felt sufficiently informed before the procedure (rv)	1.35	0.53	1.43	0.60	1.27	0.46	203.0
03	I experienced the waiting period before the procedure as stressful	2.05	0.72	2.10	0.94	2.00	0.44	229.0
04	I experienced the preparations on the operating table as stressful	1.56	0.73	1.67	0.86	1.45	0.60	206.5
05	I experienced the closeness of the medical equipment as alarming	1.63	0.79	1.67	0.91	1.59	0.67	228.5
06	I felt sufficiently informed during the procedure (rv)	1.40	0.62	1.43	0.68	1.36	0.58	224.0
07	I felt safe and secure during the procedure (rv)	1.84	0.81	1.67	0.91	2.00	0.69	163.0
08	I experienced the procedure as threatening	1.42	0.79	1.52	0.81	1.32	0.78	189.0
09	I experienced the communication with the medical staff as calming (rv)	1.67	0.78	1.48	0.81	1.86	0.71	149.0*
10	I experienced the operating room as alarming	1.93	0.99	2.33	1.11	1.55	0.67	137.0*
11	I experienced the whole procedure as stressful	1.95	0.79	2.14	0.85	1.77	0.69	174.0
12	I experienced the medical staff as competent (rv)	1.14	0.41	1.10	0.44	1.18	0.40	202.0
13	I was in pain during the procedure	1.65	0.78	1.86	0.91	1.45	0.60	176.5
14	I was able to relax during the procedure (rv)	2.74	0.76	2.52	0.93	2.95	0.49	156.5*
15	I trusted the medical staff (rv)	1.33	0.52	1.19	0.51	1.45	0.51	164.0*
16	I experienced painful sensations	1.51	0.77	1.62	0.81	1.41	0.73	198.0
17	I was afraid of complications	1.84	0.84	1.86	0.79	1.82	0.91	216.5
18	Lying on the operating table was uncomfortable	2.09	0.84	2.00	0.95	2.18	0.73	194.5
19	I experienced the ambient noises as disturbing	1.44	0.59	1.38	0.67	1.50	0.51	192.5
20	I felt out of control	1.70	0.99	1.95	1.12	1.45	0.80	168.5
21	I experienced the restricted freedom of movement as uncomfortable	2.16	0.87	2.14	1.01	2.18	0.73	220.0
22	I experienced the entering and exiting of the operating room by the medical staff as disturbing	1.16	0.37	1.14	0.36	1.18	0.40	222.0
23	I could reduce the stress associated with the procedure through distraction	2.67	0.97	2.57	1.08	2.77	0.87	207.5
Mean	Perceived medical intervention load	1.73	0.33	1.76	0.40	1.70	.26	223.5

Note: rv = reversely poled (patients answered all items on the same answering format: 1 = *not at all*; 2 = *a little*; 3 = *fairly*; 4 = *very much*; however, reversely poled items were recalculated by 5 – score; thus higher values indicate more load; in Table 2 the recalculated values are reported); * $p < .05$.

Statistical analysis

The normal distribution of variables was tested with the Kolmogorov-Smirnov test (K-S test) and standardized values (*z*-scores) of skewness and kurtosis (absolute values > 2.58 were considered significant at $p < .01$). Skewed absolute HRV parameter values were log transformed to approach normal distribution.

To analyze the Time (preoperative vs. postoperative) × Intervention (CEA vs. CAS) interaction in dependent variables, analysis of variance for repeated measures with treatment group (CEA vs. CAS) by preoperative and postoperative intervals of physiological measures was conducted. Post hoc analysis was performed for significant effects. Three 5-min intervals starting 15, 10, and 5 minutes before the start of the interventions, when patients were being prepared for CEA or CAS, were chosen for calculating the preoperative mean. Three 5-min intervals starting 295, 300, and 305 minutes after the end of the interventions, when patients were resting in the post-anesthesia care unit and the effects of procedure specific medication (e.g. sedation) should have mostly ceased, were chosen for calculating the postoperative mean. These intervals were selected to rule 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 or Spearman's rank correlation coefficients were used. Patient characteristics and ratings were compared with the independent or dependent samples t-test, the non-parametric Mann-Whitney test, or the X^2 test, as appropriate. An alpha level of .05 was applied for all statistical tests and effect sizes were calculated.

