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RESEARCH ARTICLE



## Cold pressor stress effects on cardiac repolarization

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### ABSTRACT

The cold pressor test (CPT) elicits strong cardiovascular reactions *via* activation of the sympathetic nervous system (SNS), yielding subsequent increases in heart rate (HR) and blood pressure (BP). However, little is known on how exposure to the CPT affects cardiac ventricular repolarization. Twenty-eight healthy males underwent both a bilateral feet CPT and a warm water (WW) control condition on two separate days, one week apart. During pre-stress baseline and stress induction cardiovascular signals (ECG lead II, Finometer BP) were monitored continuously. Salivary cortisol and subjective stress ratings were assessed intermittently. Corrected QT (QTc) interval length and T-wave amplitude (TWA) were assessed for each heartbeat and subsequently aggregated individually over baseline and stress phases, respectively. CPT increases QTc interval length and elevates the TWA. Stress-induced changes in cardiac repolarization are only in part and weakly correlated with cardiovascular and cortisol stress-reactivity. Besides its already well-established effects on cardiovascular, endocrine, and subjective responses, CPT also impacts on cardiac repolarization by elongation of QTc interval length and elevation of TWA. CPT effects on cardiac repolarization share little variance with the other indices of stress reactivity, suggesting a potentially incremental value of this parameter for understanding psychobiological adaptation to acute CPT stress.

### ARTICLE HISTORY

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### KEYWORDS

Cardiac repolarization; ventricular repolarization; cold pressor test; sympathetic nervous system; HPA-axis; stress

### 1. Introduction



In response to danger and threat, vertebrates exhibit a complex psychobiological stress response. Several neuroendocrine stress mechanisms are activated, and their precise adjustment and coordination are crucial for adaptation when confronting different challenges. The hypothalamus–pituitary–adrenal (HPA) axis, with its main hormonal end-product cortisol (in humans), as well as the sympathetic nervous system (SNS) play key roles in stress responding. The latter is also thought to underlie peripheral concomitants of emotional arousal which also constitutes an essential element of the stress response (Chrousos et al., 2013).

SNS activation results in the release of norepinephrine (NE) from post-ganglionic sympathetic nerves, as well as (further) catecholamines into the systemic blood stream. This results in well-established cardiovascular effects, such as elevation of blood pressure (BP) and heart rate (HR), increased myocardial (e.g. ventricular) contractility and excitability, as well as a shortening of the pre-ejection period (Schächinger et al., 2001). Indeed, changes in HR and BP are among the most often reported indices in human stress research (Allen et al., 2014; Finke et al., 2018). Other cardiac mechanisms, such as cardiac repolarization, have received less attention, although stress has been associated with cardiac arrhythmias in patients with

heart disease (Eliot & Bull, 1985) as well as healthy individuals (Lown et al., 1976).

Parameters of ventricular repolarization, such as the QT interval and T-wave amplitude (TWA), although closely related to HR, have been discussed as independent, noninvasive biomarkers of SNS activity (Andrássy et al., 2007; Furedy, 1987). Sympathetic stimulation by means of epinephrine infusion has been shown to prolong QT interval (Darbar et al., 1996; Magnano et al., 2006) and diminish TWA (Drost et al., 2022). An elongation of QT interval was observed during emotional or mental stress (Andrássy et al., 2007; Bhide et al., 2016; Merz & Pardo, 2000). Similarly, mental stress has been linked to decreased, inversed, or biphasic T-waves (Andrássy et al., 2007; Rau, 1991; van Lien et al., 2015).

The cold pressor test (CPT) is among the most frequently employed stress induction protocols in human research (Lamotte et al., 2021; Lovallo, 1975). It reliably evokes a stress response with a strong SNS and HPA-axis activation (Bachmann et al., 2018; Elias & Ajayi, 2019) making it a valuable paradigm for studying the physiological and psychological aspects of stress reactivity. However, to our knowledge, cold-stress evoked changes in QT interval length and TWA have received very little attention in experimental research so far. Furthermore, it remains uncertain whether potential stress effects on ventricular repolarization are redundant to established (cardiovascular, neuroendocrine, subjective) indices of

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stress reactivity, or represent a different and new source of variance in stress adaptation. This study aims to replicate and extend previous findings regarding ventricular repolarization during cold exposure of a single hand (Stancák et al., 1996) by employing a bilateral feet CPT paradigm and adding the examination of QTc interval length as a supplemental index of cardiac repolarization. Moreover, the study seeks to elucidate whether changes in ventricular repolarization under cold stress are associated with standard biomarkers of stress responsivity.

