

Sex Differences in Cortisol Response to Noxious Stress

*Christiane Zimmer, PhD, †Heinz-Dieter Basler, PhD, ‡Helmut Vedder, and
‡§Stefan Lautenbacher, PhD

**Department of Clinical Psychology, University of Freiburg, Freiburg, Germany; †Departments of Medical Psychology, and ‡Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany; and §Department of Physiological Psychology, University of Bamberg, Bamberg, Germany*

Abstract:

Objectives: Evidence has accumulated that men and women show different responses to noxious stimuli, with women exhibiting greater sensitivity to pain than men. Data concerning sex differences in cortisol response patterns have revealed inconsistent results so far. The purpose of the present study was to examine sex differences in subjective pain and cortisol response to a noxious stressor.

Methods: Seventy-six subjects (39 male and 37 female) were investigated by a modification of the cold pressor test that consisted of intermittent immersion of the hand into ice water (plunge test, PT). The PT was conducted twice, in consecutive trials, to guarantee a sufficient exposure to the noxious stressor for eliciting cortisol responses. In each trial, tolerance time and pain ratings visual analog scale (VAS) were assessed. Seven saliva samples (c1–c7) were collected to determine cortisol levels at baseline (c1–c2), directly before (c3) and 20 minutes after noxious stress (c4), and during recovery period (c5–c7).

Results: We found no significant sex differences in tolerance time in trial 1, but highly significant differences in tolerance time in trial 2, with higher tolerance times in men. No significant sex differences were found for the VAS ratings of pain intensity and unpleasantness in the 2 trials. In contrast, a significantly larger cortisol increase in men was observed compared with women. Analysis of covariance revealed that this result could not be attributed to sex differences in cortisol level at baseline and in tolerance time.

Discussion: The present study demonstrates that men show a larger cortisol response to a noxious stressor than women that is not attributable to sex differences in subjective pain. The conclusion of a causal relation between larger cortisol responses and higher pain tolerance thresholds in men is tempting but yet speculative.

Key Words: cold pressor test, plunge test, pain, sex differences, cortisol

It is well-known that pain is multidimensional in nature with subjective, behavioral, and physiological components. Important information about the underlying mechanisms of pain can come from investigations of each of these components. Endocrine responses to noxious stressors and their relation to the subjective experi-

ence of pain have rarely been investigated, although analgesic and anti-inflammatory properties of stress hormones are likely. One such hormone is cortisol.

The cortisol response to stress has been tested by means of a variety of stressors. Physical stressors such as medical diagnostic procedures produce a strong cortisol elevation of about 200% above baseline.¹ Even more moderate physical stress produces reliable cortisol responses.¹ There have been many studies in which psychologic stressors (eg, public speaking or a mental arithmetic task) have shown marked cortisol responses as well.^{2,3} However, evidence for changes in cortisol level in response to experimental pain stimuli is rather scarce.

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Correspondence and reprints: Christiane Zimmer, PhD, Department of Clinical Psychology, University of Freiburg, Engelberger Str. 41, 79085 Freiburg, Germany. E-mail: zimmer@psychologie.unifreiburg.de.

Studies using the cold pressor paradigm^{4–8} have suggested an increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, including a cortisol response. However, nothing is known of whether this is true for both women and men.

Considerable evidence indicates that women and men often show divergent responses to noxious stimuli. Women tend to exhibit greater sensitivity to pain than men, with some forms of experimental pain (eg, pressure) producing more stable sex differences than others (eg, heat).^{9–11} The investigation of sex differences in HPA axis responses following stressful stimulation has revealed inconsistent results. Frankenhäuser et al^{12–13} obtained no sex differences in cortisol responses after psychosocial stress in an achievement situation. In contrast, Kirschbaum et al^{2,14} found consistent sex differences in cortisol responses after public speaking and a mental arithmetic task. Men showed a 1.5- to 2-fold elevation in cortisol responses compared with women. It has been hypothesized that gonadal steroids, especially estradiol, are important modulators of the HPA axis and responsible for the sex differences.¹⁵

Consequently, there is evidence that women show a greater sensitivity to pain whereas men seem to respond with a stronger cortisol secretion to various stressors. The aim of the present study was to investigate whether an acute pain stressor produces different patterns of cortisol response in women and in men. As pain stressor, we applied a modification of the cold pressor test (CPT) called the plunge test (PT),¹⁶ which we modified further to enhance its stressfulness. Furthermore, we investigated whether the cortisol response is related to the subjective response to pain.