Regarding sample size calculation, 34 patients (17 per group) were estimated for 80% power and α = .05, when defining a significant Time (preoperative vs. postoperative) × Intervention (CEA vs. CAS) interaction 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; $f = 0.25$).

For statistical analysis, only data of patients with valid recordings (no GA; exclusion in case of severe arrhythmia) covering the period of question (15min before the intervention until 5h afterwards) and valid questionnaire data were analyzed. Therefore, *n* is indicated for each analysis.

Results

Patient characteristics

Fifty-two patients with a mean age of 69 ± 10 years, mean BMI of 28 ± 5, and stenosis degrees of more than 80% took part in the study. The groups were comparable (no significant differences) regarding aspects of their medical history, risk factors, and sociodemographic characteristics (Table 1).

Twenty-eight 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) were performed. The carotid plaque was removed in all surgeries. No patients suffered from neurological deficits postprocedurally. One patient developed a neck hematoma postprocedurally and received revision surgery on the same day (excluded from analysis). Concerning CAS, recanalization was achieved in all patients and stenting was performed in all but one patient, who underwent CEA afterwards (excluded from analysis).

Relationship between the pNNxx family and HF

In order to investigate whether the pNNxx parameters (with xx 20 – 30 ms) are related to the well-established pNN50 parameter and therewith presumably reflect vagal activity, pNNxx values were correlated with the HF parameter. For the preoperative time, significant positive relationships ($p < .001$) of HF with pNN20, $r_s = .71$, pNN25, $r_s = .75$, pNN30, $r_s = .75$, and pNN50, $r_s = .62$, were found. For the postoperative time, significant positive relationships ($p < .001$) of HF with pNN20, $r_s = .88$, pNN25, $r_s = .87$, pNN30, $r_s = .86$, and pNN50, $r_s = .72$, were found.

Heart rate variability in the course of CEA and CAS

See Table 3 for descriptive statistics of the means of the three preoperative and postoperative time intervals of each parameter before transformation.

See Table 4 for the results of the 2 (Time: preoperative vs. postoperative) × 2 (Intervention: CEA vs. CAS) repeated measures ANOVA for all parameters and Figure 1 for the graphical display of effect sizes (partial η^2) of the Time × Intervention interaction.

Significant interaction effects were found for the time domain parameters log SDNN, log pNN20, log pNN25, and log pNN30, but not for pNN05, pNN10, log pNN40, and log pNN50. Regarding log SDNN, post hoc analysis revealed significant differences for the CAS group between the pre- and postoperative time (pre < post) and significant differences between the CAS and CEA groups at the postoperative time (CAS > CEA). For log pNN20, log pNN25, and log pNN30, post hoc analysis revealed significant differences for the CAS group between the pre- and postoperative time (pre < post).

Regarding frequency domain parameters, a significant interaction effect was found for log TP. Post hoc analysis revealed significant differences for the CAS group between the pre- and postoperative time (pre < post) and between the CEA and CAS groups at the postoperative time (CAS > CEA). No significant interaction effects were found for log LF and log HF. A significant main effect of Intervention was found for log TP. Post hoc analysis revealed significant differences between the treatment groups, with higher values for the CAS group.

Anxiety and perceived medical intervention load

No significant difference was found for the PMIL between patients undergoing CEA (*Md* = 1.70) and CAS (*Md* = 1.67), *U* = 223.5, *ns*, *r* = -.03, *n* = 43 (see Table 5 for descriptive statistics).

