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Abstract

Background and aims: Endogenous pain modulation can be studied in humans by conditioned pain modulation (CPM): pain induced by a test stimulus is attenuated by a distantly applied noxious conditioning stimulus. The detection of impaired CPM in individual patients is of potential importance to understand the pathophysiology and predict outcomes. However, it requires the availability of reference values.

Methods: We determined reference values of CPM in 146 pain-free subjects. Pressure and electrical stimulation were the test stimuli. For electrical stimuli, we recorded both pain threshold and threshold for the nociceptive withdrawal reflex. Cold pressor test was the conditioning stimulus. The 5th, 10th and 25th percentiles for the three tests were computed by quantile regression analyses.

Results: The average thresholds increased after the conditioning stimulus for all three tests. However, a subset of subjects displayed a decrease in thresholds during the conditioning stimulus. This produced negative values for most of the computed percentiles.

Conclusions: This study determined percentile reference values of CPM that can be used to better phenotype patients for clinical and research purposes. The negative value of percentiles suggests that a slightly negative CPM effect can be observed in pain-free volunteers.

Implications: Pain facilitation rather than inhibition during the conditioning stimulus occurs in some pain-free volunteers and may not necessarily represent an abnormal finding.

Keywords: conditioned pain modulation; references values; cold pressor test; pressure pain thresholds; electrical pain thresholds.

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1 Introduction

Dysfunctional endogenous pain modulation is considered a relevant contributor to chronic pain [1, 2]. In humans, endogenous pain modulation can be studied by conditioned pain modulation (CPM) [3]: in the presence of a functional endogenous pain modulation, pain induced by a test stimulus is expected to be attenuated by a noxious conditioning stimulus applied at a distant body site.

Several studies have applied CPM paradigms to compare pain patients to pain-free subjects. Some studies found less effective CPM in patients than in pain-free subjects, indicating that dysfunctional endogenous modulation may be one of the mechanisms underlying pain conditions [4, 5]. However, other investigations did not find CPM to be dysfunctional in pain patients [6, 7]. These discrepancies may be due to different patient populations and different methods to induce CPM. Moreover, it is possible that CPM is not impaired in all patients with the same diagnosis, but only in a subgroup of them [8]. In a large epidemiological study, we found that 23.7% of patients with chronic pain had a decrease in pressure pain tolerance threshold after cold pressor test, suggesting that endogenous modulation is malfunctioning in this subset [9]. The remaining patients had various increases in

pressure pain thresholds, but the lack of reference values did not allow an estimation of the proportion of patients with normal and abnormal CPM. While an increase in pain threshold is considered an indication of functional endogenous modulation, the magnitude of increase that defines functional CPM is unknown.

Reference values of CPM would allow a better phenotyping of individual patients according to the likelihood of having dysfunctional CPM, thereby improving the understanding of the individual pathophysiology of pain. Furthermore, there is some evidence that altered CPM may predict persistent pain or the efficacy of medications [10–13]. Also in this regard, the availability of reference values would allow patient phenotyping according to their CPM functional status, hopefully improving the ability to predict the course of the disease or the efficacy of treatments. While descriptive data on CPM in pain-free subjects are available [14, 15], we are not aware of studies that determined reference values.

The aim of the present study was to determine reference values of CPM for electrical and mechanical stimuli, using the cold pressor test as the conditioning stimulus, in a cohort of pain-free adults.

2 Materials and methods

2.1 Design and setting

The study was carried out at the University Department of Anesthesiology and Pain Medicine, Inselspital Bern, Switzerland, according to good clinical practice guidelines and in accordance with the Declaration of Helsinki. Approval by the local Ethics Committee (KEK 066/13) was obtained. The study was registered with clinicaltrials.gov (NCT02377180). All participants gave written informed consent prior to enrolment.

