Cardiovascular Effects of Mental Stress in Healthy Volunteers

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Abstract

Mental stress causes a physiological response and is often assessed by heart rate variability. In this work, we investigated cardiovascular parameters other than heart rate variability.

We performed a stress test with 44 healthy volunteers and evaluated 17 cardiovascular parameters measured with a CNSystems Task Force® Monitor, several self-reported measures as well as cortisol and α-amylase concentrations from saliva samples. By statistical testing we determined the cardiovascular parameters that exhibited the clearest response to the stress test. In addition, we attempted the classification of cardiac cycle states using a random forest classifier that was evaluated with Cohen's kappa κ in a leave-one-subject-out cross-validation.

From the cardiovascular parameters, heart rate, cardiac output, cardiac index, mean blood pressure, and left ventricular work index yielded significant results. Cardiac cycle state classification reached $\kappa = 0.58$. While the self-reported measures showed clear stress responses, salivary cortisol and α-amylase concentrations remained mostly unaffected.

The presented study provides insights into the physiological response to mental stress. We identified the parameters that showed a clear stress response, with the strongest effect found for the elevated left ventricular work index.

1. Introduction

The human response to psychological stress evolves in two systems, the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis (HPA axis). While the reaction of the HPA axis takes longer (within minutes), the reaction of the ANS is fast (within seconds) [1]. The HPA axis alters the salivary cortisol concentration [2]. The ANS, consisting of sympathetic and parasympathetic nervous system, influences cardiac control mechanisms, vascular tone, and salivary α-amylase concentration. While often heart rate variability is calculated to identify cognitive strain [2], we examine the impact of mental stress in this work based on other cardiovascular parameters.

2. Methods and Materials

The TU Dresden Ethics Committee[1] granted permission to conduct the study described below prior to commencement (EK 411092019).

2.1. Participants

All participants gave informed consent prior to the study and reported to be healthy and not pregnant. Table 1 shows the characteristics of the participants in the study.

Table 1: Participants characteristics of the study.

Parameter		Mean ± SD	Range
Age	in years	25.8 ± 5.3	18 – 39
Weight	in kg	68.8 ± 11.4	53.5 – 100
Height	in cm	175.5 ± 9.0	160 – 194
BMI	in kg/m^2	22.2 ± 2.5	17.4 – 29.9
Female: 16		Male: 28	Total: 44

2.2. Stimulation

To investigate the effects of mental stress, we set up a study consisting of six blocks (see Fig. 1). Mental stress was induced in the second block by the Mannheim Multicomponent Stress Test (MMST) [3], which took 8–10 min including a training phase. The stress test was enclosed by two 5 min rest periods. To include the response of the HPA axis, three 10 min rest blocks followed. During all rest blocks, the same relaxation video was played.

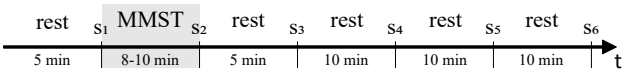


Figure 1: Design and timeline of the study. s_i marks the assessment break after each block i = 1...6.

[1] Institutional review board officially registered at the Office for Human Research Protections (IRB00001473, IORG0001076).

2.3. Data Collection

We collected data with a Task Force® Monitor 3040i (CNSystems Medizintechnik GmbH, Graz, Austria). The device acquired a 2-lead electrocardiogram (Einthoven I and II) at 1000 Hz, an impedance cardiogram at 500 Hz, continuous blood pressure with the vascular unloading technique at 100 Hz, and oscillometric blood pressure at the right upper arm. From these signals, the device calculated 17 cardiovascular parameters for haemodynamic monitoring of every cardiac cycle (see Table 2). For details on the calculation of these parameters, we refer to [4].

Table 2: Overview over the cardiovascular parameters.