When looking at the 23 items in detail, the 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 (*Md* = 3.0) < CEA (*Md* = 4.0), *U* = 149.0, $p < .05$, item 10 ("I experienced the operating room as alarming."), CAS (*Md* = 1.0) < CEA (*Md* = 2.0), *U* = 137.0, $p < .05$, item 14 ("I was able to relax during the procedure."), CAS (*Md* = 2.0) < CEA (*Md* = 3.0), *U* = 156.5, $p < .05$, and item 15 ("I trusted the medical staff"), CAS (*Md* = 4.0) = CEA (*Md* = 4.0), *U* = 164.0, $p < .05$.

The PMIL correlated positively with trait anxiety, $r_s = .36$, $n = 39$, *p* (one-tailed) < .05, and postoperative state anxiety, $r_s = .55$, $n = 42$, *p* (one-tailed) < .001. There was no significant difference in the PMIL between male (*Md* = 1.61) and female (*Md* = 1.70) patients, *U* = 179, *n* = 43, *ns*, and no relationship between a patient's PMIL and the duration of the procedure, $r_s = -.11$, $n = 39$, *ns*.

There were no significant group differences in anxiety (see Table 5 for descriptive statistics). State anxiety scores were significantly higher preoperatively (*M* = 40.03) than postoperatively (*M* = 32.74), $t(37) = 4.33$, $p < .001$ (one-tailed). Women did neither differ from men in their preoperative (female: *M* = 39.28, *n* = 18; male: *M* = 41.26, *n* = 23), *t*

Table 3. Means (*M*) and standard deviations (*SD*) of the pre- and postoperative means for all parameters for the whole patient sample and separately for both treatment groups (CEA and CAS).

Parameter	Mean Interval	Whole sample *N* = 35		CEA *n* = 17		CAS *n* = 18	
		M	*SD*	*M*	*SD*	*M*	*SD*
pNN05	pre	62.71	16.90	63.39	12.24	62.07	20.72
	post	61.92	21.48	56.46	23.20	67.08	18.92
pNN10	pre	45.10	20.09	46.08	15.44	44.17	24.10
	post	45.98	24.51	40.21	23.71	51.44	24.65
pNN20	pre	20.42	18.85	19.92	12.46	20.89	23.75
	post	25.45	22.31	20.71	18.11	29.92	25.36
pNN25	pre	14.07	17.26	12.48	8.82	15.57	22.75
	post	17.33	19.46	12.78	12.81	21.64	23.71
pNN30	pre	11.37	16.55	9.43	6.97	13.20	22.25
	post	13.98	17.87	9.44	10.02	18.27	22.46
pNN40	pre	7.33	14.56	4.90	4.22	9.62	19.89
	post	9.35	15.00	5.28	6.05	13.19	19.58
pNN50	pre	5.49	13.29	3.07	2.95	7.79	18.26
	post	6.59	12.78	3.07	3.71	9.92	17.01
SDNN	pre	38.57	19.62	37.75	17.70	39.34	21.76
	post	41.95	23.62	30.75	14.45	52.52	26.00
LF	pre	358.93	528.17	239.51	254.76	471.72	684.92
	post	429.06	687.40	220.46	274.33	626.08	888.59
HF	pre	169.74	402.42	96.17	73.57	239.21	555.21
	post	190.99	362.68	107.34	104.13	269.99	489.14
TP	pre	1535.74	1964.18	1133.42	1076.85	1915.70	2511.95
	post	1867.71	2483.47	1015.94	1151.88	2672.16	3110.59

Note: pre = mean of the three preoperative 5-min intervals; post = mean of the three postoperative 5-min intervals; for abbreviations of parameters see text. .

Table 4. ANOVA results with effect sizes (partial η²) of HRV parameters.