## 2. Methods

### 2.1. Sample

The data presented in this article were collected as part of a larger study aimed at validating an automatized CPT protocol (Bachmann et al., 2018). Twenty-eight healthy male volunteers (mean age  $26 \pm 3$  years) were recruited through university mailing lists and flyers. All participants had normal body weight (BMI between 19 and  $25 \text{ kg/m}^2$ ). Prior to participation in the study, a telephone screening was conducted to examine whether any exclusion criteria were met. Exclusion criteria were as follows: (1) any medical (especially chronic or cardiovascular) conditions, (2) diagnosed psychiatric diseases, (3) regular use of medication or drugs (except occasional NSAIDs use), (4) intolerance of cold temperature, (5) Raynaud's disease, (6) history of syncope, (7) feet infection, and (8) smoking more than five cigarettes daily. All participants were requested to abstain from heavy exercise and alcohol or caffeine consumption the night before as well as the morning of the experiment. This study was conducted as a within-subject repeated measures design, so all participants came to the lab twice. In line with the rules of the Declaration of Helsinki, the study was approved by the local ethics committee (Landesärztkammer Rheinlandpfalz, application no. 837.158.15 (9926)). All participants signed written informed consent and received a monetary reward for their participation after the second experimental day.

### 2.2. General procedure

A detailed description of the study procedure is provided elsewhere (Bachmann et al., 2018). Participants came to the lab on two days one week apart at the same time of the day between 1 pm and 5 pm. Each participant was subjected to a bilateral feet CPT and a warm water (WW) control condition on separate days. The order of conditions was randomized across participants. Participants were not informed that they would undergo both conditions (CPT and WW), nor about the specific conditions they were assigned to each experimental day.

Participants were seated on a height-adjustable chair and placed their bare feet into still empty tubs before electrodes and cuffs were attached for continuous physiological assessment. The experiment included various resting periods (for a detailed description of the study protocol refer to Bachmann et al. (2018)). Yet, this study only reports immediate pre-stress

(2 min before stress) and stress (3 min) data. Salivary cortisol samples as well as subjective ratings of arousal, stress, and pain were provided at predefined time points before and after the stress protocol.

Experimental timing was controlled by E-Prime software (E-Prime®, Psychology Software Tools, Inc., Sharpsburg, PA). After the detachment of recording devices, participants spent an hour in a waiting room engaging in non-arousing activities. During that time further salivary cortisol samples were collected.

### 2.3. Stress induction (cold pressor test)

Both feet of the participants were either exposed to ice water ( $2\text{--}3^\circ\text{C}$ , CPT) or WW ( $36\text{--}37^\circ\text{C}$ , WW) for exactly 3 min. The tubs were automatically filled with water and the timing was controlled by Lab-VIEW software (National Instruments™, Munich, Germany).

During the screening interview participants were informed that although the CPT would likely cause pain, it would not cause any tissue damage because the water temperature could never fall below  $0^\circ\text{C}$ . Participants were also informed that paramedical staff was available at any time in case of an emergency and that they would be continuously monitored through cameras. During the CPT procedure, there was no interaction between the participants and the experimenter, although the participants could contact the experimenter at any time *via* intercom. No external clues revealed the remaining time of the procedure. None of the participants discontinued the CPT procedure voluntarily prior to the full duration of 3 min. One person experienced a pre-syncope state during the cold water stimulation and the test was terminated by staff. This participant was not included in the study.

