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Validation of an automated bilateral feet cold pressor test

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ABSTRACT

The Cold Pressor Test (CPT) is often used in psychobiological research. However, the classical CPT version (unilateral hand immersion into ice-water) involves some disadvantages: hands may be needed for further applications, attentional drift towards the affected sensory hemi-field and/or physiological activation of the contralateral hemisphere may produce a laterality bias. Furthermore, instruction-induced motor activity may bias physiologic reactivity. To avoid these problems, a fully automated bilateral feet CPT was developed and tested for validity and feasibility. The test procedure is based on computerized control of water influx and efflux. This allows for maximal standardization and precise timing. Furthermore, water is kept in permanent flow to prohibit formation of stable temperature layers in skin proximity. Laterality bias, instructions effects and motor responses (e.g. lifting feet out of a water basin) are avoided.

In a counterbalanced within-subject design, 28 healthy male students were exposed to the CPT and to a warm water control (CNT) condition twice, one week apart. Cardiovascular parameters, salivary cortisol and subjective ratings (stress, arousal and pain) were assessed before, during, and after interventions.

The CPT profoundly affected physiology as well as subjective ratings. Expectation effects (immediately before testing) were small. Furthermore, post-CPT (presumably compensatory/counter-regulatory) effects on heart rate and stroke volume were found.

In conclusion, the automated bilateral feet CPT is a valid and feasible stress test modification. Hemodynamic, subjective and endocrine stress responses are substantial, suggesting that this test version represents an advanced and suitable tool in human stress research.

1. Introduction

Today, the Cold Pressor Test (CPT) is a commonly used and widely accepted stress protocol in human experimental stress research. It is frequently employed to evoke physiological and psychological stress reactions in healthy individuals. The CPT was first described by Hines and Brown (1932) and applied to study cardiovascular functioning, and to describe blood pressure (BP) responsivity in predisposition to arterial hypertension (Kasagi et al., 1995; Menkes et al., 1989; Wood et al., 1984), and Autonomic Nervous System (ANS) dysfunction (Kumar and Ahuja, 1998; Santambrogio et al., 1991; Santangelo et al., 1991).

The CPT procedure reliably activates the sympatho-adrenomedullary system (SAMS) and thereby leads to an immediate increase in circulating levels of adrenaline and noradrenaline, a rise in heart rate and force of contraction, peripheral vasoconstriction and energy mobilization (Ulrich-Lai and Herman, 2009; Victor et al., 1987). In such, this rapid activation represents the classic "fight or flight" or first-wave stress response (Cannon, 1929a, 1929b; McEwen and Sapolsky, 1995). Besides sympathetic nervous system (SNS) activation in the periphery, there is evidence of other biochemical changes induced by the cold exposure, e.g. dopamine release in the brain (Hughes et al., 1986) or exaggerated levels of endogenous opioids (McCubbin, 1993). While the vascular SNS response is commonly observed, the response in heart rate (HR) shows substantial inter-individual variability (Jauregui-Renaud et al., 2001; Mourot et al., 2009). Also, skin blood flow (Mizeva et al., 2015), sudomotor (De Marinis et al., 2012), respiratory (Santarcangelo et al., 2013), and pupillary (Davis et al., 2013) stress responses have been studied by the CPT. While some authors have presented evidence that CPT stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis and results in elevated release of cortisol (al'Absi et al., 2002; Skoluda et al., 2015), others have reported only mild (Larra et al., 2014) or absent (Duncko et al., 2009; McRae et al., 2006) cortisol responses to the classic CPT procedure. Adding a social component to the test apparently increases HPA activation (Schwabe et al., 2008).

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Beside applications of the CPT in clinical assessment of CV and ANS dysfunction, this test is a standard pain test. Pain due to local cooling can be classified by its quality and/or its quantity depending on the water temperature. In a zero degrees hand CPT for instance, deep aching pain seems to reach its maximum at about 1 min and approaches the unbearable level. It's followed by a “pins and needles” sensation until “adaptation” after about 5 min, when pain is no longer perceived (Wolf and Hardy, 1941). The CPT was used as model for tonic pain to relate human pain responsivity to psychological trait factors and reveal individual differences (Chen et al., 1989). By cooling of the dorsal hand, Klement and Arndt (1992) showed that nociceptors of cutaneous veins mediate cold pain in humans. Preoperative cold pressor pain also promised to be a good predictor of pain after surgery and therefore indicating patient needs for postoperative treatment (MacLachlan et al., 2016; Mobilio et al., 2011). To date, the CPT is a commonly used experimental pain induction technique in pediatric pain (Birnie et al., 2012), clinical (Leonard et al., 2015) and cognitive research (Bjekic et al., 2017).

In psychobiological research, the CPT has been used to investigate stress influence on Central Nervous System (CNS) functions like attention, emotion, memory processing and fear conditioning, as well as other behavioral responses. Post-acquisition CPT was shown to enhance memory consolidation (Hamacher-Dang et al., 2013; Lass-Hennemann et al., 2011), especially for arousing materials (Cahill et al., 2003). Larra et al. (2014) found, that a beta-adrenergic response component of the CPT and stress-related HR increase may play a role in this memory consolidation effect. The CPT applied prior to extinction training may also improve fear extinction in healthy men (Antov et al., 2015). Other studies showed that the CPT influences EEG attention correlates (Sanger et al., 2014) and awareness of cardiac signals (e.g. cardioceptive accuracy) depending on internal versus external deployment of attention (Schulz et al., 2013). The CPT was used to indicate interactions of stress and startle processing: while CPT stress facilitated autonomic startle responsiveness (e.g. HR and electrodermal activity (EDA)), no such facilitation was found for somatic motor eye blink reactivity (Deuter et al., 2012). While CPT stress facilitated affective processing of dissimilar mates, a control group showed preferences for self-resembling mates of the opposite sex (Lass-Hennemann et al., 2010). Furthermore, the CPT was used to demonstrate that stress affects cradling behavior (Suter et al., 2007).