2.2 Subjects

Subjects were recruited by advertisement in local newspapers, among members of local clubs and associations and by word of mouth. In- and exclusion criteria were mentioned in the advertisement. Exclusion criteria were chronic pain, pain at the time of testing, intake of any analgesic medication within 24 h before the test, intake of antidepressants, opioids, benzodiazepines or anticonvulsants within 1 week before the test, any neurological disease and sensory deficits.

We aimed at recruiting 150 subjects. A sample size calculation was not performed. One-hundred and eighteen subjects responded to an advertisement in local newspapers. Eighty-seven of them were recruited and successfully tested. Of the remaining 31 subjects, 27 could not be called back or reached by phone for an appointment, one was no longer willing to participate and three did not show up for the experiment. Furthermore, we distributed the advertisement by e-mail among local clubs and associations (sport clubs, choir singers, music societies, etc.) that were identified by internet search in the region around Bern. Another 59 subjects could be recruited by this effort. After reaching a total sample size of 146 subjects, we stopped the recruitment efforts, as we felt they would not be worth only four additional subjects. Participants received a compensation of 50 Swiss Francs for the inconvenience, time and travel expenses.

2.3 Variables of interest

The following variables were recorded: gender, age, weight, height, body mass index, Beck Depression Inventory fast screen (BDI) [16], state trait anxiety inventory (STAI Trait) [17] and Pain Catastrophizing Scale [18]. The average sleep quality during the week before the experiment was rated by the participants on a 0–10 numeric rating scale (NRS), with 0 = poorest and 10 = best imaginable sleep quality.

2.4 Conditioned pain modulation

Figure 1 illustrates the time course of the experiment. Pressure and electrical stimulation were the test stimuli. The cold pressor test was the conditioning stimulus. The experiment was carried out in a quiet room, with the participants placed comfortably in supine position. The upper

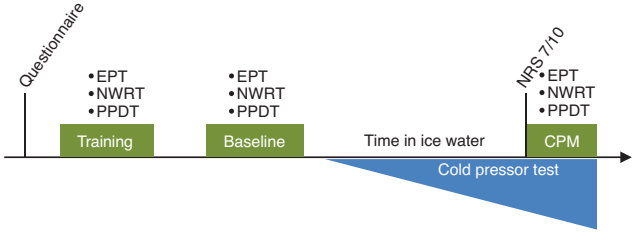

Fig. 1: Time course of experiment. EPT = electrical pain threshold; NWRT = nociceptive withdrawal reflex threshold; PPDT = pressure pain detection threshold; NRS = numeric rating scale (0 = no pain, 10 = worst pain imaginable).

body was elevated by 30–45 degrees. A series of training measurements was performed until the subjects were familiar with the procedure. After multiple training measurements, baseline values were recorded using one single measurement at each test-site. Single measurements, as compared to three, do not lead to relevant measurement error in the tests that we applied [19].

2.4.1 Pressure pain threshold

Pressure pain threshold (PPT) was measured at the 2nd toe of the dominant side using an electronic algometer with a probe of 1 cm^2 (Somedic AB, Horby, Sweden). Pressure was increased by 30 kPa/s, up to a maximum of 1,200 kPa. Once the pressure sensation turned to pain, the subjects stopped the measurement by pressing a button. If 1,200 was reached, this was considered as PPT even if the subject did not press the button. This occurred in only two subjects, and only during the conditioning stimulus.

2.4.2 Electrical pain threshold and nociceptive withdrawal reflex

Electrical pain thresholds (EPT) and the nociceptive withdrawal reflex (NWR) were measured using electrical stimulation with bipolar surface electrodes, placed distal to the lateral malleolus of the dominant side (innervation area of the sural nerve). Electromyography (EMG) recordings were obtained from cutaneous electrodes applied to the middle of the biceps femoris muscle. A constant current stimulator was used for stimulation and reading the EMG responses (NCS System, Evidence 3102 evo, Neurosoft, Russia). A 25 ms, train-of-five, 1 ms, square-wave impulse, perceived as a single stimulus, was delivered to the malleolar electrodes. The current intensity was increased from 1 mA in steps of 1 mA, until the sensation became painful (EPT) and a biceps femoris reflex with an amplitude exceeding 20 μV for at least 10 ms in the 50–150 ms post-stimulation interval was detected (NWR).