### 2.5. Physiological measurements

#### 2.5.1. Cardiovascular parameters

Cardiovascular parameters were continuously recorded using Finometer (Finapres Medical Systems B.V., Amsterdam, The Netherlands) attached to the left middle finger. Additionally, ECG data were recorded in a standard lead II configuration, amplified with AccuSync®71 (AccuSync®, Milford, CT), high-pass filtered ( $0.05 \text{ Hz}$ ) and digitized with 16-bit resolution at a sampling rate of 1 kHz (BrainVision Recorder V. 1.20.0801, Brain Products GmbH, Munich, Germany).

WinCPRS (version 1.162 Absolute Aliens Oy, Turku, Finland) was used to derive RR intervals (RRI), systolic blood pressure (SYS), corrected QT interval (QT interval corrected for HR using the Bazett formula:  $\text{QTc} = \text{QT} / \text{RR}^{0.5}$ ) and TWA.

#### 2.5.2. Salivary cortisol

Saliva cortisol samples were collected using plain synthetic swabs (Salivette Cortisol, Sarstedt, Nümbrecht, Germany) 5 min before as well as 17, 25, 27, 46, and 55 min after CPT or WW procedure. Until all samples of a participant were obtained, the samples were kept at room temperature and then stored at  $-20^\circ\text{C}$ . After thawing the samples for

biochemical analysis, the fraction of free cortisol in saliva was established using a time-resolved immunoassay with fluorescence detection (Dressendörfer et al., 1992). Inter- and intra-assay coefficients of variation were between 7–9% and 4–7%, respectively.

### 2.5.3. Subjective ratings

Subjective ratings of stress were provided five minutes before and immediately after stress on visual analog scales (VAS) ranging from 0 (“not at all”) to 100 (“extremely”). Immediately after stress, participants also indicated pain aversion (“How unpleasant was the pain during the procedure?”), pain intensity (“How intense was the pain during the procedure?”) and tenseness (“How tense did you feel during the procedure?”). These individual responses were subsequently added to create a composite measure of pain.

## 2.6. Data reduction and statistical analysis

All cardiovascular variables were tested for baseline differences using paired t-tests and then baseline-corrected by subtracting the mean value of the pre-stress phase from each data point, for each participant and cardiovascular parameter respectively. Based on average values during the STRESS (or control) period, delta ( $\Delta$ ) scores were thus computed for each cardiovascular parameter as well as subjective ratings, serving as indices of stress reactivity. For cortisol data, baseline correction involved subtracting each participant’s pre-stress measurement from subsequent measurements. The area under the curve with respect to increase (AUCi) was then calculated for each participant to quantify HPA reactivity.

For each dependent variable (cardiovascular parameter, AUCi, ratings), paired t-tests were calculated to assess differences between CPT and WW condition. Additionally, intercorrelations between all reactivity measures were examined. For illustration purposes only, cardiovascular data points are depicted as the average value within 15-s intervals.

Data from one participant were discarded because of technical problems during data recording and one participant had to be excluded because of ventricular extrasystoles. Thus, the final sample analyzed consisted of 26 participants. Subjective stress ratings were missing from one, and pain ratings from two participants. All statistical analyses were performed using RStudio version 4.1.2 (RStudio Team, 2020). The mean and the standard error of the mean (SEM) are presented in tables and figures.

## 3. Results

### 3.1. Cardiovascular parameters

Figure 1 illustrates the time course of cardiovascular parameters across conditions. Paired t-tests revealed no significant differences in pre-stress baseline between conditions (all  $p > 0.3$ ).

Significant stress reactivity (differences between CPT and WW interventions) was found for all cardiovascular parameters, indicating shorter RRI, higher SYS, longer QTc,

and elevated TWA during CPT stress (see Figure 1 and Table 1).

### 3.2. Salivary cortisol

Mean AUCi was significantly higher after CPT compared to the WW condition ( $t(25) = 4.03$ ,  $p < 0.001$ ).

### 3.3. Subjective ratings

Participants had significantly higher reactivity in subjective ratings of stress ( $t(25) = 4.88$ ,  $p < 0.001$ ) and pain ( $t(24) = 17.46$ ,  $p < 0.001$ ) in the CPT condition compared to the WW condition.