Even if most often, the classical one-hand immersion is used, multiple versions of the CPT have been reported. Variations range from bilateral hands (Suter et al., 2007), unilateral foot (Saab et al., 1993) and bilateral feet immersion (Frings et al., 2013; Larra et al., 2015), to elbow (Sanger et al., 2014), forearm (Brusselmans et al., 2015; Cheng et al., 2014) and forehead stimulation (Hood et al., 2015; Peckerman et al., 1991), to single finger cooling (Rintamaki et al., 1993; Sendowski et al., 1997). Another relatively naturalistic alternative to the traditional Cold Pressor Tests is the whole-body cold exposure which can be realized in a cold chamber (Kelsey et al., 2000) or by a tube-lined suit (Wilson et al., 2007). On the first glance, the cardiovascular response patterns evoked by all these different versions of the Cold Pressor Test seem to be reliable and stable over time (Saab et al., 1993). However, when it comes to detail, one version might be preferred to the others.

Classically, the test is performed by immersing a subject's hand into ice water for a short period of time, usually 2 to 4 min. Thus, the classic CPT is short, easy to handle and allows for reasonably exact experimental timing. However, this classic version entails some practical disadvantages also due to the fact that only one hand is immersed. Firstly, the respective hand cannot be used for anything else during the test procedure (e.g. blood pressure recording by Finapres-type beat-to-beat measurements, manual report or manual button pushes). Secondly, unilateral stimulation with ice water is known to induce laterality specific effects that may interfere with other dependent variables, and even influence the stress response itself. This problem not only refers to peripheral cooling of the limbs but also to hemispheric specificity. Based on autonomic responses to lateralized cold pressor and facial cooling tasks, McGinley and Friedman (2015) could confirm reports of right hemisphere dominance in sympathetic regulation. As compared to right-side cold pressor and facial cooling, left-side cold pressor elicited generally larger sympathetic nervous system (SNS) reactivity.

In terms of rendering both hands free and avoiding laterality effects, using two feet instead of one hand seems to be advisable. The bilateral feet CPT was found to be even more adequate if a stronger neuroendocrine stress response is required (Larra et al., 2015). In a comparative study, the authors could show that the bilateral feet version by contrast with the classic unilateral hand procedure induced enhanced cortisol responses, higher increases in heart rate and elevated subjective reactions. However, there are some remaining problems with the bilateral feet CPT. Participants have to conduct movement when either immersing or taking out their limb(s), and nonspecific motor activation may occur. Furthermore, application of classic CPT versions necessitates quite a lot of interaction between the experimenter and the participant, and this might interfere with the test protocol and lower the level of standardization.

In order to minimize the potentially confounding effects of motoric activation and interaction and to prevent the risk of losing standardization, an automated version of the bilateral feet Cold Pressor Test was developed. Based on a computerized mechanism, influx and efflux of the water is regulated automatically. Thus, participants neither need to lift their feet nor to actually interact with the experimenter. Additionally, preventing the formation of stable temperature layers next to the skin, the water around the feet is kept in permanent flow. The current study was conducted to verify validity and feasibility of this CPT variant.

Furthermore, there was a focus on stress reactivity in terms of cardiovascular hemodynamics. It's well known from previous research that the cardiovascular system reacts to cold water stress with an immediate increase followed by a decline eventually coming back to resting state within minutes. Accordingly, we expected stress-related changes in heart rate, blood pressure and associated parameters like cardiac output and total peripheral resistance. In our previous studies, we also have seen differences in cardiovascular activity between early and late CPT time intervals, which is why we splitted the intervention into two halves of similar length. With regard to the temporal effects within the stress period, the study is explorative. Particularly, we were interested in four (A–D) specific research questions concerning the exact cold exposure time. Research questions A and B deal with the change from baseline to the first and to the second half of the cold exposure period, respectively. Research question C directly compares hemodynamic effects of the first and the second half of the CPT. Finally, research question D addresses the magnitude of (pre-test) expectation effects. We did not explicitly expect any differences in the late stages.

2. Materials and methods

2.1. Sample

Twenty-eight male, healthy students (all Caucasian) (age: 26 ± 3 yrs.) were recruited by internet announcement posted at the University of Trier. All participants had normal weight (BMI between 19 and 25 kg/m^2) and height between 1.55 and 2.00 m, as well as maximal shoe size of 13 (EU size 47). Exclusion criteria (checked before participation by phone interview) were any evidence of acute or chronic disease of the circulatory system (e.g. known arterial hypertension, resting blood pressure above 140/90 mm Hg, history of fainting, Raynaud's disease, venous/arterial thrombosis or a family history of cerebral or aortic aneurism) as well as acute or history of psychiatric morbidity, heavy amblyopia, smoking more than five cigarettes per day, illicit drug use or current medication except the occasional use of pain killers (paracetamol, acetylsalicylic acid, NSAIDs), increased subjective sensitivity to cold, dermatologic lesions, burns or