METHODS

Subjects

Forty-two men and 42 women between 19 and 29 years of age took part in the study; all participants were

university students (see Table 1). Twenty-five of the women were taking oral contraceptives. Of the women without oral contraceptives, 9 participated while in the post-menstrual or follicular phase (days 1–14) of their natural menstrual cycle and 8 while in the luteal or premenstrual phase (days 15–end). They all reported a regular menstrual cycle with an average of 29 days (SD = 1.7). Body mass indices (BMI) for both sexes (women: M = 20.56, SD = 1.98, men: M = 22.75, SD = 1.94) indicate that the sample consisted of normal weight subjects. Since nicotine has been found to have an impact on the reactivity of the HPA axis¹⁷ smokers were excluded from the study. The study protocol was approved by the medical ethics committee of the University of Marburg. All subjects provided written informed consent and were paid for participation.

Experimental procedure

To control for the circadian rhythm of cortisol, all experimental sessions took place between 5 PM and 8 PM. After a 10-minute rest period, blood pressure (BP) and heart rate (HR) were assessed and the first saliva sample (c1) was collected (see Fig. 1). Following this, subjects filled out questionnaires assessing sociodemographic data, distress (KAB¹⁸), and state anxiety (STAI¹⁹). This was followed by a resting phase of 60 minutes during which 2 more saliva samples (c2, c3) were collected, one after 40 and another after 60 minutes. The pain stressor was then applied (see plunge test). Immediately after the pain stressor, pain intensity and pain unpleasantness were measured by use of two VASs. Sample c4 was taken 20 minutes after the exposure to the pain stressor. The further post-stress period took another 45 minutes. Every 15 minutes a saliva sample was collected (c5, c6, c7). During the session, subjects sat mainly upright at a table or in front of the water bath for immersion of the upper limbs during the plunge test. A single female experimenter conducted all testing sessions.

TABLE 1. Demographic, cardiovascular, and psychological data

	Total sample (n = 76)	Women (n = 37)	Men (n = 39)
Age	22.32 ± 2.62	21.32 ± 2.04	23.26 ± 2.78
Term	3.11 ± 4.13	2.19 ± 3.11	3.97 ± 4.78
Height	1.78 ± 0.09	1.71 ± 0.06	1.84 ± 0.07
Weight	69.34 ± 12.44	60.38 ± 8.12	77.85 ± 9.52
BMI	21.79 ± 2.22	20.70 ± 2.04	22.83 ± 1.88
Systolic blood pressure	126.47 ± 16.66	115.30 ± 14.40	137.08 ± 10.69
Diastolic blood pressure	73.30 ± 8.07	69.54 ± 7.83	76.87 ± 6.61
Heart rate	74.72 ± 12.64	74.51 ± 12.95	74.92 ± 12.51
Anxiety (STAI)	34.30 ± 5.56	35.13 ± 5.36	33.51 ± 5.71
Current distress (KAB)	2.33 ± 0.58	2.41 ± 0.62	2.24 ± 0.54

Values are mean ± standard deviation. BMI, body mass index; STAI, State-Trait Anxiety Inventory; KAB, Kurzfragebogen zur aktuellen Beanspruchung.

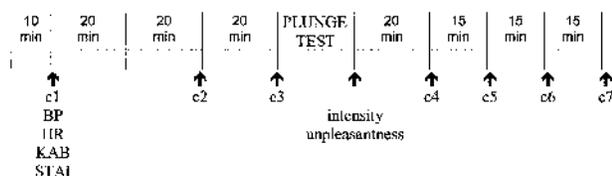


FIGURE 1. Experimental procedure and times of measurement of blood pressure (BP), heart rate (HR), saliva cortisol (c1–c7), current distress (KAB), state anxiety (STAI), pain intensity (intensity) and pain unpleasantness (unpleasantness).