2.4.3 Cold pressor test

Subjects placed their non-dominant hand in ice-saturated water at a temperature of 1.5 ± 1 °C. As soon as the pain reached an intensity of 7 on the 0–10 NRS (0 = no pain, 10 = worst pain imaginable), or after a maximum time of 2 min, single assessments of NWR/EPT and PPT, in the specified order, were performed, while the subjects were keeping their hand in the water. Changes were expressed both as differences in absolute values and as percent changes from baseline. The time until cold pain reached NRS 7/10 was noted.

2.5 Statistical analyses

Baseline values of QST are presented as means ± SD. The CPM effect is reported both as absolute difference between the measurement during and before the cold pressor test, as well as the percent change from baseline. This is in accordance with published recommendations on CPM testing [20].

Quantile regression analyses were performed to calculate reference values for CPM effect. This analysis can be used to estimate quantiles within a given sample, without requiring normal distribution of measurements [21]. Quantile regression is similar to multiple regression. However, instead of estimating the mean of the dependent variables, it estimates their quantile distribution. The percentile values that are calculated can be regarded as the critical values of the tests, thereby reflecting their reference values. Two sets of regressions were performed using electrical and pressure CPM as dependent variables, respectively. Age, sex, body-mass index (BMI), sleep quality, BDI, STAI trait and catastrophizing scale were independent variables. This is in accordance with previous studies that found associations of quantitative sensory tests and CPM with demographic variables, psychosocial factors, and sleep [22–25]. The 5th, 10th and 25th percentile were estimated, analogous to previous studies [22, 26], using bootstrapped standard errors with 1,000 replications and the "sqreg"-command in STATA (STATA SE 13, College Station, TX, USA).

3 Results

Of the 177 screened subjects, 146 participated in the experiment. Eighty of them were females (54.8%). The mean (SD) age was 42.5 (17.4) years. Sixty-six subjects were 18–39 years old, 54 subjects 40–59 years old, and 26 over 60 years old. A detailed description of the population can be found in Table 1.

3.1 Baseline measurements

Baseline values of EPT, PPT and NWR before the cold pressor test are displayed in Table 2. There were 2 missing values for EPT and 1 for PPT because of device malfunction. The

Table 1: Descriptive variables, presented as mean (SD) or as number of subjects (percent).

	n = 146
Sex (female)	80 (54.8%)
Age (years)	42.5 ± 17.4
18–39 years	66 (45%)
40–59 years	54 (37%)
>60 years	26 (18%)
BMI (kg/m²)	23.3 ± 3.2
Sleep (NRS 0–10)	7.5 ± 1.6
BDI	1.2 ± 1.6
STAI Trait	33.6 ± 7.6
CATA	9.9 ± 6.4
Dominant side (right)	133 (91%)

BMI = body mass index; Sleep = sleep quality during 1 week before the experiment on a 0–10 numeric rating scale (0 = worst and 10 = best imaginable sleep quality); BDI = Beck depression inventory fast screen (range 0–21); STAI = State-Trait Anxiety inventory (range 20–80); CATA = catastrophizing scale (range 0–52).

Table 2: Baseline quantitative sensory tests.

	n	Mean ± SD
EPT (mA)	144	9.11 ± 6.3
PPT (kPa)	145	412 ± 185
NWR (mA)	73	10.2 ± 5.7
Cold pressor time (s)	146	37 ± 34

Results of baseline quantitative sensory tests. EPT = electrical pain threshold; PPT = pressure pain threshold; NWR = nociceptive withdrawal reflex threshold. Two and one subject had missing values for EPT and PPT, respectively, due to measurement device malfunction.