Name		Unit
HR	(instantaneous) heart rate	bpm
CO	cardiac output	l/min
CI	cardiac index	l/(min*m^2)
SV	stroke volume	ml
SI	stroke index	ml/m^2
TPR	total peripheral resistance	dyne*s/cm^5
TPRI	total peripheral resistance index	dyne*s*m^2/cm^5
dBP	diastolic blood pressure	mmHg
mBP	mean blood pressure	mmHg
sBP	systolic blood pressure	mmHg
ppBP	pulse pressure	mmHg
ACI	acceleration index	100/s^2
EDI	enddiastolic index	ml/m^2
IC	contractility index	1000/s
LVET	left ventricular ejection time	ms
LVWI	left ventricular work index	mmHg*l/(min*m^2)
TFC	thoracic fluid content	1/kOhm

The participants completed a short questionnaire after each block (see Fig. 1). The questionnaires assessed the perceived stress on a 10-point Likert scale and included the 5-pictogram self-assessment Manikin (SAM) [5] with the dimensions valence, arousal and dominance. Meanwhile, saliva samples were collected in Salivettes (Sarstedt AG & Co. KG, Nümbrecht, Germany). Every assessment break for questionnaire and saliva sample took 3–4 min.

2.4. Evaluation

The evaluation was split into three parts: (A) stress response investigation, (B) cardiac cycle state prediction, and (C) reference measure investigation. While (A) aimed to determine the cardiovascular parameters that exhibited the clearest response to the stress test within the block structure, (B) addressed the question of how well each individual cardiac cycle can be assigned to the states of rest and stress, and (C) targeted the stress response in the reference measures (questionnaires and saliva samples).

(A) Stress response investigation: From the last 5 min of each block, the mean value of each parameter was calculated for each participant. Since the means were not normally distributed, only parameter-free tests were applied. At first, a Friedman test was applied to check whether a parameter showed a significant effect across the blocks. Only those parameters that showed a significant effect ($p < 0.001$) were investigated with pairwise Wilcoxon ranksum tests to identify between which blocks significant differences occurred. If a parameter differed significantly ($p < 0.001$) between the stress block and all five rest blocks, the effect size (rank-biserial correlation) of the parameter was computed. We chose high p-values to avoid effects of natural variation (e.g. regulatory processes) and focus on distinct parameter changes.

(B) Cardiac cycle state prediction: In order to see how well individual cardiac cycles can be assigned to the states of rest and stress, a random forest classifier was evaluated with Cohen's kappa κ in a leave-one-subject-out cross-validation setup. κ is defined as [6]:

$$\kappa = (ACC - p_0)/(1 - p_0), \tag{1}$$

and compares the classification accuracy ACC (share of correct predictions in the test set) against the accuracy of random guessing p_0. To ensure a balanced dataset ($p_0 = 0.5$), the rest beats were randomly sampled from blocks 1, 3, 4, 5, and 6, where the number of rest beats was determined by the number of stress beats from block 2. The classification was performed one time with the full feature set, and one time with a reduced feature set including only the parameters identified as significant in (A). This procedure was repeated with normalized values to reduce intersubject differences. The normalization was performed for each participant and each parameter by division through the mean value of the first block (initial rest).

(C) Reference measure investigation: The relationship of the reference measures to the cardiovascular parameters was assessed in a correlation analysis, where Spearman's ρ was calculated between the mean values from (A) and the reference measures, both normalized as described in (B). Evaluation of the saliva samples for cortisol and α-amylase concentrations was performed by a professional laboratory (Dresden LabService GmbH, Dresden, Germany), which stated: "Saliva samples were frozen and stored at −20 °C until analysis. After thawing, Salivettes were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were both below 9 %."

3. Results

In the **stress response investigation (A)**, 12 cardiovascular parameters showed significant effects in the Friedman tests (see Table 3). Five of these parameters were

identified to significantly differ between the stress block and all five rest blocks (see Table 4): HR, CO, CI, mBP, and LVWI. They reached effect sizes of 0.31, 0.28, 0.30, 0.38, and 0.46 respectively, which are considered medium (0.3) to large (0.5) for rank-biserial correlation [7]. Figure 4 shows the distributions of these parameters. TFC as well as dBP and sBP almost fulfilled the significance criterion. They scored significant results for 4 out of 5 rest blocks with block 3 missing.