Plunge test (PT)

The PT was conducted twice on 2 consecutive trials. On the first trial, subjects were told to immerse the right hand and forearm up to 15 cm above the wrist in a cold-water bath held at 5°C. On the second trial, the left hand and forearm were immersed. The water temperature was controlled with a precision of 0.01°C by a thermostat (Variostat, Huber), and the water was whirled by a force and suction pump to prevent local warming around the subject's limb. While the cold pressor test requires a continuous immersion, the PT makes use of intermittent exposures of the hand to the ice water. In contrast to the protocol of Worthington,¹⁶ who used preset periods of 20 seconds immersion and 10 seconds rest, we used variable periods to reduce the predictability and the controllability of the pain stressor and to increase the stress. For that purpose, the duration of the immersion and rest periods was randomized to be 5, 10, or 15 seconds. Subjects had control over the total time of exposure (they were instructed to endure the pain until they could no longer tolerate the ice water) but they were not informed about the duration of each immersion and rest period and consequently had no control over the time course of exposures to the ice water.

Psychologic assessment

Psychologic assessment examined pain experience, distress, and state-anxiety. Pain intensity was assessed through horizontal visual analog scales (VAS), with lines 10 cm long, to allow for the assessment of pain intensity and pain unpleasantness. The VAS for pain intensity was labeled with verbal anchors from "no pain" to "worst possible pain." Pain unpleasantness was labeled with "not at all unpleasant" to "extremely unpleasant." The "Kurzfragebogen zur aktuellen Beanspruchung" (KAB; "short scale for current distress")¹⁸ was designed to measure distress by presenting 6 pairs of positive and negative adjectives which define a polar rating scale (tense/calm, uneasy/easy, unconcerned/concerned, restless/relaxed, skeptical/trusting, comfortable/uncomfortable). State anxiety was assessed by use of the German version of the "State-Trait Anxiety Inventory" (STAI).¹⁹

Assessment of salivary cortisol

Saliva was collected by asking the subjects to chew for 60 seconds on a cotton roll and putting it into a plastic tube ("Salivette," Sarstedt, Rommelsdorf, Germany). The salivettes were stored in a -20°C freezer until further analysis. Salivary cortisol concentration was assayed by use of an ELISA kit (DRG Instruments, Germany). The intra-assay coefficient of variation was <5.5% and the corresponding inter-assay coefficient of variation was <6.5%. The lower detection limit was 3.1 nmol/l. The competitive immunoassay requires 1.5 hours incubation time and shows robust and reproducible performance.

Systolic and diastolic blood pressure (BP) and heart rate (HR)

BP and HR were measured by means of an automatic monitor (Omron M4-N, Omron) at the beginning of the experiment.

Statistical analyses

Since many studies have demonstrated consistent sex differences in pain variables. Sex differences in pain tolerance, pain intensity (VAS) and pain unpleasantness (VAS) were assessed by means of a multivariate analysis of variance (MANOVA) with the pain variables as dependent variables and sex as the between-subject variable. Results regarding normality of sample distributions, homogeneity of variance-covariance matrices and linearity were satisfactory. In univariate analyses of variance (ANOVA), the sex differences in each single pain parameter were evaluated.

To test for sex differences in cortisol responses to the PT, a 2-factorial analysis of covariance (MANCOVA) with repeated measures was conducted. Sex was used as the between-subject variable and 6 cortisol samples were used as within-subject variables: c2 (20 minutes before the PT), c3 (immediately before the PT), c4 (20 minutes after the PT), and the 3 measurements (c5 to c7) in intervals of 15 minutes that reflected the post-stress recovery period. To control for different baseline levels, the first cortisol sample at the beginning of the session (c1) was included as covariate. In addition, an adjustment was made for pain tolerance by using it as a second covariate. Results of the evaluation of normality, homogeneity of variance-covariance matrices, and linearity were satisfactory.

Additionally, correlations between pain parameters and cortisol response were computed. Cortisol responses to the pain stressor were obtained by calculating the differences between cortisol levels directly before the PT (c3) and the maximum level which occurred either 20 (c4) or 35 minutes (c5) after the PT. The alpha-level was set to 0.05 throughout.