Table 3: CPM effects as absolute values (difference between the measurement during and before the cold pressor test), and in percent change from baseline.

	n	Mean difference ± SD	Percent ± SD
PPT	145	98 ± 103	27.5 ± 26.6
NWR	64	1.2 ± 2.5	16.8 ± 28.6
EPT			
Overall	144	1.5 ± 1.6	17.7 ± 20.3
Females	80	1.2 ± 1.6	14.5 ± 19.3
Males	64	1.8 ± 1.5	21.8 ± 21.0

CPM = conditioned pain modulation; PPT = pressure pain thresholds; NWR = nociceptive withdrawal reflex threshold; EPT = electrical pain threshold.

baseline NWR could be recorded in only 73 of the 146 subjects (50%), as pain become intolerable before a reflex could be elicited. Among those 73 subjects, 64 showed a measurable reflex during the cold pressor test.

3.2 CPM with pressure pain thresholds

Pressure pain thresholds rose by 98 kPa from baseline (SD 103), which corresponds to a 27.5% increase (SD 26.6) (Table 3). Multiple linear regression with pressure CPM as dependent variable showed none of the explanatory variables to have a significant influence on the CPM effect [$F(7, 134) = 0.5$, $p = 0.83$, $r^2 = 0.02$]. The percentiles of reference values are presented in Table 4 for both absolute values in kPa and percent change. They are also illustrated in Fig. 2A.

Table 4: Reference values of conditioned pain modulation as absolute values (difference between the measurement during and before the cold pressor test), and in percent changes from baseline.

	5th percentile	10th percentile	25th percentile
Absolute change from baseline			
PPT (kPa)	−32 (−60 to −3)	−8 (−24 to 8)	22 (5–38)
NWR (mA)	−3 (−4.8 to −1.1)	−1 (−2.5 to 0.5)	0 (−0.5 to 0.5)
EPT (mA)			
Overall	−1 (−1.6 to 0.4)	0 (−0.6 to 0.6)	0 (−0.6 to 0.6)
Females	−1 (−1.8 to −0.2)	0 (−0.8 to 0.8)	0 (−0.2 to 0.2)
Males	−1 (−1.9 to −0.1)	0 (−0.8 to 0.8)	1 (0.6–1.4)
Percent change from baseline			
PPT (%)	−7.5 (−13.6 to −1.3)	−2.1 (−5.9 to 1.7)	6.5 (1.7–11.2)
NWR (%)	−16.7 (−35.2 to 1.9)	−12.5 (−21.6 to −3.4)	0 (−4.2 to 4.2)
EPT (%)			
Overall	−10 (−19.9 to −0.2)	0 (−6.0 to 6.0)	0 (−7.2 to 7.2)
Females	−10 (−28.4 to 8.4)	0 (−9.9 to 9.9)	0 (−2.9 to 2.9)
Males	−8.3 (−19.7 to 3.0)	0 (−8.6 to 8.6)	9.9 (4.8–15.2)

Pressure pain thresholds (PPT), nociceptive withdrawal reflex thresholds (NWR) and electrical pain thresholds (EPT). 95% Confidence intervals are in parentheses and were estimated using bootstrapped standard errors with 1,000 replications.