Table 3: Results of the Friedman tests to investigate whether the cardiovascular parameters differ significantly between the blocks (***: $p < 0.001$).

Param.	p-value	Param.	p-value	Param.	p-value
HR	***	**TPRI**	***	**EDI**	***
CO	***	**dBP**	***	**IC**	***
CI	***	**mBP**	***	LVET	0.0879
SV	0.0014	**sBP**	***	**LVWI**	***
SI	0.0014	ppBP	0.2975	**TFC**	***
TPR	***	ACI	0.0012		

Table 4: Results of the Wilcoxon ranksum tests for pairwise comparison of the stress block with the rest blocks. N_{sig} gives the number of significant tests (***: $p < 0.001$).

Params.	Block 1	Block 3	Block 4	Block 5	Block 6	N_{sig}
HR	***	***	***	***	***	**5**
CO	***	***	***	***	***	**5**
CI	***	***	***	***	***	**5**
TPR	0.0047	0.0357	0.1873	0.3751	0.7527	0
TPRI	0.0039	0.0460	0.1758	0.4140	0.8154	0
dBP	***	0.0035	***	***	***	4
mBP	***	***	***	***	***	**5**
sBP	***	0.0065	***	***	***	4
EDI	***	0.0059	0.0117	0.0057	0.0250	1
IC	0.0291	0.7438	0.9071	0.9164	0.6659	0
LVWI	***	***	***	***	***	**5**
TFC	***	0.0013	***	***	***	4

Table 5 summarizes the results of the **cardiac cycle state prediction (B)**. The classifier performed better when the parameters were normalized and when the full feature set was used.

Table 5: Results of cardiac cycle state prediction with a random forest classifier. Cohen's kappa κ calculated with $p_0 = 0.5$.

κ	No normalization	Normalization to initial rest
Full feature set	0.30	0.58
Reduced feature set	0.23	0.46

Fig. 2 and 3 summarize the results of the **reference measure investigation (C)**. Highest correlations ($p < 0.001$, $|\rho| > 0.3$) were found for: perceived stress with HR (0.38), CO (0.34), CI (0.34), and LVWI (0.36); SAM valence with HR (-0.35); SAM arousal with CO (0.33), CI (0.33), and LVWI (0.32); SAM dominance with CO (-0.36), CI (-0.36), and LVWI (-0.31). Cortisol and α-amylase showed generally low correlations. While strong variance covered the cortisol and α-amylase response, perceived stress level and SAM arousal increased, and SAM valence and SAM dominance decreased during the stress block (see Fig. 3).

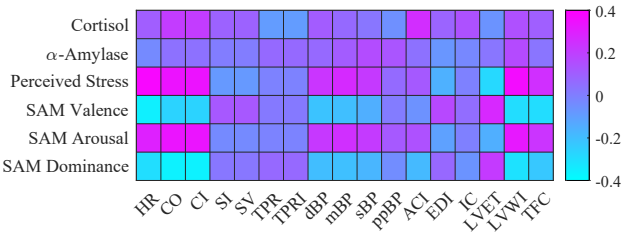


Figure 2: ρ-heatmap of the Spearman correlations between the normalized cardiovascular parameter means and the normalized reference measures.