RESULTS

Subject characteristics

The original sample size of 84 dropped to 76 due to the occurrence of multivariate outliers (2 women, 3 men) and the withdrawal of 3 women because of strong autonomic reactions to the PT. Table 1 shows means and standard deviations for the resulting sample of $n = 76$ (37 women and 39 men) regarding age, weight, height, and BMI as well as cardiovascular and psychologic variables at baseline. Women and men did not differ in the psychologic variables as measured by STAI and KAB ($F(2/73) = 0.92$; n.s.) showing both moderate distress and state anxiety. As presented in Table 1, cardiovascular parameters differed significantly between the sexes ($F(3/72) = 20.48$; $P < 0.001$). Univariate tests revealed that men had a higher systolic ($F(1/74) = 56.46$; $P < 0.01$) and diastolic blood pressure ($F(1/74) = 19.52$; $P < 0.01$) than women. There were no differences in heart rate ($F(1/74) = 0.02$; n.s.).

Sex differences in pain reports

Analysis of variance did not indicate a statistically significant multivariate effect of sex on the pain variables ($F(6/69) = 1.78$, n.s.). However, inspection of the data suggested sex differences in some of them. Univariate analysis revealed that there was a significant sex difference in tolerance time for the second PT trial ($F(1/75) = 7.59$; $P < 0.01$) and a marginally significant difference in tolerance time for the first PT trial ($F(1/75) = 3.04$, $P < 0.10$), with higher tolerance times in men in both cases (see Fig. 2). There were no sex differences in the VAS ratings of pain intensity and pain unpleasant-

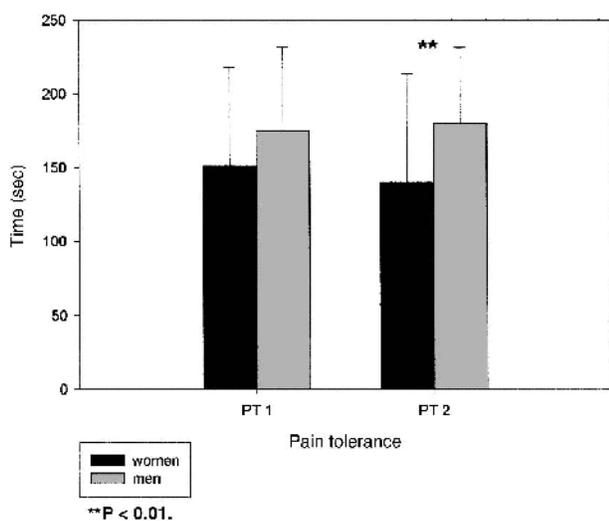


FIGURE 2. Means and standard deviations in pain tolerance for plunge test 1 (PT1) and plunge test 2 (PT2) in women and men.

ness. Since the multivariate effect was not significant, the sex differences in tolerance time should be interpreted with caution.

Cortisol responses

Multivariate analysis of covariance (MANCOVA) with repeated measures was used to test for sex differences in cortisol response patterns. Since the cortisol values at baseline (c1) and the tolerance times in the plunge test (total of PT1 and PT2) could also be expected to impact on the data, these 2 variables were used as covariates. The cortisol levels at baseline (c1) were $M = 7.14$ nmol/l ($SD = 4.28$) for women and $M = 7.40$ nmol/l ($SD = 3.95$) for men which was a nonsignificant sex difference. Tests of within-subject contrasts revealed significant differences between pre- and post-stress cortisol levels ($F(1/72) = 5.89$; $P < 0.05$) indicating that saliva cortisol was significantly increased by the PT in both sexes (see Fig. 3). Furthermore, a multivariate test displayed a statistically significant difference of the cortisol response between the sexes ($F(5/68) = 2.53$; $P < 0.05$). Tests of within-subject contrasts revealed that men showed a significantly larger increase of cortisol than women comparing the values immediately before (c3) with those obtained 20 minutes after exposure (c4) to the noxious stressor ($F(1/72) = 17.62$; $P < 0.05$) (see Fig. 3). No significant sex differences in cortisol responses emerged in the remaining part of the experiment. Therefore, as baseline cortisol and tolerance time was controlled for, the observed sex differences in cortisol responses cannot be attributed to these factors.