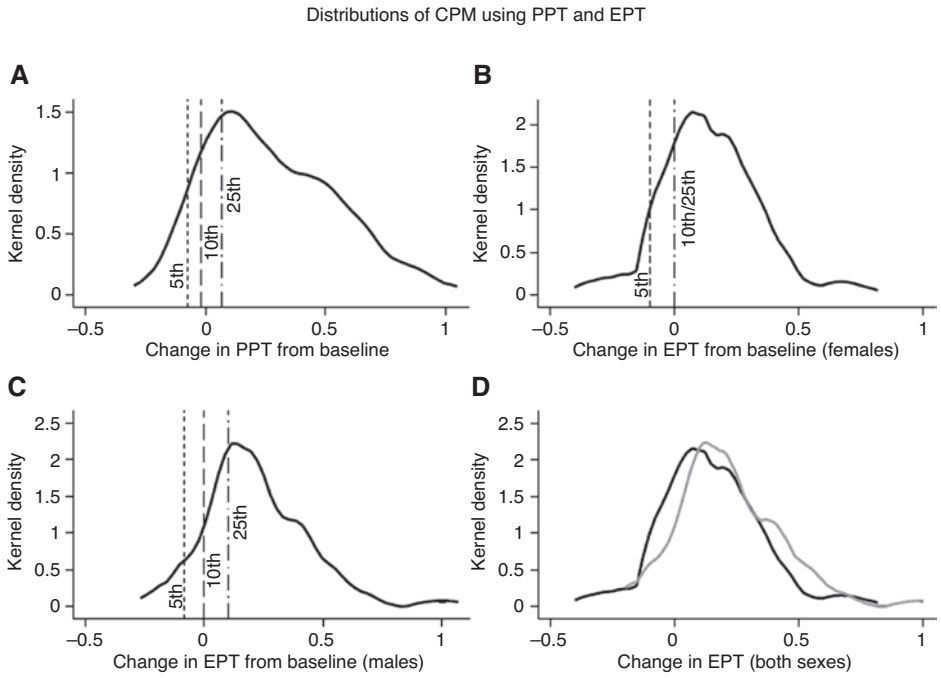

Fig. 2: Illustration of the distribution of conditioned pain modulation (CPM) for the pressure pain paradigm (A) and for the electrical pain paradigm in females (B) and in males (C). The short-dashed line indicates the 5th percentile, the long-dashed line indicates the 10th percentile and the dashed-dotted line indicates the 25th percentile of reference values (10th and 25th coincide in fig. B). To illustrate the difference between males and females, both graphs (B) and (C) are combined in (D). The y-axis indicates the Kernel density of the distribution, which can be interpreted as a smooth approximation to the histogram, as the width of the histogram bars becomes very small. PPT = pressure pain thresholds; EPT = electrical pain thresholds.

3.3 CPM with electrical pain thresholds

Electrical pain thresholds rose by 1.5 mA from baseline (SD 1.6), corresponding to a 17.7% increase (SD 20.3). Multiple linear regression with electrical CPM as dependent variable showed that sex had a significant influence on the magnitude of CPM effect, with a regression coefficient of −0.078 ($p = 0.036$). This indicates that female sex was associated with a 7.8% lower electrical CPM effect than male sex. The remaining independent variables (age, BMI, sleep quality, BDI, STAI and catastrophizing scale) did not influence CPM [$F(7, 134) = 1.32$, $p = 0.24$, $r^2 = 0.06$]. CPM effects and percentiles of reference values for EPT are therefore displayed separately for males and females (Tables 3 and 4, Fig. 2B–D).

3.4 CPM with nociceptive withdrawal reflex

NWR thresholds rose by 1.2 mA (SD 2.5) from baseline, which corresponds to a 16.8% increase (SD 28.6) (Table 3). Multiple linear regression with reflex CPM as dependent variable showed none of the explanatory variables to have a significant influence on the CPM effect [$F(7, 55) = 0.29$, $p = 0.95$, $r^2 = 0.04$]. The percentiles of reference values are presented in Table 4 for both absolute values and percent changes. Because of the many missing values, we omit the presentation in a figure.

4 Discussion

This study determined reference values of CPM elicited with electrical and pressure test stimuli, with cold pressor test as conditioning stimulus. These reference values may be used to phenotype patients according to the likelihood to display functional or dysfunctional endogenous pain modulation.