Parameter	*df*	I		T		T × I	
		F	*partial η²*	*F*	*partial η²*	*F*	*partial η²*
pNN05	1	0.74	.02	0.07	.00	2.75	.08
pNN10	1	0.52	.02	0.03	.00	2.74	.08
Log pNN20	1	0.08	.00	0.49	.01	4.50*	.12*
Log pNN25	1	0.12	.00	0.24	.01	4.19*	.11*
Log pNN30	1	0.19	.01	0.24	.01	4.44*	.12*
Log pNN40	1	0.49	.01	0.76	.02	2.72	.08
Log pNN50	1	0.66	.02	0.77	.02	1.70	.05
Log SDNN	1	3.43	.09	0.27	.01	12.39**	.27**
Log LF	1	2.93	.08	0.00	.00	3.86	.10
Log HF	1	0.18	.01	0.06	.00	0.88	.03
Log TP	1	4.29*	.11*	0.42	.01	5.87*	.15*

Note: * $p < .05$; ** $p < .01$; *df* = degrees of freedom; *F* = *F* ratio; partial η^2 = partial eta-squared; I = main effect of Intervention; T = main effect of Time; T × I = Time × Intervention interaction.

Table 5. Descriptive statistics (number [*N*], mean [*M*], and standard deviation [*SD*]) of trait anxiety (STAI X2), preoperative state anxiety (STAI X1 pre), postoperative state anxiety (STAI X1 post), and perceived medical intervention load (PMIL) for the whole patient sample and separately for patients undergoing CEA or CAS.

	Whole sample *N* = 52			CEA *n* = 28			CAS *n* = 24		
	N	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*
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 load	43	1.73	0.33	21	1.76	0.40	22	1.70	0.26

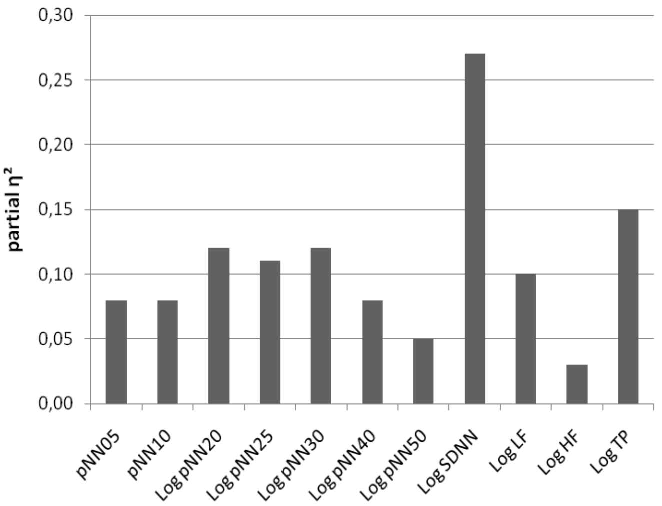

Figure 1. Effect sizes (partial eta-squared) for the Time × Intervention interaction of all HRV parameters.

(39) = -.54, *ns*, nor in their postoperative state anxiety levels (female: $M = 35.2$, $n = 20$; male: $M = 31.69$, $n = 26$), t (44) = 1.41, *ns*. Positive relationships between patients' trait and preoperative state anxiety, $r = .69$, $n = 40$, p (one-tailed) < .001, and between trait and postoperative state anxiety, $r = .51$, $n = 43$, p (one-tailed) < .001, were observed.

Discussion

As the study's main focus, differential cardiovascular load caused by CEA and CAS under LA has been demonstrated by HRV measurements. As expected, SDNN, TP, and pNNxx values generally increased after CAS and decreased after CEA. No significant Time × Intervention interactions, however, were found for HF and LF. A significant main effect of Intervention was found for TP (CEA < CAS). Taken together, the results support the assumption of greater HRV after CAS compared to CEA. This is, to some extent, in line with the results of Sigaudo-Roussel, *et al.* [21] who observed HRV reductions when comparing preoperative values to those six weeks later in patients after CEA, suggesting that the surgical procedure might have generally burdened patients with more cardiovascular load compared to the minimally invasive intervention, thus resulting in reduced overall HRV in the postoperative period.