Correlations

In the total sample, the increase of cortisol defined by the difference between the cortisol level immediately before the PT and the maximum level afterward (either at c4 or at c5) showed an inconsistent relationship with the pain variables. Whereas in trial 1 significant correlations were calculated with both the VAS ratings of pain ($r = 0.30$; $P < 0.01$) and the unpleasantness of pain ($r = 0.25$; $P < 0.05$), no relationship was detected in trial 2. In neither trial was pain tolerance related to the cortisol response. The latter was also true for a separate analysis of the sexes, although intensity and unpleasantness of pain was significantly related to the cortisol response in women, but not in men (see Table 2). The difference of the relationship between the sexes, however, does not seem very impressive. Even for pain intensity in trial 1, a variable that demonstrates the strongest relationship with cortisol levels in women, the power of a test used to calculate the probability of sex differences in the correlation coefficients was only 60% at an alpha level of 0.05

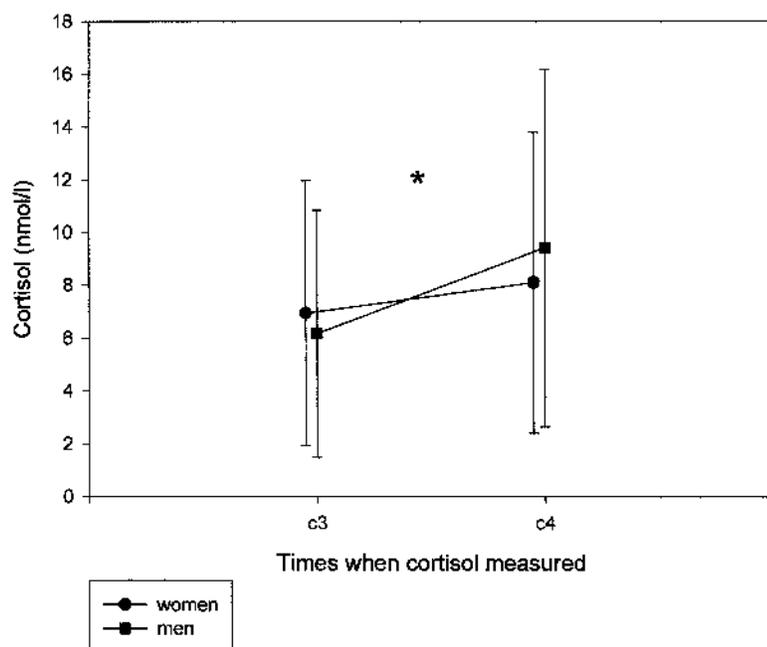


FIGURE 3. Means and standard deviations of salivary cortisol concentrations directly before the PT (c3) and 20 minutes after the PT (c4) in women and men. * $P < 0.05$ indicates a significant interaction between sex and salivary cortisol concentrations in response to the PT.

*Interaction sex x cortisol c3 compared to c4: $P < 0.05$.

(2-tailed power computation for the assessment of a difference in 2 correlations).

DISCUSSION

The present study aimed at investigating sex differences in cortisol responses to a noxious stressor. The major findings were (1) the applied modification of the cold pressor test, that is, the modified plunge test (PT), produced reliable increases in salivary cortisol levels, (2) these increases were significantly larger in men than in women, and (3) subjective pain experience in contrast to the endocrine responses was significantly stronger in women than in men. These results will be discussed in turn.

In the present study, the PT was used in a modified form with the intention to make the interval of immersion unpredictable to the subject and, thereby, enhance

TABLE 2. Correlations between cortisol reaction and pain reports in women and men

	PT	Women	Men
Pain tolerance	PT1	-0.05	0.11
	PT2	-0.06	0.05
Pain intensity	PT1	0.52†	0.05
	PT2	0.35*	-0.17
Pain unpleasantness	PT1	0.24	0.20
	PT2	0.33*	-0.02

PT, both trials of the plunge test; PT1, plunge test trial 1; PT2, plunge test trial 2.

* $P < 0.05$, † $P < 0.01$.

the stressfulness of the procedure. As expected, exposure to this stimulus resulted in significant increases of salivary cortisol. This finding is in line with those studies that show increases of the cortisol level as a response to the CPT.⁴⁻⁸ Consequently, the modified PT appears to be a useful instrument in experimental pain research. This is further supported by the substantial size of the cortisol response. We found a responder rate of 83% (responding is defined as an increase of at least 15%) and an average increase of 394% above baseline level.