4.1 CPM effect

The conditioning cold pressor test induced an average increase in thresholds for all three test modalities. However, over 10% of pain-free subjects had negative CPM effects for PPT and NWR, and one out of four subjects did not show an increase in electrical pain thresholds during the cold pressor test. The lack of positive CPM

effect in pain-free subjects has been observed in previous studies [14], and the reasons remain unclear. It has to be stressed that the construct validity of the CPM paradigm in measuring endogenous pain modulation in humans is unknown. This uncertainty is due to lack of a reference standard to assess sensitivity, specificity and likelihood ratios of CPM paradigms [27]. It is possible that CPM has limited sensitivity in measuring endogenous pain modulation. In this case, the negative CPM effect in part of pain-free participants would represent false negative results in detecting functional endogenous pain modulation. An alternative explanation is that endogenous pain modulation is truly impaired in individuals who display a negative CPM effect, and this impairment does not translate into the presence of a pain syndrome. If this is true, an intriguing question would be whether these individuals are more likely to develop a pain syndrome in the future, compared to those who display a positive CPM effect. Large-scale longitudinal studies over a time course of several years would be required to answer this question.

Previous studies on CPM in large samples are sparse and have been mostly descriptive in nature. Locke et al. [14] examined 125 pain-free volunteers and found that 116 of them (92%) exhibited a CPM effect that was greater than the inherent measurement error of their test stimulus (i.e. <5.3%). Nine subjects (8%) did not show a positive CPM effect, which is roughly consistent with our findings. Differences in baseline pain thresholds between males and females were detected, but the CPM effect did not differ between genders. Skovbjerg et al. investigated CPM in a sample of 2,199 Danish people, whereby having pain was not an exclusion criterion [15]. Females had lower CPM than males, and no association of CPM with age or BMI was detected. The average CPM effect expressed in percent change from baseline was 32–39%, similar to the effect observed in the present study.

4.2 Potential applications

The percentiles that we determined can be used as reference to assess CPM in individual patients (Table 4). The choice of the 5th, 10th or 25th percentile as cut off for normal values depends on the particular clinical or scientific question. Only few patients would be identified as having dysfunctional pain modulation when the 5th percentile is chosen as cut-off. The number of cases categorized as having dysfunctional CPM increases progressively by choosing the 10th and 25th percentile. Therefore, the choice of the cut-off depends on the specific consequences of categorizing individual patients as having functional or dysfunctional CPM.

Noticeable in this regard is the finding that the majority of percentile reference values is negative, which is explained by the non-negligible proportion of subjects who had a CPM-effect less than zero. It seems illogical that decreases in pain thresholds after application of conditioning stimulus, even if modest, may be considered as normal. A "normal" decrease in pain threshold is against the common understanding of the CPM concept, whereby functional endogenous modulation should always be associated with increases in pain thresholds. However, it has to be considered that this assumption is derived from animal models. In humans, a simple test paradigm consisting of a test and a conditioning stimulus is unlikely to reflect the complex neuronal, cognitive and emotional processes involved in endogenous pain modulation. The main implication of this finding is that a slightly negative CPM effect does not necessarily reflect abnormal CPM. As mentioned above, a negative CPM effect in part of pain-free subjects has been observed in previous investigations. Therefore, we assume that if those investigations had had a sufficient sample size or had calculated reference values, they would have likely estimated negative percentiles.

4.3 Strengths and limitations

To our knowledge, the present study is the first one that specifically aimed at determining reference values of CPM. We applied a statistical approach that is designed to estimate reference values, in particular the percentiles of CPM, taking into account the potential influence of covariates [21]. A larger sample size may have allowed a more precise estimation of the percentiles. This is particularly true for the NWR, which could not be elicited in a large proposition of subjects. This phenomenon has been observed previously [28]. While the substantial number of missing values of NWR may have compromised the estimation of the reference values, we decided to present the analysis in the light of the lack of available data. Clearly, the estimates pertaining to the NWR have to be taken with caution. A final limitation is that the results apply to three of the several available CPM paradigms.

5 Conclusions

We determined percentile reference values of CPM that can be used to phenotype patients for clinical and

research purposes. A noticeable finding is the negative value of the majority of percentile reference values. This suggests that slightly negative CPM values, specifically slight decreases in pain thresholds after conditioning stimulus, are not necessarily an abnormal finding.

Authors' statements

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Conflict of interest: Authors state no conflict of interest.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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