### 3.4. Correlation analysis

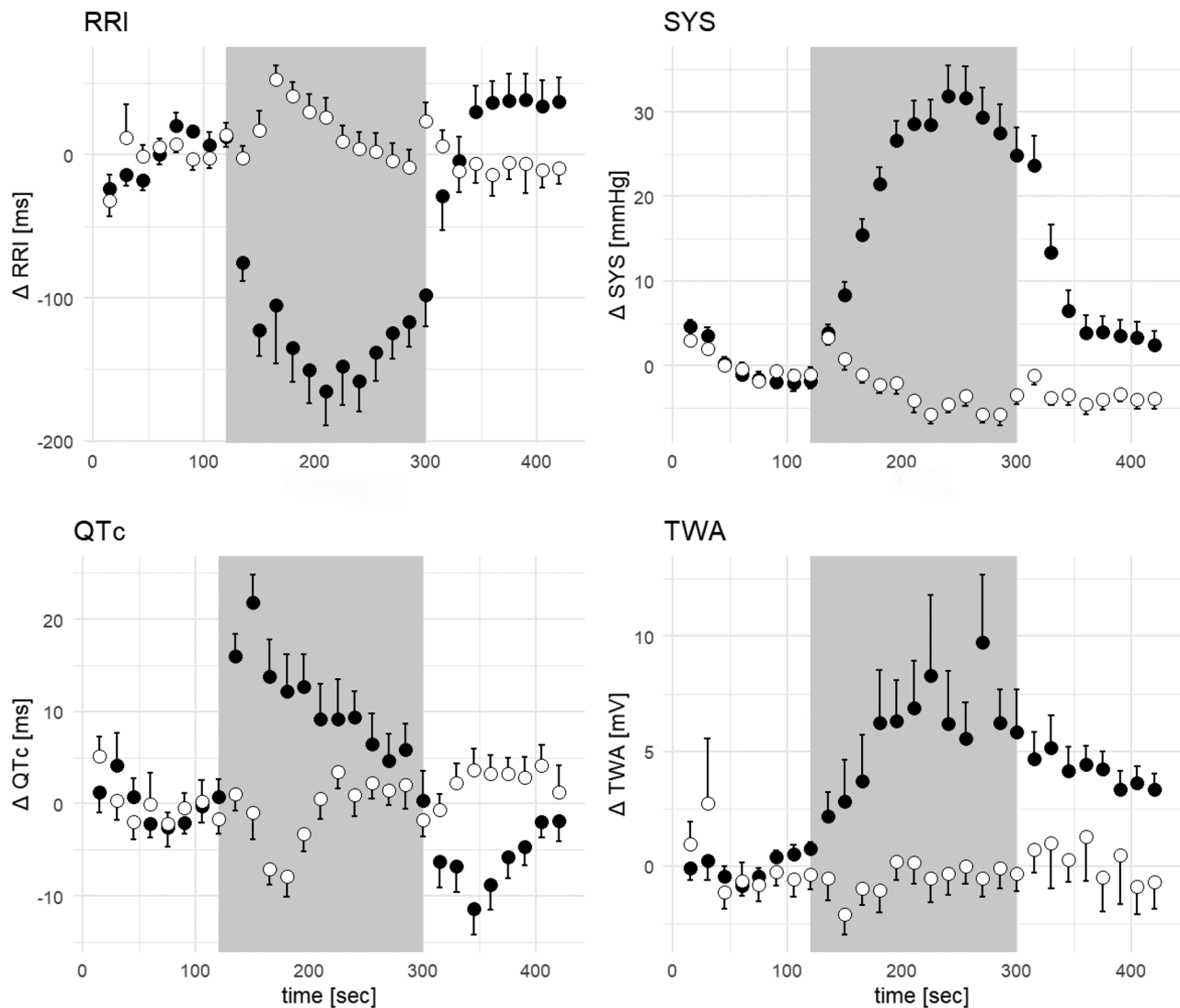
The full correlation table is provided in Table 2. Significant correlations were present between RRI and QTc, RRI and AUCi, RRI and subjective stress as well as AUCi and subjective stress. QTc correlated with TWA.