In addition, we found a significant effect of the subject's sex on cortisol responses to the PT, with men showing a stronger response than women. This cannot be attributed to different baseline levels of cortisol or to a different duration of exposure to the stressor (tolerance time) because these variables were used in the analysis as covariates. These findings corroborate the results of previous studies that also demonstrated stronger cortisol responses in men when exposed to other types of stressors apart from noxious stimuli, for example, psychosocial stressors. This could mean that the male HPA axis is more susceptible to stress. In fact, a study about the contribution of gonadal steroids as possible mediators of the cortisol response in healthy subjects¹⁵ suggests that female gonadal hormones exert an important influence on HPA-responsiveness under psychosocial stress. The authors report individual differences in salivary cortisol levels that can be partly explained by estradiol-dependent changes. To our knowledge this study is the first published to demonstrate that a

differential response of the HPA axis also occurs during noxious stimulation.

In addition to the cortisol response, we also found sex differences in pain tolerance with men showing higher tolerance than women. This result, too, is in accordance with previous studies. Numerous authors have reported sex differences in tolerance to pain stimuli.^{9–11} In our study, the expected effect of sex was not observed in the first, but only in the second trial. This may be a consequence of the sample size. As there was a tendency toward a higher tolerance in men already in the first trial, the expected outcome might have been more obvious by use of a bigger sample. Another explanation for this finding may be the method we used for the assessment of tolerance. The modified PT with randomized immersion and rest periods could be responsible for a possible increase of the error of measurement of pain tolerance. Stimulation was intentionally started and stopped at random intervals with the consequence that subtle differences in pain tolerance might have been missed. Another explanation for the occurrence of a significant sex difference in pain tolerance only in the second trial might be a different response to the noxious stressor in the first trial. Women appeared to decrease pain tolerance, men to increase. There is a growing literature that the effect of stress on the pain system is sex-related. Some forms of stress have been found to increase pain sensitivity in women but not in men and the other way round.^{20–22}

Finally, in our study no sex differences were found in the VAS ratings of pain intensity and unpleasantness. This is likely due to the longer exposure of the men to the noxious stressor compared with the women. The higher pain sensitivity of women might not have become obvious because the duration of pain stimulation was reduced for them.

It is tempting to assume that the greater increase in cortisol levels in men has contributed to their higher pain tolerance in the second trial of the PT. A potential analgesic effect of cortisol might have produced increased tolerance in men some minutes later, in the second trial. Such a hypothesis of a potential analgesic action of cortisol is supported by the results of those clinical studies that found an association between hypocortisolism and a variety of painful disorders. Geiss et al²³ reported an attenuated elevation of cortisol secretion in patients with persisting sciatic pain after discectomy in comparison with patients presenting with low levels of pain. Hypocortisolism might play a role in the development of disorders like fibromyalgia, chronic pelvic pain, or rheumatoid arthritis due to the lack of possible protective properties of cortisol.^{24,25} In contrast, Lautenbacher et al^{26,27} did not observe any effect of varying levels of plasma cortisol on experimental heat pain. Also the cor-

relations computed in our study, at first glance, seem to suggest the opposite of an analgesic effect: a pain increasing action of cortisol, especially in women.

Although a clear-cut answer to the effect of cortisol on the pain system is still missing, our correlational analyses underscore the importance of the temporal relationship between cortisol activity and pain. The cortisol level before the onset of pain may determine how strong the pain finally becomes. The intensity of pain may in turn determine the stressfulness of the situation and, thereby, the size of the increase in cortisol level. This relationship might be reflected in our correlations suggesting that a strong pain is associated with a strong increase of cortisol. The increase of cortisol may in turn determine the amount of pain at later stages due to the potential analgesic properties of cortisol. This relation might explain why men exhibited a larger increase in cortisol level and tolerated pain better in the second trial. Such a series of cause-effect relations is difficult to investigate, but it should be considered in future studies.

In summary, the present study provided clear evidence that men respond to noxious stressors by stronger increases of cortisol than women and that this finding is independent of the subjective experience of pain. The conclusion of a causal relationship between larger cortisol responses and higher pain tolerance thresholds in men is tempting but still speculative.

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