The study furthermore focused on an evaluation and comparison of effect sizes of several HRV parameters. In line with Mietus, *et al.* [24], Kim, *et al.* [23], and Trimmel [8,10] pNNxx thresholds around 25 ms mirrored subtle differences in HRV and in particular vagal activity that were less effectively captured by the usually applied 50 ms threshold. In the present investigation, pNN20, pNN25, and pNN30 showed the highest effect sizes, whereas parameters with lower (pNN05 and pNN10) or higher (pNN40 and pNN50) thresholds showed somewhat smaller effect sizes. Considering the effect sizes as well as the association with HF, pNN20, pNN25, and pNN30 seem more favorable than pNN50 and can be considered as indicators of vagal activity, however displaying higher effect sizes than pNN50 and HF. This advantage of using pNNxx statistics other than the traditional 50 ms threshold also supports findings in other research areas, such as fetal development [30], the impact of psychotropic medication on HRV in schizophrenic patients [23], flight phobia [9], and disturbed well-being [10]. The time domain parameter SDNN displayed the greatest Time × Intervention interaction effect and effect size, however indicating HR variability from unspecific origin. Regarding the frequency domain parameters, a significant interaction effect along with the second highest effect size was demonstrated for TP (an indication of overall HRV), and the results concerning LF and HF were rather inconclusive.

The differential impact of the interventions on HRV cannot be attributed to differences in anxiety, as no group differences in anxiety were found in ratings. Regarding the perceived medical intervention load, the only differences in 4 out of 23 items could be explained by the fact that the intervention room used for CAS might seem less frightening than the "real" operating room. Moreover, an anesthesiologist monitors the patients throughout the CEA procedure, which might enhance communication, increase trust in the medical staff, and foster relaxation. The reassuring effect of someone attending specifically to the patient was also reported by McCarthy, *et al.* [26].

This, as well as the increased use of sedatives during CEA, might at least partly explain the finding that the longer and more invasive procedure was subjectively not associated with more load. There was furthermore no association with the duration of the procedure or the patients' gender. In line with previous findings [26,27], patients were generally satisfied with the procedures and associated factors (e.g. provision of information, communication) and didn't report to have experienced the procedures as very stressful events.

Patients from both groups showed high preoperative state anxiety which dropped postsurgically, as previously shown [31-34]. This decline can be explained by the patients' fast recovery and the patients' relief that surgery was over. Pre- and postoperative state anxiety were positively associated with trait anxiety, as reported previously [35]. Though frequently reported [31,36,37], no gender differences in anxiety were observed in the investigated sample. As trait and postoperative state anxiety were positively related to the perceived medical intervention load (PMIL), strategies to reduce patients' anxiety before surgery are important to prevent detrimental effects on health and subjective well-being and to achieve beneficial effects for perioperative compliance, adaptation (e.g. reduced need for sedatives), and recovery [35,38,39].

Constraints of the present study firstly concern the non-random allocation of patients to the interventions. This grouping is disadvantageous concerning internal validity, but goes along with high ecological validity as it is representative for clinical practice. Moreover, randomization wouldn't have been feasible with regard to the best medical treatment for each patient. Secondly, concomitant medications might have had an influence on HRV, as also discussed by Yakhou, *et al.* [22]. In fact, all patients suffered from medical conditions necessitating drugs (e.g. 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 analysis. The study didn't influence clinical practice and all patients were maintained on their normal and postsurgically revised medication schedule.

As a high HRV, specifically high vagal and low sympathetic activity, is important regarding possible associations between HRV and morbidity (e.g. hypertension or CHD) and mortality, any medical intervention should positively affect ANS modulation of HR [13,40]. Future research could address long-term treatment effects, pay more attention to the intraoperative situation, and take into account the impact of medication. The role of sedatives with respect to the subjective perception of the medical interventions also deserves closer attention.

Summing up, findings of the present study showed an interaction of intervention and changes in HRV parameters over time, in terms of greater HRV after CAS compared to CEA but no group differences in subjective ratings of trait anxiety, pre- and post-state anxiety, and perceived medical intervention load (PMIL).

Acknowledgments

The authors express their gratitude to the Hanusch Hospital, in particular to the teams from the surgical and radiological departments, where the study was conducted.

Conflicts of interest

None

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