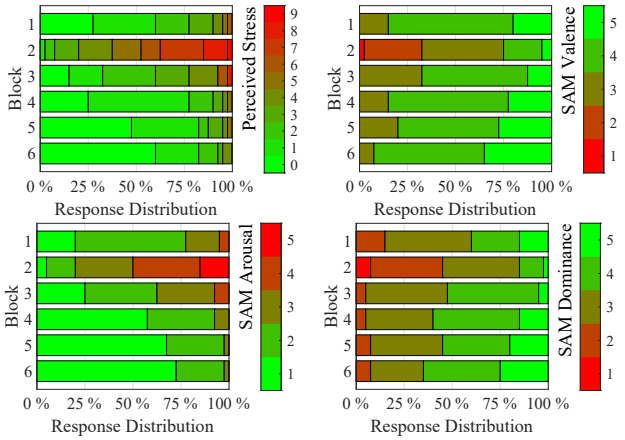
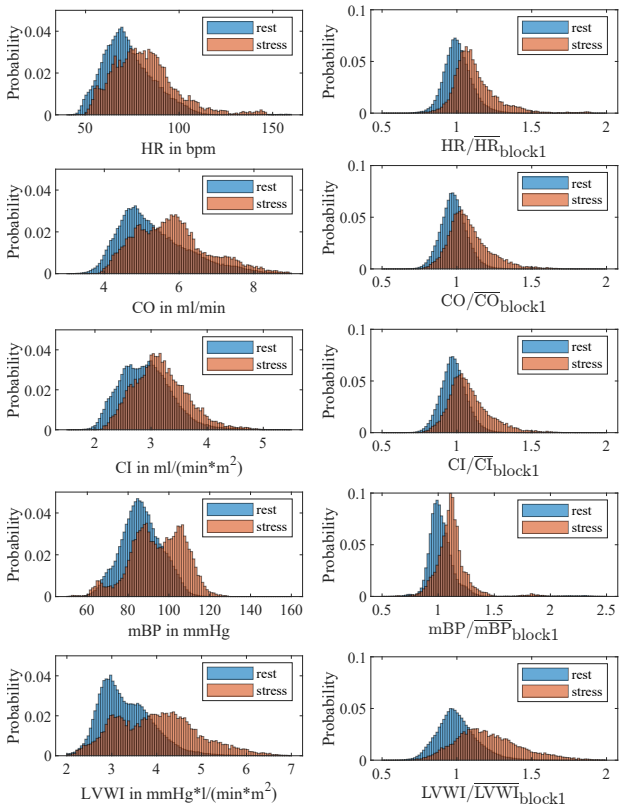


Figure 3: Results of the self-reported reference measures from the questionnaires after each block.

4. Discussion

Our results showed that mental stress triggers cardiovascular effects in healthy volunteers. These effects were mainly mediated by the ANS, as the saliva sample analysis provides only limited evidence for a response of the HPA axis. It is known that stress does not necessarily affect both HPA axis and ANS [8]. However, the self-reported measures clearly indicated mental strain.

While a positive chronotropic effect is explicable (elevated HR), the positive inotropic effect and peripheral vasoconstriction appear less pronounced: Although SV, SI, TPR, and TPRI did not meet the significance criteria,



(a) Original data. (b) Data normalized to initial rest.

Figure 4: Distributions of the cardiovascular parameters identified through the stress response investigation. The data originated from all beats of all participants separated by state. Each histogram consists of 100 bins.

mBP did. It should be noted that some of the measures are highly correlated. From the identified cardiovascular parameters, CI equals CO divided by body surface area [4], a constant approximated from width and height of a participant. LVWI is linearly related to the product of mBP[2] and CI [4].

Except for mBP, the correlation analysis of (C) indicated validation of the stress response investigation (A). Increased perceived stress is associated with increased HR, CO, CI, mBP, and LVWI. We suspect that varying recovery delays (see Table 4) affected $|\rho|$ of the blood pressure parameters. The low correlations of salivary cortisol and α-amylase can be explained by the high dispersion of these measures and their delayed response to stimulation.

The cardiac cycle state prediction showed that intersubject differences hamper satisfactory classification. Normalization improved the prediction quality as it roughly doubled κ for both feature sets. Since the full feature set yielded better results, residual information must remain in the cardiovascular parameters outside the reduced feature set. The results of the Wilcoxon ranksum tests imply that especially dBP, sBP, and TFC hold this information. It should be noted that the classification was set up with a balanced dataset. While the assumption of identical occurrence probabilities of rest and stress was of interest to the study from a methodological perspective, its validity to a realistic monitoring scenario is certainly limited.

In conclusion, we found significant effects of medium to large size in the cardiovascular parameters HR, CO, CI, mBP, and LVWI that indicate ANS activity. While a distinct response of the HPA axis could not be observed, subjective perception of stress was clearly evident.

[2]Corrected by a constant for pulmonary artery occluded pressure [4].

Acknowledgments

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