## 4. Discussion

The objective of this study was to investigate the effects of the CPT on cardiac repolarization, and comparing potential repolarization effects with established markers of cardiovascular and endocrine stress reactivity. Our results demonstrate that exposure to cold stress induces an elongation of the QTc interval and an elevation of TWA. Furthermore, there was minimal correlation between the measures of cardiac repolarization and common endocrine (i.e. cortisol) and cardiovascular stress indices.

In line with our results, prolongation of QTc interval length has been observed after mental stress (Andrássy et al., 2007; Bhide et al., 2016; Merz & Pardo, 2000), epinephrine infusion (Ackerman et al., 2002; Darbar et al., 1996; Kaufman et al., 2005; Magnano et al., 2006), and physical exercise (Yu & Soffer, 1952). Pharmacological experiments suggest that changes in QT interval length are driven by changing ANS activity, especially the level of circulating catecholamines (Akhras & Rickards, 1981; Browne et al., 1982; Magnano et al., 2002). Insulander et al. (2003) reported stronger QT interval length effects from mental stress as compared to epinephrine infusion, suggesting that neural autonomic activity may play a more important role than circulating catecholamines. Furthermore, it is worth noticing that QT interval prolongation represents a well-established manifestation of general hypothermia (Aslam et al., 2006; de Souza et al., 2007). Although it is impossible that 3-min feet immersion in ice-cold water induces systemic hypothermia, some unknown mechanism might mediate similar effects on ventricular repolarization.

Contrary to previous studies (Andrássy et al., 2007; Drost et al., 2022; Hatch & Borcharding, 1991; Rau, 1991), our findings did neither reveal flattening nor inversion of the T-wave. Instead, we identified a significant elevation of TWA during CPT stress. This finding aligns with the results of Stancák



**Figure 1.** Baseline corrected (15s mean  $\pm$  SE) cardiovascular signals (RRI: RR interval length, SYS: systolic blood pressure, QTc: corrected QT interval, TWA: T-wave amplitude) during cold pressor test (CPT) and warm water (WW) control condition. Grey area indicates time of intervention.

**Table 1.** Paired t-test results for each cardiovascular parameter.

	$M_D$	95% CI	$t$	$df$	$p$
RRI	-143.26	[-183.14, -103.37]	-7.40	25	<0.001
SYS	25.89	[21.43, 30.35]	11.96	25	<0.001
QTc	10.92	[5.76, 16.09]	4.35	25	<0.001
TWA	6.24	[2.19, 10.30]	3.17	25	0.004

RRI: RR-interval; SYS: systolic blood pressure; QTc: corrected QT interval; TWA: T-wave amplitude

**Table 2.** Pearson correlation of reactivity ( $\Delta$  CPT -  $\Delta$  WW) for all dependent stress variables.

	RRI	SYS	QTc	TWA	AUCi	Stress	Pain
RRI	1.00						
SYS	-0.29	1.00					
QTc	-0.45*	0.14	1.00				
TWA	-0.24	0.16	0.50**	1.00			
AUCi	-0.59**	0.28	-0.13	-0.03	1.00		
Stress	-0.43*	0.02	0.14	-0.08	0.49*	1.00	
Pain	-0.07	0.11	-0.28	-0.10	0.26	0.48*	1.00

RRI: RR-interval; SYS: systolic blood pressure; QTc: corrected QT interval; TWA: T-wave amplitude; AUCi: area under the curve with respect to increase; Stress: subjective stress ratings; Pain: subjective pain ratings

\* $p < 0.05$ , \*\* $p < 0.01$ .

et al. (1996) and Hintsala et al. (2014), who observed increased TWA during repeated 1-min hand immersion and 15-min full body cold stress exposure. The full-body cold exposure (Hintsala et al., 2014) likely induced a substantial hypothermic effect, and cannot directly be compared to our comparatively brief 3-min feet cold immersion procedure. Yet, the combination of cold exposure and sympathetic activation might have led to a similar altered ventricular repolarization pattern of heightened TWA. Our results contrast with findings of Roth et al. (1992) who investigated stress reactivity in patients with panic disorder. The authors reported reduced TWA during a 1-min cold exposure of the dominant foot in both patients and healthy controls. The disparity in their results and ours underscores the complexity of TWA responses to various stressors and suggests that individual history and health conditions as well as other factors, such as the nature and duration of stressors, may impose complex impact on TWA. Interestingly, CPT stress may elicit T-wave changes similar to those seen in vigorous exercise (Kennedy & Mayhew, 1971; Whyte & Sharma, 2010). However, more research is required

to fully understand why CPT stress effects on ventricular repolarization differ from mental stress or epinephrine infusion effects.

The significant correlation between  $\Delta$  RRI and  $\Delta$  QTc, but not between  $\Delta$  RRI and  $\Delta$  TWA, might relate to the fact that QTc and RRI share a common mathematical term (HR), and align with findings of previous studies, observing limited or negligible associations between HR and T-wave metrics (Andersen et al., 2008; Hintsala et al., 2014). While we observed a correlation between  $\Delta$  QTc and  $\Delta$  TWA, neither index correlated with standard sympathetic or neuroendocrine stress measures. Thus, our study may provide preliminary evidence that alterations of ventricular repolarization during stress may be independent of SNS changes, and suggesting an additional potential as a supplementary stress biomarker.

$\Delta$  RRI was significantly correlated with  $\Delta$  cortisol reactivity, highlighting the interaction between SNS and HPA-axis through complex feedback mechanisms. SNS-activation stimulates CRH release from hypothalamus, while cortisol can enhance sympathetic stress effects (Chrousos, 2009). Subjective pain and stress ratings were not associated with markers of repolarization, nor with cortisol levels. Indeed, subjective stress perception may not always align with objective physiological or neuroendocrine stress markers (Campbell & Ehlert, 2012; Dickerson & Kemeny, 2004). Temporal misalignment between the subjective and physiological stress assessment may explain this discrepancy. Real-time emotional ratings might yield more accurate results compared to pre-post measures (Schlotz et al., 2008).

## 5. Limitations

Several limitations should be considered when interpreting the results of this study. First, this study was not preregistered, thus the results presented should in part be interpreted as exploratory rather than confirmatory in nature. Second, alterations in repolarization patterns are influenced by multiple factors including SNS and PNS activity as well as electrolyte balance and neurohormonal factors. While this study primarily focused on the influence of SNS activity, other determinants were beyond its scope. Third, this study exclusively involved healthy, young male participants. Consequently, the results might not apply to clinical subgroups with dysfunction of SNS or HPA-axis, nor to individuals with a different ethnic origin, as these groups often show differences in ECG patterns (Santhanakrishnan et al., 2016). Moreover, sex differences have been described in the endocrine stress response (Kudielka & Kirschbaum, 2005), as well as the QT interval (Genovesi et al., 2007; Meher et al., 2014). As such, our findings should be replicated in diverse populations and female participants.

## 6. Conclusion

In conclusion, our results demonstrate that the CPT elicits changes in ventricular repolarization by elevating TWA, which contrasts to TWA decrease during contrast mental stress and

epinephrine infusion. Reactivity of ventricular repolarization indices and other (standard) stress markers share limited common variance. This implies that QTc and TWA stress changes reflect a new source of variance in stress research and may thus contribute to a deeper understanding of cardiac adaptation to stress.

## Disclosure statement

We report no potential conflict of interest.

## Notes on contributors

**Lisa Drost**, MSc, is interested in the physiological responses to stress and the relationship between the autonomic nervous system and cognitive processes.

**PD Dr. Johannes B. Finke**, is a senior researcher at the University of Siegen. His research primarily focuses on affective learning processes, stress and coping as well as emotional and cognitive processes, e.g. attentional biases.

**Dr. Petra Bachmann's** research focuses on the psychophysiological and emotional responses to stress.

**Dr. Med. Hartmut Schächinger** is a full professor at the University of Trier and specializes in the impact of stress on psychophysiology and cognition. He is interested in interoception and cognitive effects tied to visceral afferent neurotraffic in vivo.

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